Alkynylation of Chiral Aldehydes: Alkoxy-, Amino-, and Thio-Substituted Aldehydes

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1. Introduction

Addition of organometallic reagents to chiral aldehydes and ketones is widespread in organic synthesis, and effective control of reaction stereoselectivity remains an important issue. The original work of Cram, Felkin, and Anh proposed models to explain the observed stereoselectivities,[1] and this subject has continued to receive considerable attention in the literature.[2] In general, these reactions are highly substrate dependent, and the absence or presence of chelation plays a crucial role as to which products are preferentially formed. When heteroatoms are adjacent (α and/or β) to the reaction center, chelation and protecting groups (or lack of) play an important part in determining reaction diastereoselectivity, more so than with related examples possessing simple alkyl groups.

The diastereoselective addition of organometallic alkynyl derivatives to chiral aldehydes is the most expedient route toward the preparation of chiral propargylic alcohols. These types of molecules are strategic building blocks in the synthesis of biologically active compounds, and effectively controlling reaction diastereoselectivity is extremely impor-

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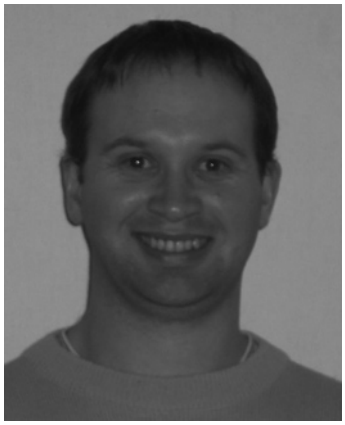


Stéphane Guillarme was born in Vannes, France, in 1973 and received his Master's degree from the University of Paris 5. He obtained his Ph.D. degree in 2002 from the University of Maine (Le Mans, France) under the supervision of Professor F. Huet. His research was mainly in the areas of acyclic nucleoside and cyclobutene chemistry. He then joined Dr. Whiting's group at the University of Durham (England) as a postdoctoral fellow and studied asymmetric aza Diels–Alder reaction of imines. He then worked as a CNRS postdoctoral researcher at the Laboratoire de glycosynthèse (Reims, France), where he developed the alkynylation of chiral aldehydes.

Karen Plé was born in Detroit, MI, in 1966. While completing her Bachelor's of Science degree in Chemistry at Wayne State University (Detroit, MI) she participated in a 1-year student exchange program in France with the Ecole Supérieure de Chimie Industrielle de Lyon (ESCIL). After finishing her studies in the United States, she returned to Lyon, where she completed her Master's degree in Organic Chemistry from ESCIL. She obtained her Ph.D. degree at the University of Reims, France, in 1993. She then received postdoctoral training with Professor Marc Julia in Paris, France, and in an industrial position with AstraZeneca Pharmaceuticals in Macclesfield, England. She was recruited as a research associate for the CNRS (Centre National de Recherche Scientifique) in 1997 and is currently working in Reims. Her research interests include natural product synthesis, especially in the field of glycochemistry.

Aline Banchet was born in 1981 in France. She received her Master's degree in Chemistry at the University of Reims in 2004. During her studies she worked on the synthesis of a chiral hydroxypyranone acetyl derivative in the Photochemistry Laboratory of Dr. N. Hoffmann. Currently she is a Ph.D. student in Reims in the Glycosynthesis Laboratory under the supervision of Professor A. Haudrechy. Her research involves the total synthesis of compounds with biological properties.

Annie Liard (born in France in 1970) received her Ph.D. degree from the University of Orsay (France) in 1997 on the total synthesis of Matrine alkaloids with Professor S. Zard. From February 1998 to August 2000 she was a postdoctoral fellow with Professor I. Marek at the Technion-Israel Institute of Technology. She worked on the development of novel synthetic methods based on titanium and zirconium chemistry. In September 2000 she joined the group of Professor J. Mortier at the University of Maine (France), where she studied the formation of arylbenzylnitrenium ions in the thermal rearrangement of isoxazolidines. From September 2001 to August 2002 she worked on the total synthesis of natural products with Professor J. Ardisson and CNRS Research Director A. Pancrazi at the University of Cergy-Pontoise. Since February 2003 she has been a lecturer of organic chemistry at the University of Reims. She is currently working with Professor A. Haudrechy on the use of carbohydrates in the synthesis of biologically active compounds.

tant. The aim of this review is to focus on the diastereoselective synthesis of propargylic alcohols via alkynylmetallic addition to chiral 2- and 3-alkoxy-, amino- and thio-substituted aldehydes as well as the different combinations of their 2,3-disubstituted counterparts. In general, addition of organometallic alkynyl derivatives to heteroatom-substituted chiral aldehydes is no different than that of other commonly used organometallic reagents (i.e., alkyl, vinyl, or aryl). The reaction schemes discussed below are thus applicable in the same manner.

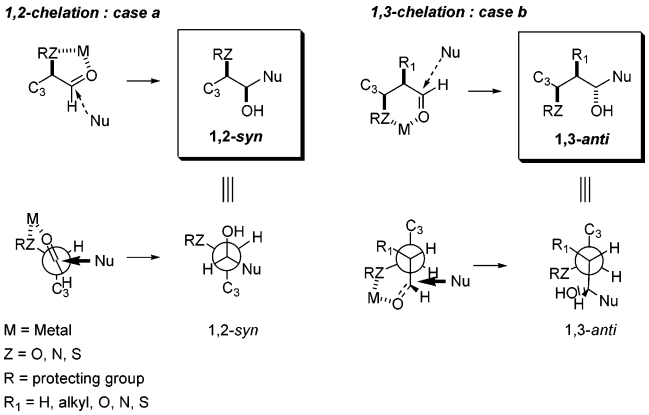
In simple cases where only one heteroatom (O, N, S) is in position 2 or 3 of the aldehyde, 1,2-chelation favors a 1,2-*syn* approach of the nucleophile (Scheme 1, case a) and 1,3-chelation preferentially directs toward a 1,3-*anti* selectivity (Scheme 1, case b). In the case of 2,3-heterosubstituted aldehydes, predicting diastereoselectivity is more complicated because of competition between the 1,2- and 1,3-bidentate metal chelation processes.

When no chelation (or a monodentate chelation) is possible, nucleophilic attack can occur from either side of the aldehyde following traditional Felkin−Anh rules and both 1,2-*syn* or 1,2-*anti* addition products are possible depending on the nature of the groups present at positions 2 and 3 (Scheme 2). If the aldehyde is chelated with a very bulky Lewis acid, steric interactions play a major role, and in this case, good 1,2-*anti* selectivity should be expected.

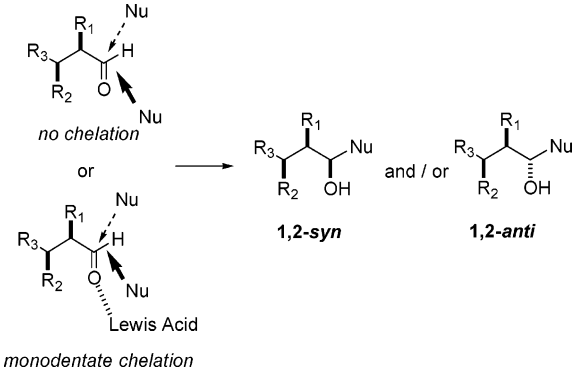
In the literature, however, stereoselectivities in these last inductions are rarely high and can only be partially explained

Arnaud Haudrechy was born in 1965 in Rouen, France. He obtained his Ph.D. degree in 1990 from the Université of Paris VI (with Professor P. Sinaÿ) in the field of carbohydrates and transition-metal chemistry (Tebbe's reagent). In 1990 he joined the group of Professor Y. Kishi (Harvard University) as a postdoctoral fellow working on preferred conformations of C-glycosides and synthesis and conformational analysis of carbon analogues of the blood group determinant H-Type II. In 1992 he joined the University Paris Sud as a lecturer in organic chemistry, working with Professor Y. Langlois on low-temperature asymmetric Diels–Alder reactions and synthesis of (+)-huperzin A, fumagillin, and spirotetronate subunit of the quartromicins (with a sequential Claisen–Ireland/metathesis concept). He is now Full Professor of Organic Chemistry at the Université de Reims Champagne-Ardenne, and his research program is focused on the use of carbohydrates for the synthesis of biologically active molecules.

Scheme 1. Cram Chelate Model for Bidentate 1,2- and 1,3-Chelation



Scheme 2. Felkin−Anh Approach with Monodentate or No Chelation



with Felkin−Anh rules. As the steric hindrance between the nucleophile and the group in position 2 (R_1) and/or the side chain (CHR_3R_2) is the deciding factor, it is sometimes difficult to find a preferred approach for the nucleophile.

The key reviews published by Reetz in 1984[2a] and Mengel and Reiser in 1999[2b] dealt with the problem of diastereofacial selectivity (chelation or nonchelation controlled) in addition reactions to chiral α- and/or β-substituted carbonyl compounds. In the second study several examples of organometallic alkynyl addition to chiral 2- and/or 3-heterosubstituted aldehydes were described, but to the best of our knowledge, no systematic study of this reaction has yet been published. In this review, we show what has been accomplished toward the stereoselective intermolecular addition of alkynyl derivatives to chiral 2- and/or 3-alkoxy-, amino-, and thio-substituted aldehydes, exploring variations of cation, solvent, temperature, and protecting-group effects. A deliberate choice was made not to treat intramolecular additions because reaction selectivity is often influenced by the inherent steric constraints of the substrate. The contribution of each metal is presented individually based on the aldehyde, but there are a large number of cases in which different metals were "tested" in order to achieve the desired selectivity. As a result, when judged necessary, a separate section at the end of each section has been dedicated to "multimetal" additions in order to clearly compare the use of different metals on a given addition reaction. Reagent control through the use of an external chiral inductor is also described in the last section. In the presentation of this review, a conscious decision was made to neglect possible aggregation states, and although this is a simplistic point of view, it is nevertheless a useful guide for the chemist in the choice of appropriate reaction conditions.

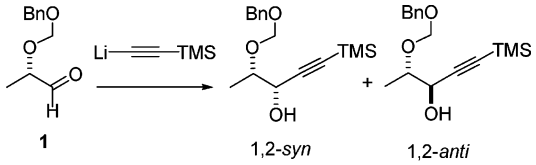
2. 2-Alkoxyaldehydes

2.1. Lithium Derivatives

The lithium cation is not a very efficient chelating agent,[3] which explains that, in general, stereoselective 1,2-*syn* inductions with this metal are poor. Normally, formation of the 1,2-*anti* product is only slightly favored, but selectivity can be substantially increased when stronger complexing solvents are used (Table 1).[4] The lithium cation is trapped by the solvent via an electron-donating effect, thus competing with chelation to the alkoxy part and favoring a 1,2-*anti* attack.

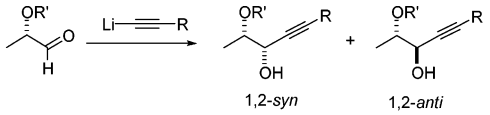
In this example the use of a benzyloxymethyl protecting group in the starting aldehyde (**1**) is probably not the best choice. Chelation with the second oxygen present on the side chain could also have an impact on reaction diastereoselectivity.

Table 1. Solvent Effects in the Lithium Alkynylation of Aldehyde 1



Solvent	Yield (%)	1,2-*syn* / 1,2-*anti*
Et_2O	75	44 / 56
THF	88	31 / 69
THF, DMEU	89	26 / 74
THF, HMPA	80	22 / 78

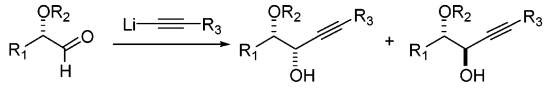
Table 2. Lithium Alkynylation in the Presence of Crown Ethers



1,2-*syn* 1,2-*anti*

Entry	R	R'	Reaction conditions	Yield (%)	1,2-*syn* / 1,2-*anti*	Ref
1	$CH_2OTBDPS$	TBS	12-C-4, THF, -78 °C	65	15 / 85	5,6
2	Ph	TBDPS	12-C-4, THF, -78 °C	74	13 / 87	6
3	Ph	TBDPS	15-C-5, THF	73	19 / 81	4

Table 3. Use of Silyl Protecting Groups to Favor 1,2-*Anti* Addition



1,2-*syn* 1,2-*anti*

Entry	R_1	R_2	R_3	Yield (%)	1,2-*syn* / 1,2-*anti*	Ref
1	CH_3	TBS	TMS	nd	17 / 83	4, 7,8
2	CH_3	TES	TMS	nd	20 / 80	9
3	CH_3	TES	CH_2OBn	80	22 / 78	10,11
4	CH_3	TES		59	28 / 72	12
5	CH_3	TBS	$COOCH_3$	60	17 / 83	13,14
6	CH_3	TBS	$COOCH_2CH_3$	55	17 / 83	15
7	CH_3	TBS	COO*t*Bu	65	17 / 83	15
8	CH_3	TES	$COOCH_3$	nd	22 / 78	13,14
9	CH_3	TBDPS	$COOCH_3$	nd	33 / 67	13,14
10	$TBSO(CH_2)_2$	TBS	TMS	81	8 / 92	16
11	$TBSO(CH_2)_2$	TBDPS	TMS	67	33 / 67	16

Addition of a complexing agent should have a similar effect on reaction selectivity as the use of a highly complexing solvent. Unfortunately, only a slight improvement was observed in the presence of the crown ether 12-C-4 or 15-C-5 (Table 2). These results seem to indicate that a non-1,2-chelating process has difficulty reaching more than a ~1:4 selectivity ratio in favor of the 1,2-*anti* product.

The steric hindrance of the alcohol protecting group in position 2 also has a notable influence on reaction selectivity. The change from a small group to a bulky one disfavors an eventual 1,2-chelation and largely displaces the induction to the 1,2-*anti* stereoisomer. Addition of various alkynyl derivatives to aldehydes having hindered silyl protecting groups in position 2 is compared in Table 3.

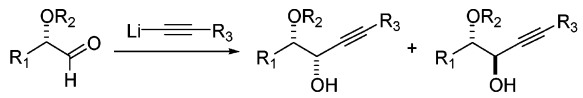
Variation of the silyl protecting group clearly showed that use of a TBS group, more sterically hindered than a TBDPS group, gave the best diastereoselectivity (Table 3; entries 5−9).

Table 4 gives various examples of alkynyl addition to chiral 2-alkoxyaldehydes with more elaborate side chains and where 1,2-*syn* to 1,2-*anti* product ratios were reported in the literature.

Overall, these examples show the same tendencies for reaction stereoselectivity: (1) a bulky protecting group in position 2 orients toward the 1,2-*anti* product (Table 4; entries 3, 4, and 8), (2) addition of a crown ether or HMPA to the reaction mixture further improves selectivity (Table 4; entries 3 and 4), and (3) in the case of a smaller benzoate protecting group in position 2, good 1,2-*anti* selectivity can be achieved in THF at low temperature (Table 4; entry 6).

The polyol segment of the antibiotic amphotericin B has been the target of several reported 1,2-*anti*-selective alkynyl addition reactions with lithium. Hanessian et al. published two cases which were surprisingly selective in favor of the 1,2-*anti* adduct (Table 5).[23] In the case of an isopropylidene

Table 4. Addition of Various Alkynes to 2-Alkoxyaldehydes



1,2-*syn* 1,2-*anti*

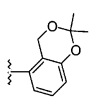
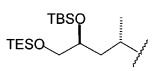
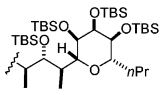
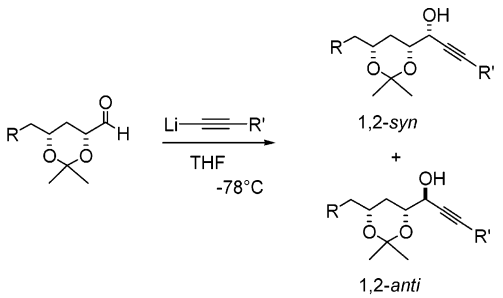
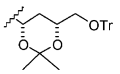
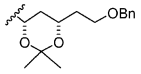
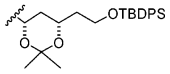
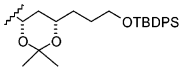
Entry	R_1	R_2	R_3	Reaction conditions	Yield (%)	1,2-*syn* / 1,2-*anti*	Ref
1	nC_5H_{11}	Bn	TMS	THF	nd	50 / 50	17
2	nC_5H_{11}	Bn		THF, -78 °C	91	50 / 50	18
3	nC_5H_{11}	TBDPS	TMS	THF	nd	27 / 73	17
4	nC_5H_{11}	TBDPS	TMS	THF/HMPA	80	16 / 84	17
				12-C-4	54	16 / 84	
5		Bz		Et_2O	67	60 / 40	19
6	$EtO_2C(CH_2)_3$	Bz	$nC_{12}H_{25}$	THF, -78 °C	nd	20 / 80	20
7	$PhSO_2(CH_2)_2$	MPM		THF, -78 °C	64	64 / 36	21
8		TBS		THF, -78 °C	97	40 / 60	22

Table 5. Selective 1,2-*Anti* Alkynyllithium Addition

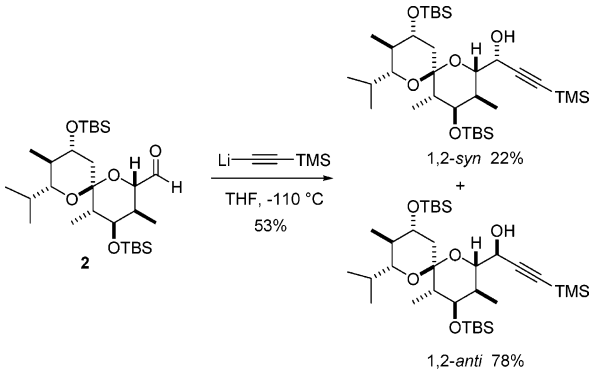


R	R'	Yield (%)	1,2-*syn* / 1,2-*anti*	Ref
OTBDPS		85	8 / 92	23
CH_2OTBS		57	24 / 76	24
CH_2OTBS		85	22 / 78	25
$(CH_2)_2OTr$		76	8 / 92	23

protecting group, the oxygen atoms do not readily participate in chelation because they are involved in a stereoelectronically favorable interaction, analogous to the anomeric effect. It is important to note that addition of lithium chloride or use of magnesium analogues did not improve the already excellent selectivity.

More recently, good 1,2-*anti* diastereoselectivity was reported in the synthesis of highly functionalized spiroketals in Bafilomycin A_1 (Scheme 3).[26]

Scheme 3

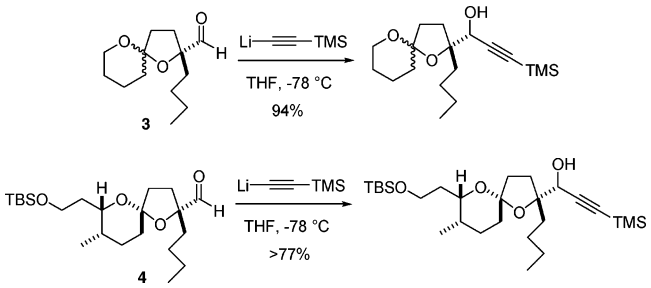


In their total synthesis of (−)-Reveromycin B, Cuzzupe et al. reported two examples of an interesting lithium acetylide addition to the spiroketal aldehydes **3** and **4**. Although no 1,2-*syn* or 1,2-*anti* diastereoselectivity can be assigned in this instance, the addition occurred in a stereoselective manner (Scheme 4).[27]

2.2. Boron Derivatives

Alkynylboron derivatives are under-evaluated and have shown promising results in addition reactions. Of the three examples reported in the literature, two were tried in an attempt to optimize reaction selectivity and were part of a

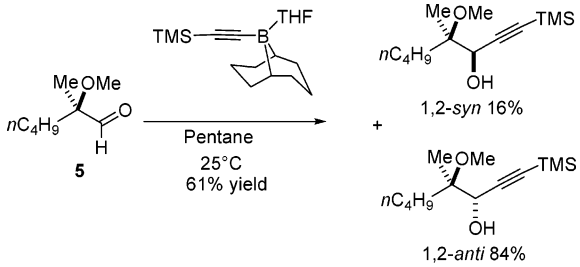
Scheme 4



study with several other metals. These examples can be found in the "multimetal" section at the end of this section.

In most cases, use of a boron derivative shows a high level of induction in favor of the 1,2-*anti* stereoisomer. This can be explained by the electrophilic activation of the aldehyde with the free Lewis acid site of the boron moiety. Evans et al. reported an elaborate example for the preparation of propargylic alcohols using *B*-(trimethylsilylethynyl)-9-borabicyclo[3.3.1]nonane and aldehyde **5** via a nonchelating species in which the 1,2-*anti* isomer was the major reaction product (Scheme 5).[28]

Scheme 5



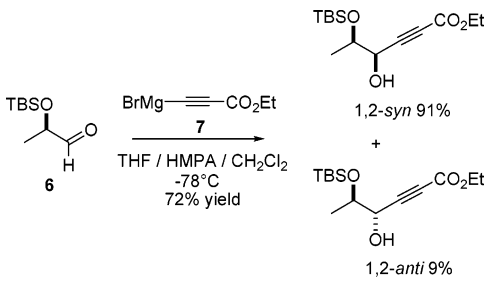
The mechanism probably starts with the exchange of one of the boron ligands by the aldehyde function followed by attack of a second alkynylboron derivative.

2.3. Magnesium Derivatives

In comparison to lithium derivatives, alkynylmagnesiums strongly favor 1,2-chelation. Consequently, there is a clear change in diastereoselectivities, with formation of a higher proportion of 1,2-*syn* diastereoisomers. Once again, many of the reported literature examples with magnesium are part of a larger study to optimize reaction stereoselectivity, and these examples can be found in the "multimetal" section at the end of this section.

In a first example, the simple aldehyde **6** gave clean 1,2-*syn* selectivity when reacted with the magnesium derivative **7** (Scheme 6).[29]

Scheme 6



The chelating ability of the magnesium metal was not affected in this instance by the use of complexing solvents (THF/HMPA).

Table 6. Magnesium Alkynylation with Complex Aldehydes

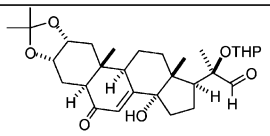
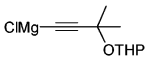
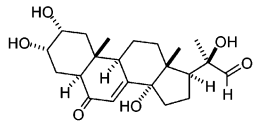
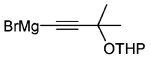
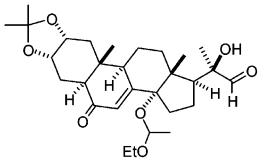
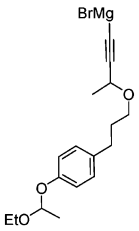
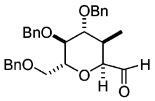
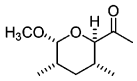
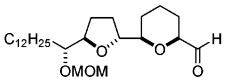
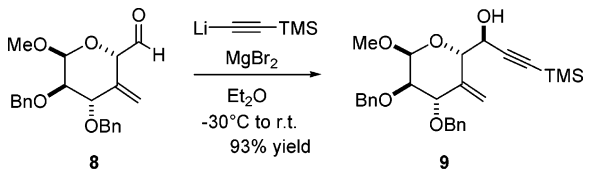
Entry	Aldehyde	Alkynyl derivative	Yield (%)	1,2-*syn*/1,2-*anti*	Ref
1			55	100 / 0	30
2			nd	100 / 0	31
3			nd	100 / 0	32
4			71	83 / 17	33
5			90	91 / 9	34
6			80 (THF) 43 (Et_2O)	42 / 58 58 / 42	35

Table 6 shows three addition reactions encountered in the synthesis of crustecdysone and ecdysteroid analogues (entries 1−3). In the first entry it was noted that the obtained compound was homogeneous by nuclear magnetic resonance (in 1967). On the basis of the chelating ability of the alkynylmagnesium derivative, it is highly probable that the major configuration was 1,2-*syn*. In entries 2 and 3 the exclusive 1,2-*syn* selectivities reported are most likely due to the presence of the unprotected hydroxyl group in position 2 of these aldehydes and their strong chelation with magnesium. Entries 4−6 are examples of more recent addition reactions where 1,2-*syn* diastereoselectivity predominates.

In their total synthesis of amphidinolide A, Pattenden et al. reported the exclusive formation of the 1,2-*syn* addition product **9** in 93% yield (Scheme 7).[36] It is important to note

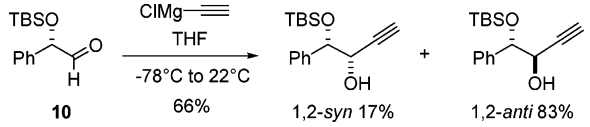
Scheme 7



that in this case the 2-alkoxyaldehyde **8** was "prechelated" with $MgBr_2$ before addition of the alkynyl derivative.

In spite of the apparent generality of magnesium-promoted 1,2-*syn* additions, Kotora and Negishi reported a curious 1,2-*anti* selectivity in their synthesis of (+)-goniobutenolide A, which they explained through steric, rather than the expected chelation, control (Scheme 8).[37]

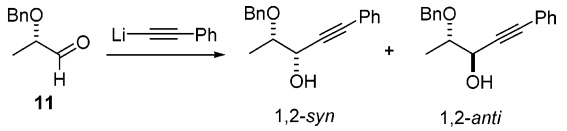
Scheme 8



2.4. Zinc Derivatives

In 1987 Mead published a detailed study of the addition of alkynylzinc derivatives to 2-alkoxyaldehydes. He showed that the use of Zn salts gave good to excellent 1,2-*syn* selectivity which was dependent on the zinc counterion as well as the reaction temperature and solvent (Table 7).[38] In several cases, reaction diastereoselectivity was confirmed after reduction of the alkyne and comparison to the known *syn* addition products of alkenylcopper reagents to 2-alkoxy-

Table 7. Zinc-Mediated Alkynyllithium Addition to Aldehyde 11



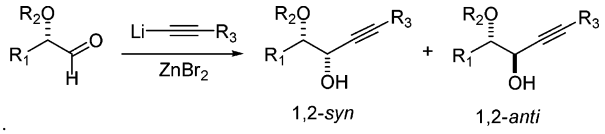
Reaction conditions	Yield (%)	1,2-*syn* / 1,2-*anti*
THF, -78 °C	/	45 / 55
$ZnCl_2$, THF, -78 °C	/	66 / 34
$ZnBr_2$, THF, -78 °C	75	81 / 19
$ZnBr_2$, THF, 0°C	70	76 / 24
$ZnCl_2$, Et_2O, -78 °C	65	88 / 12
$ZnBr_2$, Et_2O, -78 °C	95	95 / 5

aldehydes in the presence of Mg(II). The model which the author proposed to explain the observed selectivity is identical to the one presented in Scheme 1.

In THF the simple addition of $ZnCl_2$ to the preformed lithium acetylide followed by aldehyde addition increased the amount of 1,2-*syn* product formed. A change in the counterion ($ZnBr_2$) further improved this selectivity, the best result being obtained when the reaction was performed at −78 °C. Changing to a weaker chelating solvent (diethyl ether) gave 95% of the 1,2-*syn* addition product in excellent yield.

In the same paper it was then demonstrated that this addition was efficient with different aldehydes and alkynyl derivatives, greater selectivity being achieved with a more sterically hindered aldehyde (Table 8, entries 1−3). Entries

Table 8. Alkynylzinc Addition to Various Aldehydes

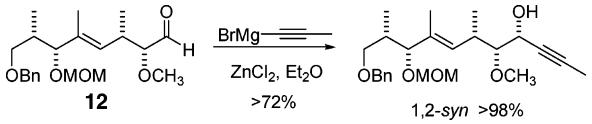


Entry	R_1	R_2	R_3	Yield (%)	1,2-*syn* / 1,2-*anti*	Ref.
1	$(CH_3)_2CH$	Bn	Ph	92	99 / 1	38
2	CH_3	Bn	nC_6H_{13}	79	84 / 16	38
3	$(CH_3)_2CH$	Bn	nC_6H_{13}	78	98 / 2	38
4	CH_3	MPM	nC_4H_9	85	87 / 13	39
5	Ph	CH_3	$(CH_2)_3Ph$	75	91 / 9	40

4 and 5 show two more recent examples in which good to excellent selectivities were obtained.

Alkynylzinc derivatives can also be generated from the corresponding magnesium ones as illustrated by Coutts et al. in their synthesis of antitumor ansamycins (Scheme 9).[41] In this case, excellent 1,2-*syn* selectivity was observed.

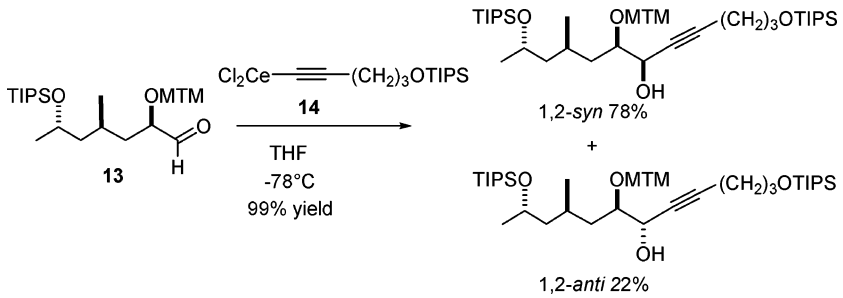
Scheme 9



2.5. Cerium Derivatives

Only a few examples have been reported in the literature concerning addition of alkynylcerium reagents to 2-alkoxyaldehydes, and the resulting inductions are variable. Ishiyama et al. observed a moderate diastereoselectivity in favor of the 1,2-*syn* product in the addition of the alkynylcerium derivative **14** (generated from the corresponding organolithium) to the linear aldehyde **13** in their synthesis of amphidinolide B (Scheme 10).[42]

Scheme 10



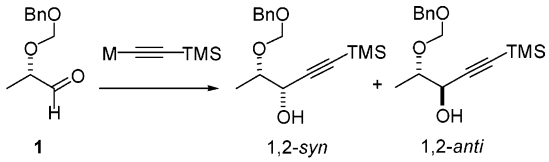
2.6. Multimetal Inductions

This section deals with the examples in which several organometallic alkynyl derivatives were individually added to chiral 2-alkoxyaldehydes in order to optimize addition selectivity. These reactions are presented from the simplest ones, with only two metals, to the more complex ones, where up to five metals were used. In most cases the lithium derivative is systematically tried first, and based on the obtained results, other metals are then tested to achieve the required addition product with good selectivity. The lithium acetylide frequently undergoes a lithium/metal exchange reaction in order to generate the desired organometallic species. The metal additive is most often used in stoichiometric amounts in the reaction mixture before addition of the aldehyde. In certain cases the exact nature of the reacting species is difficult to explain, and the metal additive may also act as a Lewis acid.

2.6.1. Case 1: Li/Mg

In the case of the simple aldehyde **1**, use of an alkynylmagnesium derivative instead of the corresponding organolithium nearly doubled 1,2-*syn* selectivity[4] (Table 9).

Table 9. Alkynylation of Aldehyde 1 with Lithium and Magnesium Reagents



Reaction conditions	Yield (%)	1,2-*syn* / 1,2-*anti*
M = Li, THF	88	31 / 69
M = BrMg, THF	80	58 / 42

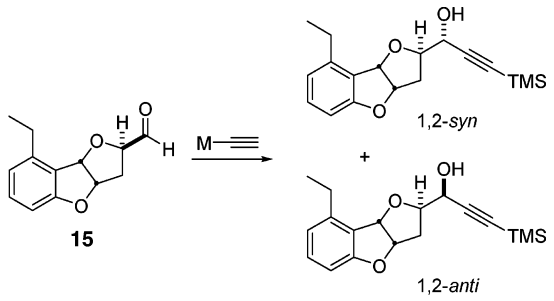
As part of the total synthesis of (±)-panacene, Feldman et al. reported addition of both alkynyllithium and magnesium derivatives to aldehyde **15** (Table 10).[43] Unfortunately, only poor yields and moderate selectivities were observed.

In a last example, in the synthesis of ecdysone inhibitors, the diastereoselectivity of the reaction products was inversed when either an alkynyllithium or a magnesium derivative was added to aldehyde **16** or its epimer **17**, the lithium reaction being more selective (Table 11).[44]

2.6.2. Case 2: Li/Mg/Ce

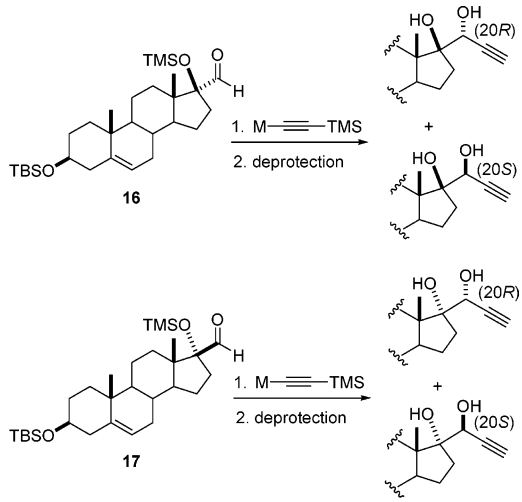
In their total synthesis of mucocin, Takahashi and Nakata studied the alkynylation of pyran-2-carboxaldehyde **18** under various reaction conditions (Table 12).[45] In this example the substrate complexity and steric hindrance of the alkynyl

Table 10. Alkynyllithium and Magnesium Addition to Aldehyde 15



Reaction conditions	Yield (%)	1,2-*syn* / 1,2-*anti*
M = Li, THF	38	40 / 60
M = Li, Et_2O	24	14 / 86
M = BrMg, THF	10	40 / 60

Table 11. Alkynyllithium and Magnesium Addition to Aldehydes 16 and 17



Aldehyde	Reaction conditions	Yield (%)	20(*R*) / 20 (*S*)
16	M = Li, THF	86	97 / 3
16	M = BrMg, THF	89	13 / 87
17	M = Li, THF	84	96 / 4
17	M = BrMg, THF	90	28 / 72

derivative had a notable influence in orienting the reaction toward the 1,2-*anti* product.

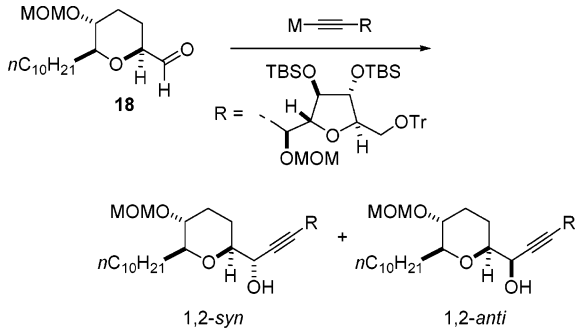
In the case of the lithium alkynyl derivative, the good stereoselectivity observed was most likely due to the bulky TBS protecting groups present on the five-membered ring and the cyclic nature of the aldehyde. In the presence of LiI, the 1,2-*anti* selectivity decreased. The use of a magnesium derivative had no effect on the product ratio because of steric factors rather than chelation control. Finally, excellent induction in favor of the 1,2-*anti* isomer was obtained when cerium chloride was added to the reaction mixture.

2.6.3. Case 3: Li/Mg/Ti

In their total synthesis of soraphen $A_{1\alpha}$, Giese et al. reported an excellent example of the influence of 1,2-chelation in the reaction of aldehyde **19** with various silyl alkynyl derivatives (Table 13).[46]

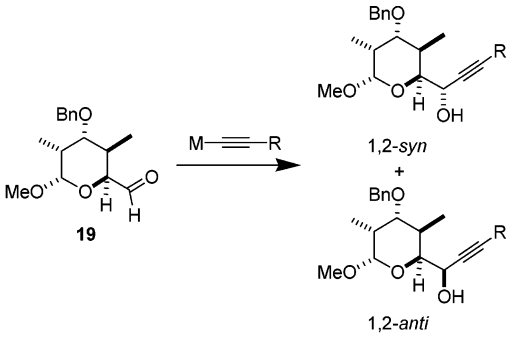
Use of the magnesium derivative gave the 1,2-*syn* isomer almost exclusively. A TBS protecting group on the alkynyl

Table 12. Alkynylation of Pyran-2-carboxaldehyde 18



Reaction conditions	Yield (%)	1,2-*syn* / 1,2-*anti*
M = Li, Et_2O, -12 → 0 °C	59	20 / 80
M = Li, LiI, Et_2O, -78 °C	23	40 / 60
M = BrMg, Et_2O, -78 °C	66	25 / 75
M = Li, $CeCl_3$, THF, -78 °C	78	7 / 93

Table 13. Addition of Various Alkynyl Derivatives to Aldehyde 19



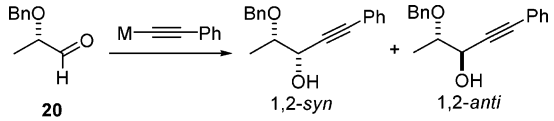
Reaction conditions	R	Yield (%)	1,2-*syn* / 1,2-*anti*
M = Li	TMS	89	67 / 33
M = Li	TBS	93	71 / 29
M = BrMg	TMS	85	95 / 5
M = BrMg	TBS	87	>96 / <4
M = Li, $TiCl_4$/Ti(O*i*Pr)$_4$	TMS	nd	11 / 89

moiety slightly increased the reaction selectivity. In contrast, when an alkynyltitanium derivative was used, a net reversal of diastereoselectivity was observed in spite of the tendency of Ti(IV) to chelate to oxygen electron pairs. In the addition of titanium enolates to α-alkoxyaldehydes Reetz et al. observed that the diastereoselectivity of the reaction depends on the titanium ligands.[47] These authors found that titanium reagents which contain alkoxy instead of chloro ligands are weakly Lewis acidic and give nonchelation control in addition reactions.

2.6.4. Case 4: Li/Mg/Ti/Zn

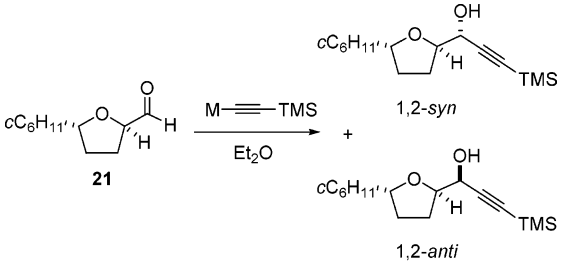
In the case of aldehyde **20**, protected with a simple benzyl group, use of an alkynylmagnesium derivative increased the amount of 1,2-*syn* adduct, and the selectivity was further enhanced when the reaction was performed in a less chelating solvent (Et_2O) (Table 14).[38,48] Use of an alkynyltitanium reagent had little effect on selectivity when compared to the corresponding organolithium. Finally, both an excellent yield and 1,2-*syn* selectivity were obtained with the alkynylzinc derivative.

Table 14. Alkynylation of Aldehyde 20



Reaction conditions	Yield (%)	1,2-*syn* / 1,2-*anti*	Ref.
M = Li, THF, -78 °C	68	41 / 59	48
M = BrMg, THF	nd	62 / 38	38
M = BrMg, Et_2O	82	74 / 26	38
M = $(OiPr)_3Ti$	53	36 / 64	48
M = BrZn, Et_2O	95	95 / 5	38

Table 15. Alkynylation of Furan-2-carboxaldehyde 21



Reaction conditions	Yield (%)	1,2-*syn* / 1,2-*anti*
M = Li, Et_2O	nd	50 / 50
M = BrMg, Et_2O, -40 °C	nd	71 / 29
M = $(OiPr)_3Ti$, Et_2O	nd	33 / 67
"zinc additive"	nd	50 / 50

In a second example, Ajamian and Gleason reported the alkynylation of the furan-2-carboxaldehyde derivative **21** (Table 15).[49] Unfortunately, high selectivities were not obtained in spite of reaction optimization with several metals. The best induction, with magnesium, resulted from a Cram chelation-controlled attack on the aldehyde. Use of the corresponding titanium reagent gave a modest reversal of selectivity, while lithium and zinc gave no selectivity whatsoever.

2.6.5. Case 5: Li/B/Ti/Sn

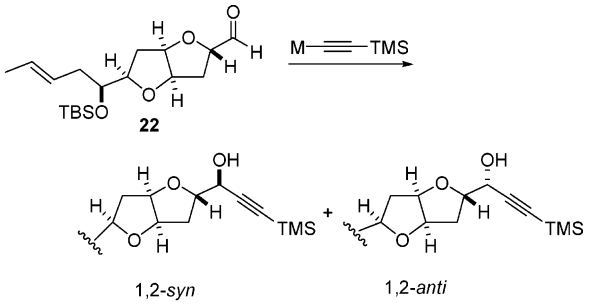
Overman et al. reported an alkynyl addition in their total synthesis of (±)-kumausallene and (±)-1-*epi*-kumausallene which showed only a very small selectivity in favor of the 1,2-*anti* diastereoisomer for alkynyllithium, -boron, and -tin derivatives (Table 16).[50] The best results were obtained with the corresponding titanium derivative.

2.6.6. Case 6: Li/B/Mg/Ti/Zn

In their study of the addition of lithium acetylides to (20*R*)-20-hydroxypregnane-22-carboxaldehydes, Dolence et al. observed that certain Lewis acids dramatically altered reaction stereoselectivity (Table 17).[51] In the case of the alkynyllithium addition, the first reaction to occur was deprotonation of the free tertiary alcohol, and as 1,2-chelation was clearly favored with this "preformed" lithium alkoxide, good 1,2-*syn* induction was observed.

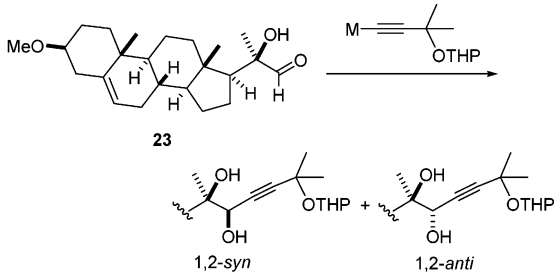
With the corresponding magnesium derivative an increase in 1,2-*syn* selectivity was observed according to normal chelation control. This was the case when the magnesium derivative was prepared separately before use (Grignard reagent) or generated from the corresponding lithium species by addition of magnesium bromide.

Table 16. Alkynylation of Aldehyde 22



Reaction conditions	Yield (%)	1,2-*syn* / 1,2-*anti*
M = Li	< 45	40 / 60
boron derivative = *n*BuLi, $BF_3{\cdot}Et_2O$	< 45	≈ 40 / 60
M = $(OiPr)_3Ti$, $TiCl_4$	77	16 / 84
M = $SnBu_3$	< 45	≈ 40 / 60

Table 17. Alkynylation of Aldehyde 23



Reaction conditions	Yield (%)	1,2-*syn* / 1,2-*anti*
M = Li, THF, -26 °C	91	70 / 30
M = BrMg, THF, -26 °C	80	87 / 13
M = $(OiPr)_3Ti$, THF, -26 °C	78	60 / 40
M = ClZn, THF, -26 °C	76	68 / 32
M = Li, BF_3, THF, -78 °C	40	0 / 100
M = Li, BF_3, THF, -26 °C	37	7 / 93

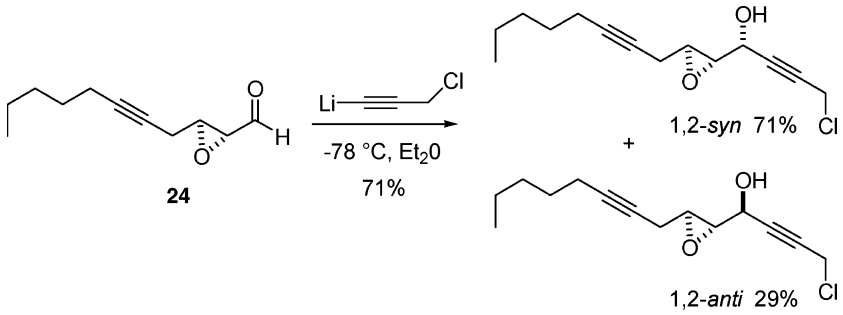
Addition of boron trifluoride to the reaction mixture resulted in a total reversal of diastereoselectivity when compared to the lithium derivative with a high level of induction in favor of the 1,2-*anti* stereoisomer. This could be explained by the electrophilic activation of the aldehyde with the free Lewis acid site of the boron moiety. When the alkynylation was performed at low temperature (−78 °C), only one stereoisomer was detected. Temperature control was crucial as demonstrated by the experiment at higher temperature (−26 °C) in which small amounts of the 1,2-*syn* isomer began to appear in the reaction.

2.7. 2,3-Epoxyaldehydes

Technically speaking, the following examples deal with organometallic alkynyl addition to chiral 2-alkoxyaldehydes but are difficult to classify as such. The presence of an epoxide function α to the aldehyde makes it difficult to say if the resulting behavior is of the "2-alkoxy" or "3-alkoxy" type.

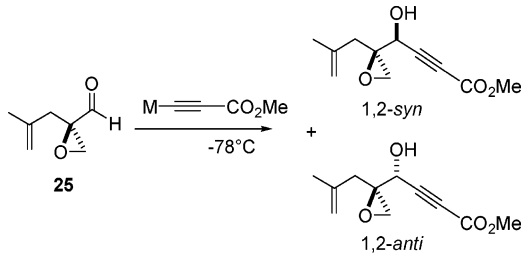
In a first example, Vasiljeva et al. reported addition of an alkynyllithium derivative to the epoxyaldehyde **24** (Scheme 11).[52] The configuration of the major product was determined to be 1,2-*syn*, even though the rest of the synthesis was carried out with a mixture of epimeric alcohols.

Scheme 11



Shahi and Koide recently reported an interesting alkynylation reaction with epoxyaldehyde **25** and silver methyl propiolate in the presence of stoichiometric amounts of the zirconium derivative Cp_2ZrCl_2 and a catalytic amount of AgOTf (Table 18).[53] The silver acetylide can be prepared in large quantities and stored before use.

Table 18. Alkynyl Addition to Epoxyaldehyde 25



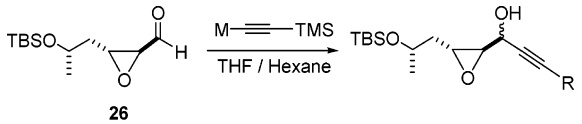
Metal	Yield (%)	1,2-*syn* / 1,2-*anti*
M = Ag, Cp_2ZrCl_2	76	nd
M = Li	50	1 / 1

The authors hypothesized that the active species was an alkynylzirconium derivative. A 6:1 ratio of diastereoisomers was obtained with no further information about the configuration of the newly created asymmetric center. When the same reaction was performed with a lithium derivative, no selectivity was observed.

In their synthesis of monocillin I, Tichkowsky and Lett reported condensation of the epoxyaldehyde **26** and lithium trimethylsilylacetylide, which gave an undetermined mixture of two diastereoisomers in a 2:1 ratio (Table 19).[54] In the presence of a stoichiometric quantity of $CeCl_3$, no selectivity was observed.

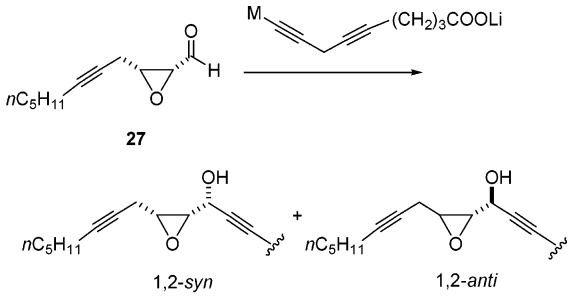
In the course of their synthesis of hepoxilins, Demin and co-workers studied the addition of various organometallic alkynyl derivatives to the epoxyaldehyde **27** (Table 20).[55] Lithium and magnesium derivatives offered only poor 1,2-*syn* selectivity, and the corresponding titanium species gave the 1,2-*anti* adduct as the major reaction product. Use of the cesium derivative gave the best 1,2-*syn* selectivity.

Table 19. Alkynyl Addition to Epoxyaldehyde 26



Metal	Yield (%)	1,2-*syn* / 1,2-*anti*
Li	93	nd
$CeCl_2$	89	1 / 1

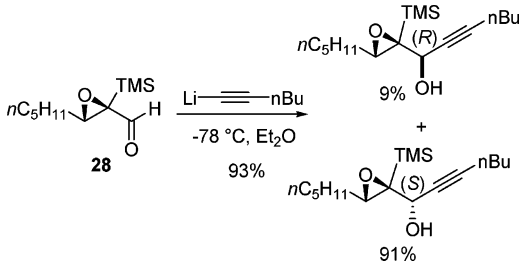
Table 20. Organometallic Alkynyl Addition to Epoxyaldehyde 27



Reaction conditions	Yield (%)	1,2-*syn* / 1,2-*anti*
M = Li, THF, -78 °C	36	64 / 36
M = ClMg, THF, -20 °C	24	54 / 46
M = (O*i*Pr)$_3$Ti, THF/hexane, 23 °C	27	12 / 88
M = Cs, THF, 23 °C	14	78 / 22

Takeda et al. reported addition of a lithium alkynyl derivative as part of a study of the diastereoselective addition of organometallic compounds to the silylated epoxyaldehyde **28** (Scheme 12).[56] The (*S*)-propargylic alcohol was formed

Scheme 12



preferentially, and the authors noted that the presence of the trimethylsilyl group was indispensable for achieving high diastereoselectivity. Use of the desilylated aldehyde gave equal amounts of the (*R*) and (*S*) alcohols using the same reaction conditions.

In all of the above "epoxyaldehyde" examples it is interesting to note that the aldehyde function reacts preferentially with the alkynylmetal derivative and complete chemoselectivity is observed.

2.8. Miscellaneous Alkynylations of 2-Alkoxyaldehydes

In many cases organometallic alkynyl addition was performed as part of an overall series of steps followed by oxidation, and no ratio of the obtained product was reported in the literature. This section regroups all of these reactions with 2-alkoxyaldehydes (Table 21).

Table 21. Compilation of Alkynylations with No Given Stereoselectivity

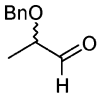
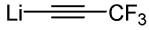
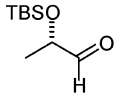
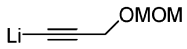
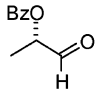
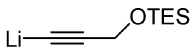
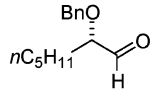
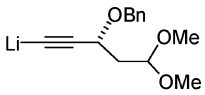
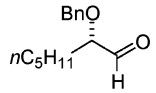
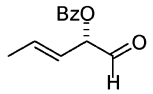
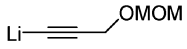
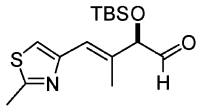
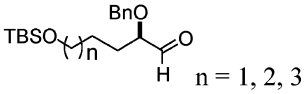
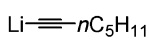
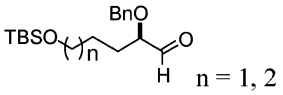
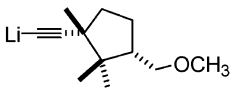
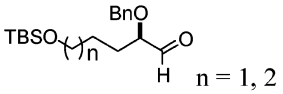
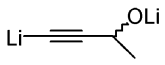
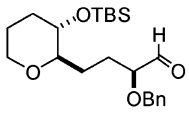
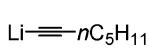
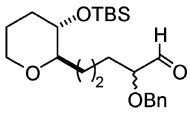
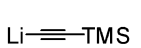
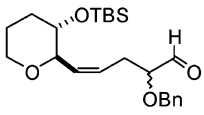
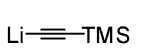
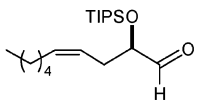
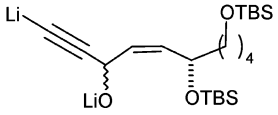
Metal	Aldehyde	Alkynyl derivative	Yield (%)	Ref
Li			94	57
Li			> 51	58
Li			82	59
Li			62	60
Li			83	61
Li			nd	62
Li			79	63,64
Li	 n = 1, 2, 3		74 (n = 1) 65 (n = 2) 66 (n = 3)	65
Li	 n = 1, 2		71 (n = 1) 65 (n = 2)	65
Li	 n = 1, 2		69 (n = 1) 68 (n = 2)	65
Li			nd	65
Li			nd	65
Li			nd	65
Li			71	66

Table 21. (Continued)

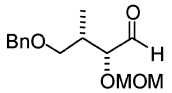
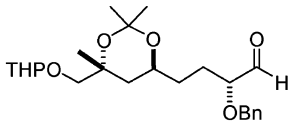
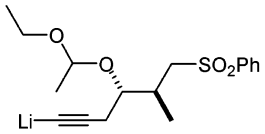
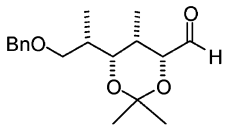
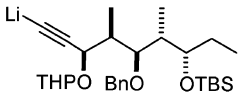
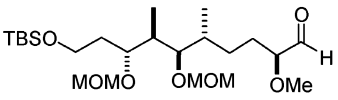
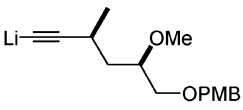
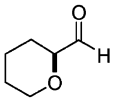
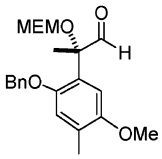
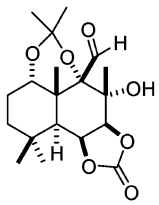
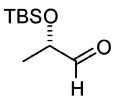
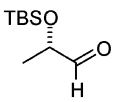
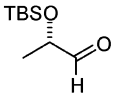
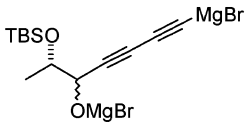
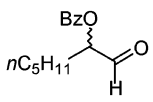
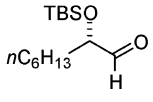
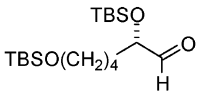
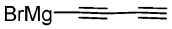
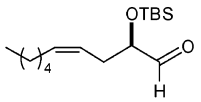
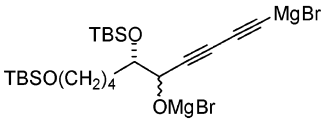
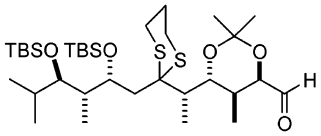
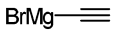
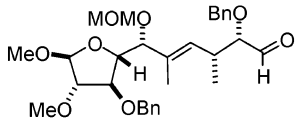
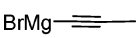
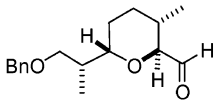
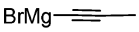
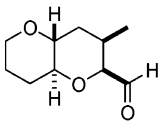
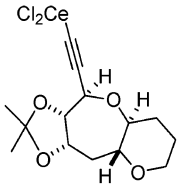
Metal	Aldehyde	Alkynyl derivative	Yield (%)	Ref
Li			> 80	41
Li			48	67
Li			94	68
Li			70	69
Li			> 70	70
Li			96	71
Li			48	72
Mg			79	73,74
Mg			76	75
Mg			78	76
		1,2-*syn* and 1,2-*anti*		
Mg			62	77
Mg			> 70	78

Table 21. (Continued)

Metal	Aldehyde	Alkynyl derivative	Yield (%)	Ref
Mg			82	79
Mg			91	79
		1,2-*syn* and 1,2-*anti*		
Mg			89	80
Mg			> 64	81
Mg			> 89	82
Ce			93	83

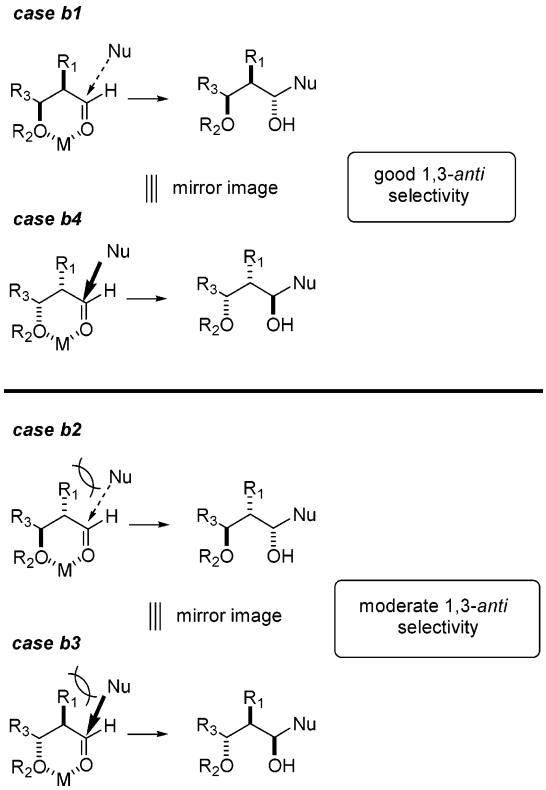
3. 3-Alkoxyaldehydes

The presence or absence of chelation also plays an important role in reaction diastereoselectivity when organometallic alkynyl derivatives are added to chiral 3-alkoxy aldehydes. When chelation is possible, four transition-state models can be envisaged, all favoring 1,3-*anti* stereoselectivity (cases b1−4, Scheme 13). Reaction stereoselectivity also depends on the relative stereochemistry of the group R_1 in position 2. Various degrees of selectivity can thus be expected because of conformational effects. It should be noted that cases b1/b4 and b2/b3 are mirror images and can subsequently be considered analogously.

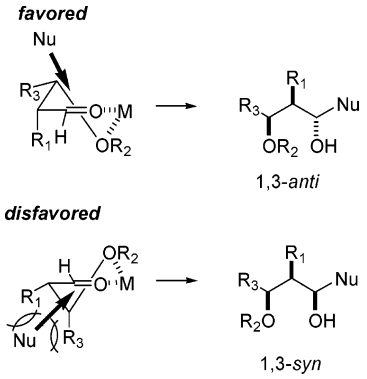
The reaction models can be better understood through the use of prechair transition states (Scheme 14). In case b1 and its mirror image b4, the incoming nucleophile attacks from the less hindered side of the aldehyde to give the 1,3-*anti* isomer as the major reaction product with good to excellent stereoselectivity. The 1,3-*syn* reaction product is disfavored because of steric interaction between the nucleophile and both R_3 and R_1.

In case b2 and its mirror image b3, none of the transition states are clearly favored (Scheme 15). The diastereoselectivity of the reaction is directly related to the size of the groups R_1 and R_3 on the starting aldehyde. If $R_1 < R_3$, the 1,3-*anti* product is favored because of the moderate steric interaction between the attacking nucleophile and R_1. Inversely, if $R_1 > R_3$, the 1,3-*syn* isomer may become the

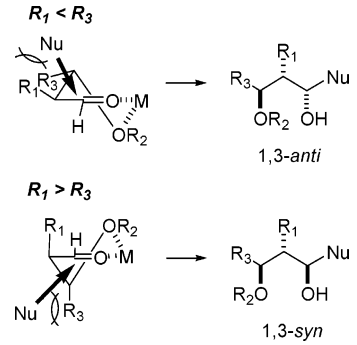
Scheme 13. Reaction Models for Bidentate 1,3-Chelation



Scheme 14. Prechair Transition-State Models: Cases b1 and b4

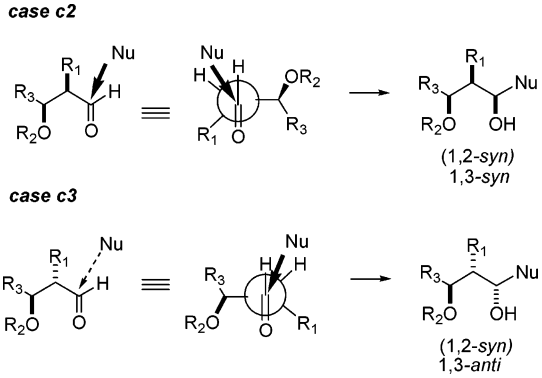


Scheme 15. Prechair Transition-State Models: Cases b2 and b3



major reaction product in spite of the increased steric hindrance between the attacking nucleophile and R_3. In both cases, a mixture of 1,3-*syn* and 1,3-*anti* products can be expected, and predicting the stereochemical outcome of the reaction is more problematic.

Scheme 16. Felkin−Anh Orientation: Cases c2 and c3



When no chelation occurs, diastereoselectivity can be predicted using the well-known Felkin−Anh orientation rule (cases c2/c3, Scheme 16). Once again, the relative configuration of the group R_1 in position 2 plays a major role and either the 1,3-*syn* or the 1,3-*anti* adducts can be formed, giving in each case a predominant 1,2-*syn* diastereoselectivity. Unfortunately, these inductions are rarely high.

3.1. Lithium Derivatives

The ambiguous chelating nature of lithium is once again highlighted in many of the reported examples of alkynyllithium addition to 3-alkoxyaldehydes. In simple cases, with only hydrogen atoms in position 2, mixtures of 1,3-*syn* and 1,3-*anti* diastereoisomers are generally formed (Table 22).

In the presence of HMPA (Table 22; entries 1 and 2), no selectivity was observed. In entry 4, remarkably good 1,3-*anti* induction was reported which was explained by the presence of LiBr involved in prechelating the 3-alkoxyaldehyde, thus favoring the 1,3-*anti* diastereoisomer. In entry 5, good induction was also reported, this being due, perhaps, to the sterically restricted starting aldehyde.

Table 22. Alkynyllithium Addition to Simple 3-Alkoxyaldehydes

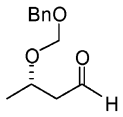
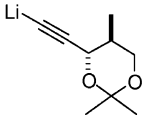
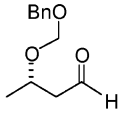
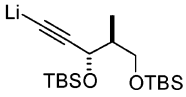
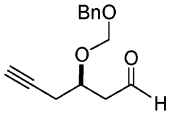
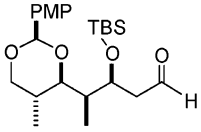
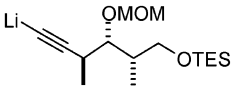
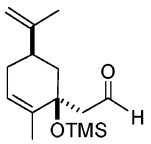
Entry	Aldehyde	Alkynyl derivative	Reaction conditions	Yield (%)	1,3-*syn* / 1,3-*anti*	Ref
1			THF, HMPA, -78 °C	nd	50 / 50	84
2			THF, HMPA, -78 °C	nd	50 / 50	84
3			THF, -40 °C	92	67 / 33	85
4			THF, LiBr, -40 °C	nd	15 / 85	86
5			THF, -78 °C	98	13 (*S*) / 87 (*R*)	87

Table 23. Alkynyllithium Addition to 2-Alkyl-3-alkoxy Aldehydes

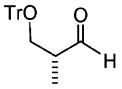
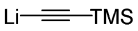
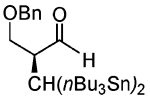
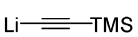
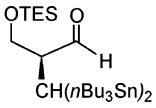
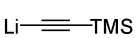
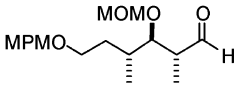
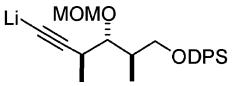
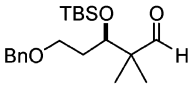
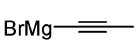
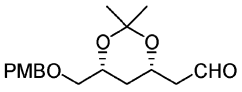
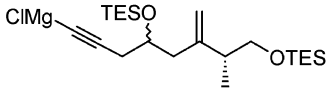
Entry	Aldehyde	Alkynyl derivative	Yield (%)	1,2-*syn* / 1,2-*anti*	Ref
1			60	67 / 33	88
2			91	85 / 15	89
3			80	71 / 29	89
4			74	(1,3-*syn* / 1,3-*anti*) 60 / 40	69

Table 24. Magnesium Alkynylation of 3-Alkoxyaldehydes

Aldehyde	Alkynyl derivative	Yield (%)	1,3-*syn* / 1,3-*anti*	Ref
		99	50 / 50	90
		85	50 / 50	91

When an alkyl group is present in position 2, the 3-alkoxyaldehydes are more prone to follow the nonchelation model where Felkin−Anh rules predominate (Table 23). For terminal 3-alkoxy aldehydes (Table 23; entries 1−3), the relative stereochemistry is given with respect to the substituent in position 2.

Toshima et al. reported a majority of 1,2-*syn* addition with a simple 2-methyl-3-alkoxy aldehyde (Table 23; entry 1). Use of a stannylated 3-alkoxyaldehyde in entries 2 and 3 by Wakamatsu et al. showed that moderate to good selectivities could be achieved, probably due to the steric hindrance of the tin group. In entry 4, Marshall and Johns reported an example of 1,3-*syn* selectivity with a more complicated substrate. The authors hoped to achieve chelation-controlled selectivity, but unfortunately, the 1,3-*syn* isomer was the major reaction product.

3.2. Magnesium Derivatives

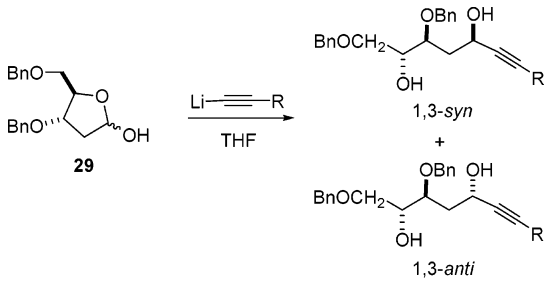
As previously discussed in section 2.3, the magnesium cation is more prone to bidentate chelation and could thus be expected to give better 1,3-*anti* selectivity with 3-alkoxy aldehydes. Surprisingly, only a few such examples exist in the literature, and the selectivities observed are small to none. In two recently reported cases a 1/1 mixture of 1,3-*syn* to 1,3-*anti* products was obtained (Table 24).

3.3. Multimetal Inductions

3.3.1. Case 1: Li/Mg

In their stereoselective synthesis of alkynyl *C*-2-deoxy-β-D-ribofuranosides, Takase et al. reported 1,3-*anti* selectivity in the addition of various lithium alkynyl derivatives to the carbohydrate aldehyde **29** (Table 25).[92] Only moderate inductions were observed with both alkynyllithium and magnesium derivatives.

Table 25. Alkynylation of Hemiacetal 29

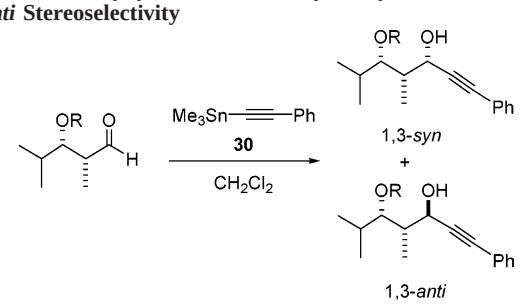


Metal	R	Yield (%)	1,3-*syn* / 1,3-*anti*
Li	TMS	90	36 / 64
Li	nC_4H_9	84	46 / 54
Li	Ph	90	34 / 66
Li	2-pyrenyl	90	34 / 66
Li	2-thienyl	97	37 / 63
Li	$CH_2OCH_2CH{=}CH_2$	89	39 / 61
BrMg	H	83	34 / 66

3.3.2. Case 2: B/Ti/Al/Sn

Among the metals presented in this section, use of stannyl alkynyl derivatives is by far the most effective way of inducing high 1,3-*anti* selectivity. Evans et al. reported addition of the alkynyl tin reagent **30** to various 3-alkoxy-aldehydes in the presence of different Lewis acids (Table 26).[93] The authors explained that the surprisingly high 1,3-*anti* stereoselectivity observed with $BF_3{\cdot}Et_2O$ was the result of the sterically undemanding nucleophile used. In this case, dominant β-heteroatom control (and not chelation control) was thought to give the 1,3-*anti* product.[94] When activation

Table 26. Tin Alkynylation of 3-Alkoxyaldehydes: Excellent 1,3-*Anti* Stereoselectivity



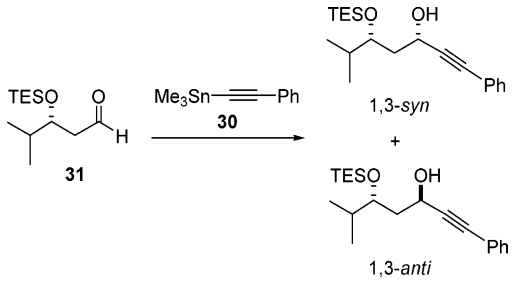
Reaction conditions	R	Yield (%)	1,3-*syn* / 1,3-*anti*
$BF_3.Oet_2$, - 40°C	Bn	48	9 / 91
Me_2AlCl, -78°C	Bn	34	3 / 97
$MeAlCl_2$, -78°C	Bn	68	4 / 96
$BF_3.Oet_2$, - 40°C	TBS	26	28 / 72
Me_2AlCl, - 40°C	TBS	50	19 / 81
$MeAlCl_2$, -78°C	TBS	81	6 / 94

was carried out in the presence of Me_2AlCl, clear 1,3-chelation occurred, giving the 1,3-*anti* product.[95] Better yields and excellent selectivities were obtained with the highly chelating $MeAlCl_2$.

When the benzyl protecting group was replaced with a TBS, the observed stereoselectivity was lower. This was probably due to the increased steric hindrance of the TBS ether in the case of $BF_3{\cdot}Et_2O$ activation, whereas a higher reaction temperature affected reaction diastereoselectivity with Me_2AlCl. Use of $MeAlCl_2$ at −78 °C gave excellent 1,3-*anti* selectivity.

Stereoselectivity was slightly increased when a TES protecting group was used and the addition reaction carried out in the presence of $BF_3{\cdot}Et_2O$ (Table 27). Activation with

Table 27. Tin Alkynylation: Lewis Acid Optimization

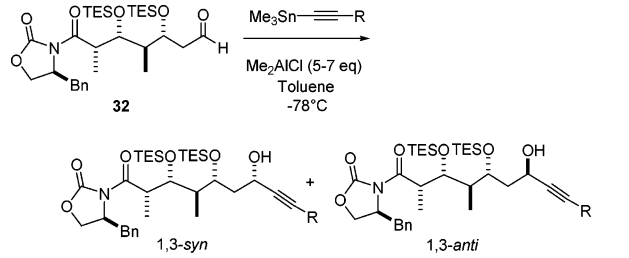


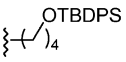
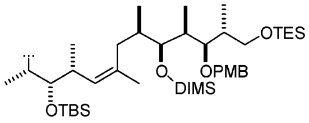
Reaction conditions	Yield (%)	1,3-*syn* / 1,3-*anti*
$BF_3.Oet_2$, -78°C, CH_2Cl_2	32	17 / 83
$TiCl_3OiPr$, -78°C, CH_2Cl_2	33	71 / 29
Me_2AlCl, -78°C, CH_2Cl_2	68	9 / 91
Me_2AlCl, -78°C, toluene	74	6 / 94

a bulkier monochelating Lewis acid ($TiCl_3OiPr$) totally reversed reaction selectivity, giving a higher ratio of the Felkin−Anh adduct. Use of Me_2AlCl gave excellent selectivity, which was moderately improved with the use of a nondonating solvent (toluene).

These optimized reaction conditions were then applied to more complex substrates as part of the synthesis of discodermolide and gave slightly lower selectivities (Table 28).

Table 28. Tin Alkynylation with Complex Substrates



R	Yield (%)	1,3-*syn* / 1,3-*anti*
	80	11 / 89
	63	18 / 82

3.4. Miscellaneous Alkynylations of 3-Alkoxyaldehydes

A compilation of alkynylations of 3-alkoxyaldehydes is given in Table 29.

4. 2,3-Dialkoxyaldehydes

Predicting reaction stereoselectivity for the addition of organometallic alkynyl derivatives to chiral 2,3-dialkoxyaldehydes is clearly more challenging. Competition between 1,2- and 1,3-chelation makes the choice of reaction conditions, notably that of the metal used, extremely important. In light of the two preceding sections, excellent inductions can be expected in the "matched" cases where 1,2- and 1,3-chelation direct toward the same major diastereoisomer.

If 1,2-chelation is favored, 2,3-dialkoxyaldehydes simply behave as 2-alkoxyaldehydes. The results should follow the same rules described in the Introduction (Scheme 1), usually giving a dominant 1,2-*syn* selectivity.

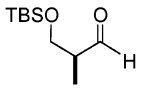
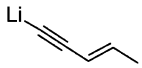
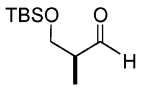
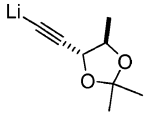
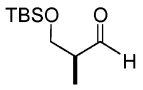
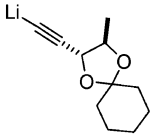
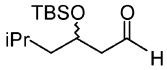
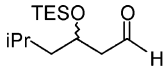
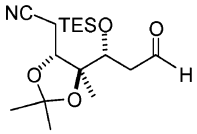
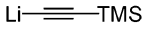
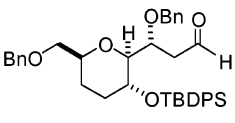
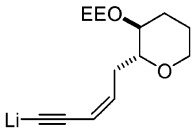
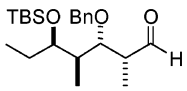
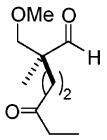
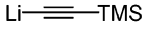
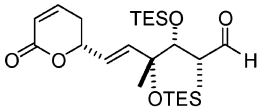
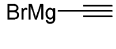
When 1,3-chelation is involved, the reaction models previously presented in section 3 (R_1 = H or alkyl, Scheme 8) also apply, the only change being the systematic presence of a (protected) hydroxyl group in position 2. Good 1,3-*anti* selectivity should be expected in cases where the two alkoxy groups are *syn*, but the steric contribution of the alkoxy group in position 2 must also be taken into account.

In the rare cases when no chelation is possible with either alkoxy group, the Felkin−Anh rules apply.

4.1. Lithium Derivatives

Many authors have described attempts at diastereoselective alkynylations with lithium derivatives, and those which were part of a larger study with more than one metal are presented in the multimetal section. The spectrum of reported inductions with lithium alone varies from high 1,2-*anti* (Table 30; entries 1 and 2) to high 1,2-*syn* (Table 30; entries 14−16) and largely depends on the substrate. The results summarized in Table 30 show that, except for rare cases, lithium is not the best choice for stereoselective addition with 2,3-dialkoxyaldehydes. For simplicity, the reaction products will be referred to as 1,2-*syn* or 1,2-*anti* in this as well as all of the following sections.

Table 29. Compilation of Alkynylations with No Reported Stereoselectivity

Metal	Aldehyde	Alkynyl derivative	Yield (%)	Ref
Li			50	96
Li			nd	96
Li			77	96
Li			nd	97
Li			nd	97
Li			99	98
Li			86	99
Li			95	68
Cl_2Ce			>68	100
Cl_2Ce			98	101

In entries 1 and 2 high 1,2-*anti* selectivity was reported. This is in surprising contrast to the good to excellent 1,2-*syn* selectivities observed for related aldehydes in entries 12, 13, and 15. Comparing these results makes it clear that the nature of all of the oxygen protecting groups has an influence on the preferred approach of the nucleophile.

Entries 3 and 4 present very similar examples where the moderate 1,2-*anti* selectivity could be explained through a nonchelated carbonyl attack (Felkin−Anh approach).

It is interesting to note that in entries 9 and 16 a clear but unexplained effect was observed by Su et al. with two diastereoisomeric aldehydes. The first aldehyde gave an almost equal mixture of addition products, while its diastereoisomer gave the 1,2-*syn* isomer almost exclusively with only traces of the 1,2-*anti* adduct.

In 1988 Lewis et al. published the synthesis of a series of L-660,631 methyl esters whose structure differed only in the alkynyl unit, this unit being incorporated by addition of the corresponding lithium alkynyl derivatives to aldehyde **33**.[122] Table 31summarizes these reactions, and it can be seen that the yields are variable and selectivities are low in favor of the 1,2-*anti* adduct for almost all of the examples given.

4.2. Boron Derivatives

Only one example was found in the literature describing addition of an "alkynylboron" derivative to the protected D-ribose **34** (Scheme 17).[123] Although it was not specified how $BF_3 \cdot Et_2O$ was used (e.g., catalytically/stoichiometrically, before or after addition to the aldehyde), it was present in the reaction mixture and is considered to be an alkynylboron

Table 30. Lithium Alkynylations with Various 2,3-Dialkoxyaldehydes

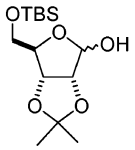
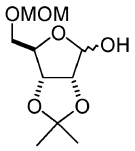
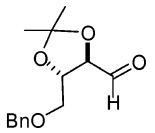
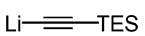
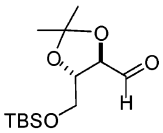
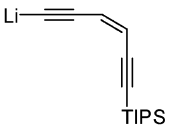
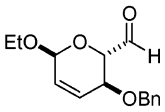
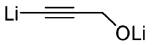
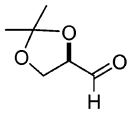
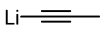
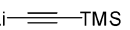
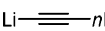
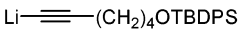
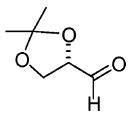
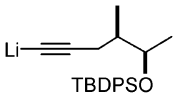
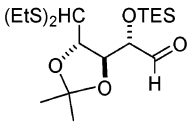
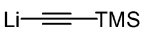
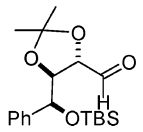
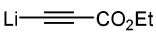
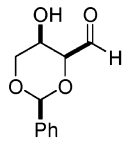
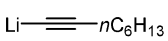
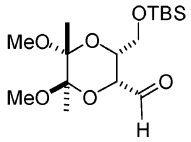
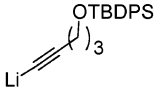
Entry	Aldehyde or hemiacetal	Alkynyl derivative	Yield (%)	1,2-*syn* / 1,2-*anti*	Ref
1			100	0 / 100	102
2			72	5 / 95	103
3			44	20 / 80	104
4			86	25 / 75	105
5			86	38 / 62	106
			75	36 / 64	
6			nd	50 / 50	107
			81,98	56 /44	108,109
			69	40 / 60	110
			84	55 / 45	111
7			>53	50 / 50	112
			91	53 / 47	113
8			81	42 / 58	114
9			69	46 / 54	115
10			83	60 / 40	116
11			nd	71 / 29	117

Table 30. (Continued)

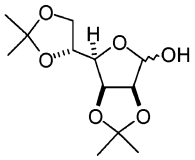
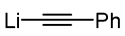
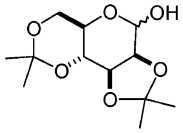
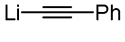
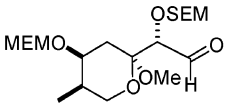
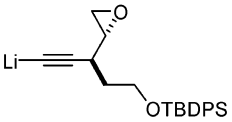
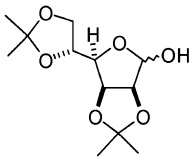
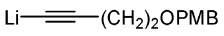
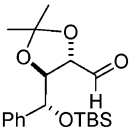
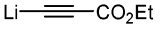
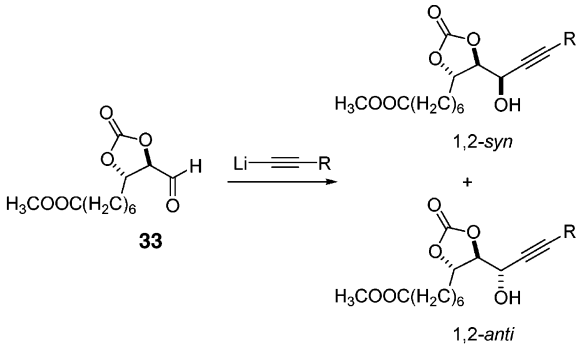
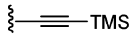
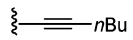
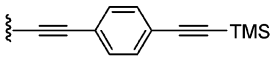
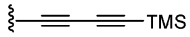
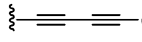
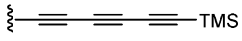
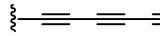
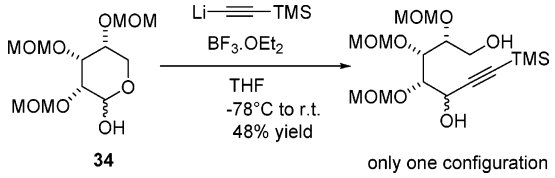
Entry	Aldehyde or hemiacetal	Alkynyl derivative	Yield (%)	1,2-*syn* / 1,2-*anti*	Ref
12			82	72 / 28	118
13			70	81 / 19	119
14			85	97 / 3	120
15			43	95 / 5	121
16			79	≈ 100 / 0	115

Table 31. Alkynyl Addition to Aldehyde 33



R	Yield (%)	1,2-*syn* / 1,2-*anti*
	46	25 / 75
	59	64 / 36
	90	33 / 67
	20	29 / 71
	46	45 / 55
	39	36 / 64
	54	26 / 74

Scheme 17



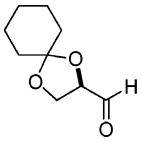
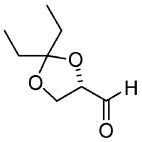
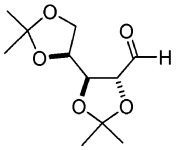
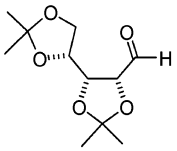
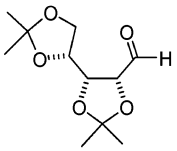
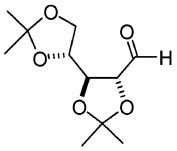
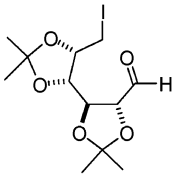
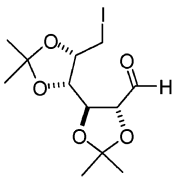
reagent. The authors gave no indication of the configuration of the newly formed carbinol center, only stating that the major adduct was obtained "as a single product with a trace of its stereoisomer".

4.3. Magnesium Derivatives

As previously seen in both sections 2 and 3, magnesium chelation of 2-alkoxyaldehydes is more effective than that of 3-alkoxy ones. As a result, strong 1,2-chelation with a 2,3-dialkoxyaldehyde could be expected to give the 1,2-*syn* isomer as the major reaction product with little "interference" from the 3-alkoxy position. When chelation is difficult or impossible, the 1,2-*anti* isomer becomes the major reaction product.

The alkynylation of carbohydrate-derived 2,3-alkoxy aldehydes has been well studied in the literature, and the stereochemistry of the obtained products is sensitive to commonly used carbohydrate protecting groups. As mentioned earlier, the oxygen atoms of an isopropylidene protecting group do not readily participate in chelation because they are involved in a stereoelectronically favorable interaction, analogous to the anomeric effect. Clear-cut

Table 32. Magnesium Alkynylation of Carbohydrate-Based 2,3-Alkoxyaldehydes

Entry	Aldehyde	Alkynyl derivative	Yield (%)	1,2-*syn* / 1,2-*anti*	Ref
1		BrMg—≡—$nC_{13}H_{27}$	90	40 / 60	124
2		BrMg—≡—CH_3	88	50 / 50	125
3		BrMg—≡	≈ 100	60 / 40	126 127
4		BrMg—≡	-- 81	60 / 40 67 / 33	128 129
5		BrMg—≡—Ph	69	28 / 72	128
6		ClMg—≡	43	44 / 56	130
7		BrMg—≡—Ph	73	30 / 70	118
8		BrMg—≡	61	30 / 70	118

stereoselectivity toward either the 1,2-*syn* or the 1,2-*anti* products is rare (Table 32).

With furan or pyran carboxaldehydes the diastereoselectivity of the addition reaction is variable and highly substrate dependent (Table 33). Excellent 1,2-*syn* selectivity was observed in only two cases (entries 3 and 6). In entry 6, extra magnesium bromide was added to prechelate the aldehyde, and use of Et_2O was essential.

Entries 7−9 (Table 33) were published as part of a study of the alkynylation of β-C-glycoside aldehydes by Michelet et al.[138] In entry 7, the 1,2-*anti* diastereoisomer was the major reaction product, most likely due to the presence of the methyl ester and ineffective 1,2-chelation. Replacing the ester by a protected alcohol caused a reversal in selectivity, which was further improved in entry 9. Deprotonation of the hydroxyl group in position 3 and efficient magnesium chelation gave the 1,2-*syn* (1,3-*anti*) product. In entries 10 and 11 with a dioxane alkoxyaldehyde, the excellent 1,2-*anti* selectivity was explained by effective β chelation control.

Table 33. Magnesium Alkynylation of Furan-, Pyran-, and Dioxane-Based 2,3-Alkoxyaldehydes

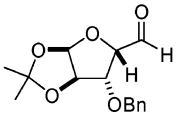
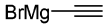
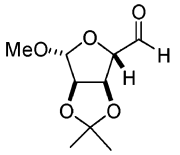
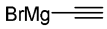
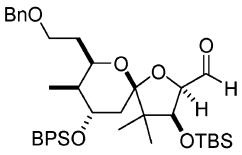
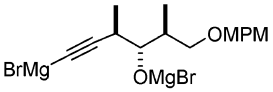
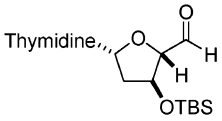
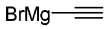
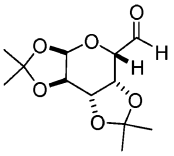
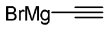
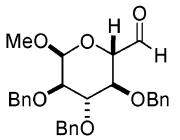
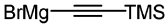
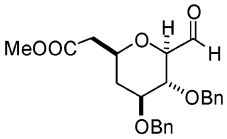
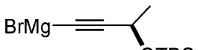
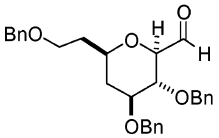
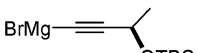
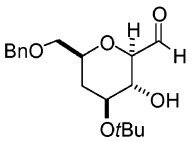
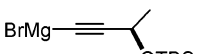
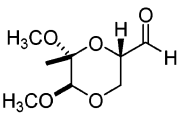
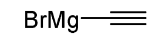
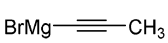
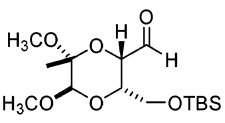
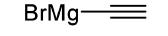
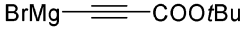
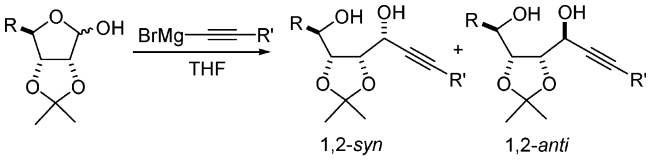
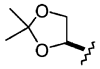
Entry	Aldehyde	Alkynyl derivative	Yield (%)	1,2-*syn* / 1,2-*anti*	Ref
1			60	55 / 45	131
2			77	50 / 50	132
3			94	94 / 6	133
4			>52	38 / 62	134
5			73 50-80	40 / 60 33 / 67	135 136
6			87	94 / 6	137
7			52	12 / 88	138
8			73	65 / 35	138
9			50	80 / 20	138
10		 	95 93	6 / 94 6 / 94	139
11		 	86 75	10 / 90 8 / 92	140

Table 34. Alkynylmagnesium Addition to Masked Aldehydes

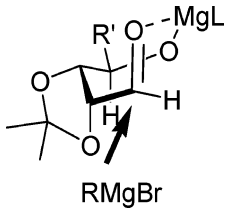


R	R'	Yield (%)	1,2-*syn* / 1,2-*anti*	Ref
CH_2OH	H	70	10 / 90	141
CH_2OTr	H	nd	≈ 1 / 99	141
	H	65	≈ 7 / 93	142
H	*n*Bu	84	0 / 100	143
H	$(CH_2)_2OBn$	88	0 / 100	143

The "masked" carbohydrate aldehyde function has also been extensively studied. In the 1970s Buchanan et al. reported the ethynylation of carbohydrate aldehydes as part of a systematic study toward the synthesis of C-nucleosides (Table 34). With an isopropylidene protecting group in positions 2 and 3, the 1,2-*anti* isomer was formed with excellent stereoselectivity.

The authors explained the high 1,2-*anti* selectivity by chelation of the magnesium with the aldehyde and hydroxyl in position 4 to form a seven-membered ring followed by attack of the nucleophile on the less hindered face of the molecule (Chart 1).[129] This same selectivity was observed more recently by Pearson and Hembre in the preparation of swainsonine analogues.[143]

Chart 1



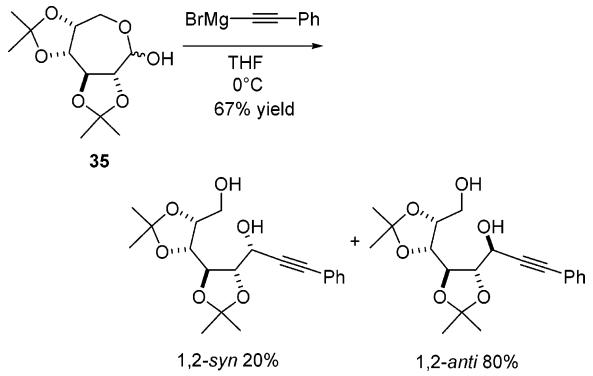
In contrast, when the sugar hydroxyl groups were protected as benzyl ethers, the 1,2-*syn* diastereoisomers became the major reaction products with moderate to excellent stereoselectivity (Table 35). It is obvious that good 1,2-chelation is favored with a benzyl protecting group in position 2 as opposed to an isopropylidene group for reasons previously discussed.

An unusual alkynylation reaction with the seven-membered ring hemiacetal **35** was described to give good 1,2-*anti* selectivity (Scheme 18). The authors offered no explanation for this result, but a cyclic chelated intermediate could be involved as previously proposed in the furan series.[118]

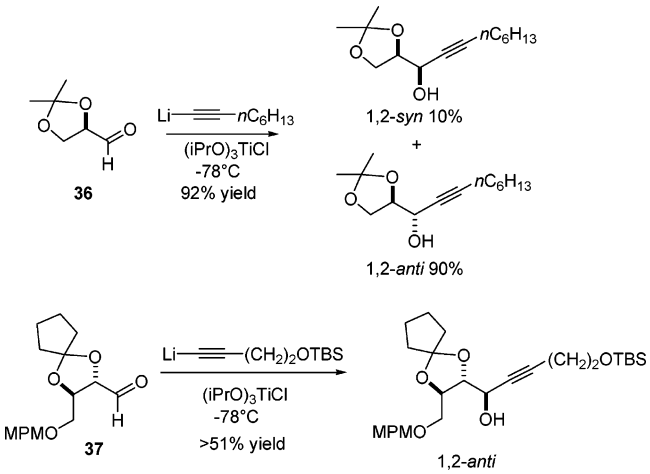
4.4. Titanium Derivatives

In general, alkynyltitanium derivatives have been reported to favor 1,2-*anti* diastereoselectivity. The 1,2-*anti* product normally results from a nonchelated transition state, using Felkin−Anh rules, and is generally better for this type of induction for simple steric reasons. Trost et al. used this characteristic to their advantage with the glyceraldehyde derivative **36**[40] as well as with aldehyde **37** in their synthesis of (+)-amphidinolide A (Scheme 19).[150]

Scheme 18



Scheme 19



4.5. Manganese Derivatives

Use of manganese alkynyl derivatives is rare, and only one article was found describing their addition to 2,3-alkoxy aldehydes (Table 36).[151] In both reported examples the 1,2-*syn* diastereoisomer was the major addition product explained through effective 1,2-chelation with the manganese metal.

4.6. Zinc Derivatives

Zinc reagents are rarely used as a first option in alkynylation reactions, and thus, few such examples exist in the literature. As previously seen with 2-alkoxyaldehydes, these compounds are very effective in inducing good to excellent 1,2-*syn* selectivity. Mead reported one example with the 2,3-dialkoxyaldehyde **38** which confirms this tendency (Scheme 20).[38]

Scheme 20

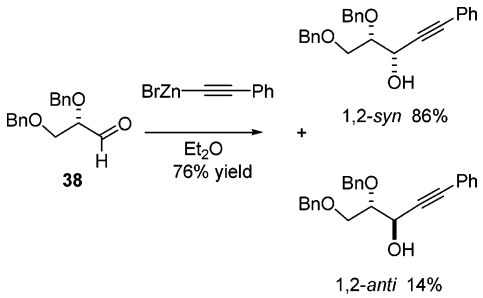


Table 35. Effect of the Benzyl Group on Reaction Stereoselectivity

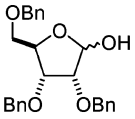
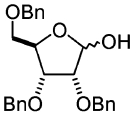
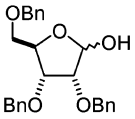
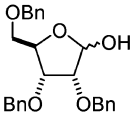
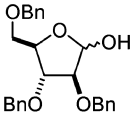
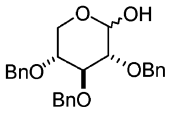
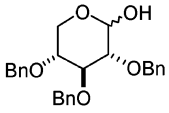
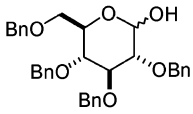
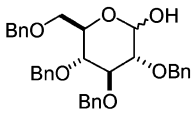
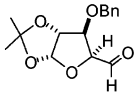
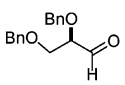
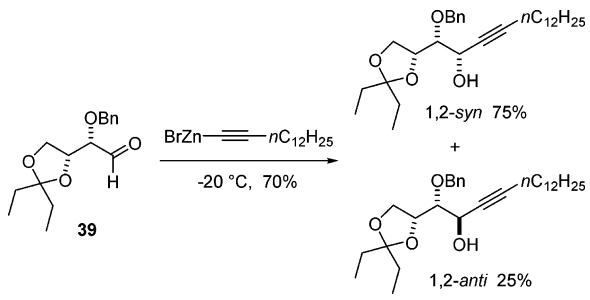
Entry	Hemiacetal	Alkynyl derivative	Yield (%)	1,2-*syn* / 1,2-*anti*	Ref
1		BrMg—≡	99	70 / 30	144
2		BrMg—≡—CO_2MgBr	73	≈ 99 / 1	145
3		BrMg—≡—R R = nC_3H_7, nC_4H_9, nC_5H_{11}	94 99 77	89 / 11 86 / 14 85 / 15	146
4		BrMg—≡—CH_2OMe	80	85 / 15	146
5		BrMg—≡	nd	100 / 0	147
6		BrMg—≡	78	92 / 8	148
7		BrMg—≡—$CH(OEt)_2$	93	100 / 0	148
8		BrMg—≡	68	71 / 29	149
9		BrMg—≡—Ph	88	63 / 37	118

Table 36. Manganese Alkynylation

Aldehyde	Alkynyl derivative	Yield (%)	1,2-*syn* / 1,2-*anti*
	IMn—≡—*n*Bu	80	86 / 14
	IMn—≡—*n*Bu	28	78 / 22

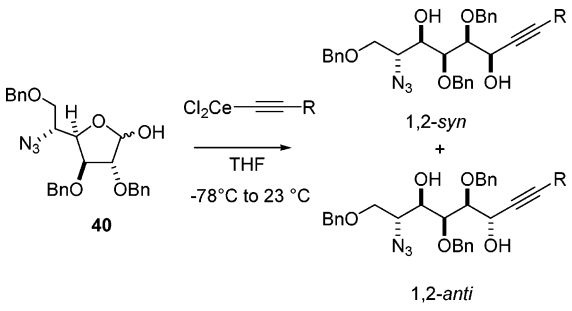
A similar diastereoselectivity was observed by Lu et al. with alkynylzinc addition to aldehyde **39** in the recently reported synthesis of L-*lyxo*-phytosphingosine (Scheme 21).[152]

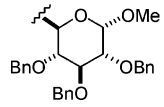
Scheme 21



Additional examples using alkynylzinc derivatives are found in the "multimetal" section at the end of this section.

Table 37. Alkynylcerium Addition to Aldehyde 40



R	Yield (%)	1,2-*syn* / 1,2-*anti*
H	82	100 / 0
	69	78 / 22

4.7. Cerium Derivatives

In their synthesis of a polyhydroxylated tetrahydro-4*H*-1,2,3-triazolo[1,5-a]azepin, Tezuka et al. reported the use of two different alkynylcerium reagents which gave the 1,2-*syn* diastereoisomers preferentially or exclusively (Table 37).[153] This result demonstrates the Lewis acid nature of the cerium derivative where the 1,2-*syn* isomer is a result of 1,2-chelation.

4.8. Multimetal Inductions

As seen in the two previous sections, many examples exist in the literature where the behavior of several metals is studied in order to optimize the alkynyl addition reaction. In the case of 2,3-dialkoxyaldehydes, fine tuning the reaction parameters is essential as the hydroxyl groups in positions 2 and 3 and their interaction with the metal may have a separate and opposite influence on the stereochemistry of the reaction products.

4.8.1. Case 1: Li/Mg

Lithium and magnesium are often the first two metals tried in alkynylation reactions because they are readily prepared and have different chelating behavior. Alkynyl addition reactions are extremely substrate dependent, and as previously seen with magnesium and various sugar aldehydes (section 4.3), use of an isopropylidene protecting group in positions 2 and 3 is not recommended for good diastereoselectivity. Induction is low with both alkynyllithium and magnesium additions to 2,3-*O*-isopropylidene-D-glyceraldehyde (Table 38, entry 1). Lithium additions to 2,3-*O*-isopropylidene derivatives of furanose sugars (entries 2−4) also gave only moderate 1,2-*anti* inductions.[154] The high 1,2-*anti* selectivity in entry 2 observed for the magnesium derivatives was explained by the same seven-membered ring formed as a result of chelation with the aldehyde and the hydroxyl in position 4 (see Chart 1).

4.8.2. Case 2: Li/Ti

A comparative study of lithium and titanium alkynyl derivatives was performed by Tabusa et al. as part of their formal total synthesis of polyoxin J (Table 39).[156] With lithium, only moderate 1,2-*anti* selectivity was obtained. The choice of the titanium reagent was shown to be important with the bulky titanium triisopropoxide giving excellent 1,2-*anti* selectivity but in low yield. The combined use of titanium(IV) isopropoxide/titanium tetrachloride gave an increased amount of addition product with excellent stereoselectivity.

Kraus and Seebach also observed a similar effect with lithium and titanium, with the 1,2-*anti* isomer becoming the major reaction product when a bulky alkynyltitanium derivative was used (Table 40).[48]

Table 38. Li and Mg Alkynyl Additions to 2,3-*O*-Isopropylidene-Protected Sugar Aldehydes

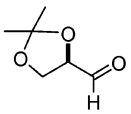
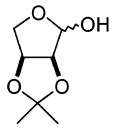
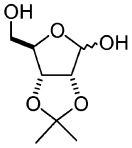
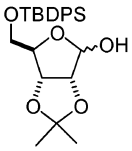
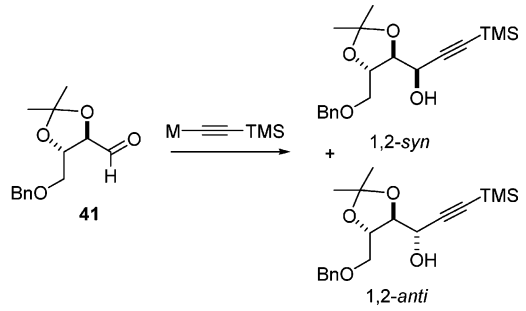
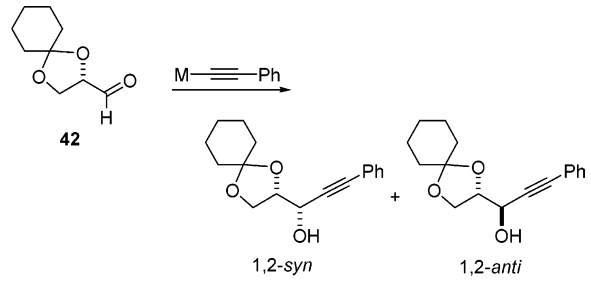
Entry	Aldehyde	Alkynyl derivative	Yield (%)	1,2-*syn* / 1,2-*anti*	Ref
1		Li—≡		50 / 50	107
		BrMg—≡	≈ 100	56 / 44	126, 155
2		Li—≡—*n*Bu	83	34 / 66	154
		BrMg—≡—*n*Bu	74	0 / 100	
3		Li—≡—*n*Bu	67	25 / 75	154
		BrMg—≡—*n*Bu	55	20 / 80	
4		Li—≡—*n*Bu	66	25 / 75	154

Table 39. Lithium and Titanium Alknylation with Aldehyde 41



Entry	Reaction conditions	Yield (%)	1,2-*syn* / 1,2-*anti*
1	M = Li	97	32 / 68
2	M = Cp_2ClTi	47	17 / 83
3	M = $(OiPr)_2ClTi$	22	24 / 76
4	M = $(OiPr)_3Ti$	27	2 / 98
5	$Ti(OiPr)_4/TiCl_4$ (1:1)	83	2 / 98

Table 40. Lithium and Titanium Alkynylation with Aldehyde 42

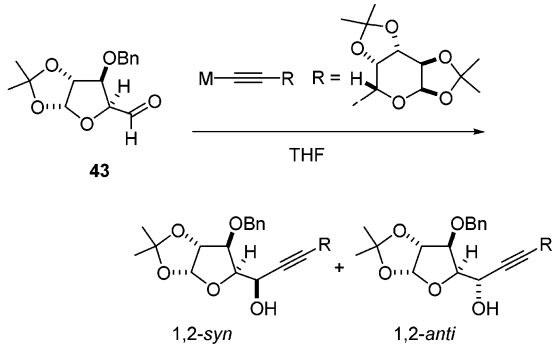


Metal	Yield (%)	1,2-*syn* / 1,2-*anti*
Li	70	58 / 42
(OiPr)$_3$Ti	33	24 / 76

4.8.3. Case 3: Li/Zn

In a similar example with the furanose aldehyde **43**, Jarosz observed a slight 1,2-*syn* preference with lithium which increased when the corresponding alkynylzinc derivative was used (Table 41).[157] The authors explained the results by 1,2-

Table 41. Comparative Alkynyllithium and Alkynylzinc Addition to Aldehyde 43

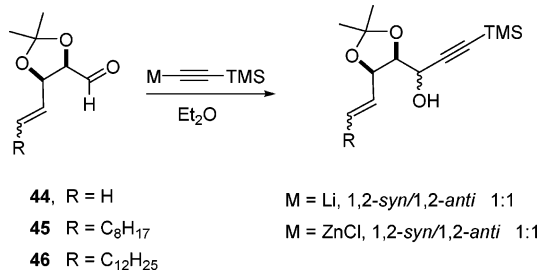


Metal	Yield (%)	1,2-*syn* / 1,2-*anti*
Li	70	67 / 33
ClZn	nd	88 / 12

chelation with lithium or zinc, zinc being the more efficient complexing agent.

Recent work in our laboratory toward the synthesis of sphingolipid derivatives showed that no selectivity could be achieved in the addition of alkynyllithium or alkynylzinc compounds to aldehydes **44**−**46** (Scheme 22).[158] Use of an

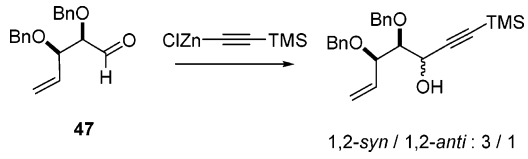
Scheme 22



isopropylidene protecting group in positions 2 and 3 proved once again to inhibit any possible metal chelation.

When the reaction was performed with the benzylated aldehyde **47** and the same alkynylzinc derivative, stereoselectivity changed slightly to give a 3/1 inseparable mixture of diastereoisomers. (Scheme 23).

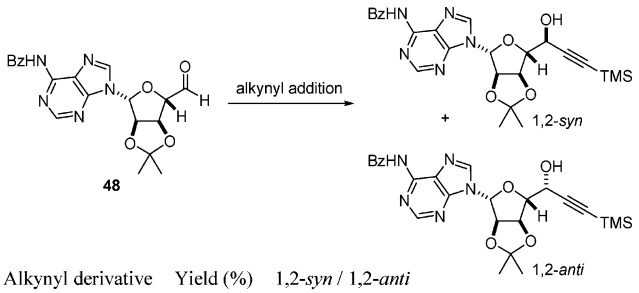
Scheme 23



4.8.4. Case 4: Mg/Zn

Addition of the alkynylmagnesium derivative **49** to the 5′-oxoadenosine aldehyde **48** has been reported by two different groups with the same moderate diastereoselectivity in favor of the 1,2-*anti* adduct.[159,160] In the more recent example the selectivity was further improved using the alkynylzinc reagent **50**, generated from a 2:1 mixture of lithium trimethylsilylacetylide and zinc chloride (Table 42).

Table 42. Alkynyl Addition to Aldehyde 48



Alkynyl derivative	Yield (%)	1,2-*syn* / 1,2-*anti*
BrMg—≡—TMS (**49**)	60-70	33 / 67
$Zn(—≡—TMS)_2$ (**50**)	59	10 / 90

The authors state that the addition is in agreement with Felkin−Anh rules, and it is probable that steric hindrance between the adenosine group and the aldehyde prevents any chelation with the organozinc reagent (Chart 2).

4.8.5. Case 5: Li/Al/Ti

Kato et al. reported addition of trimethylsilylacetylide to the furan-2-carboxaldehyde **51** with low selectivity (Table

Chart 2

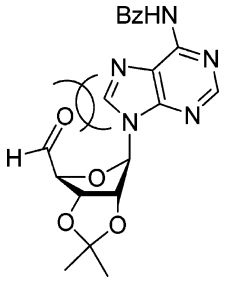
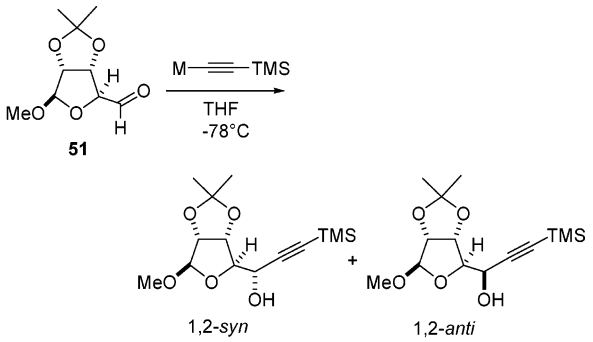


Table 43. Li, Al, and Ti Trimethylsilylacetylide Addition to the Furan-2-carboxaldehyde 51



Reaction conditions	Yield (%)	1,2-*syn* / 1,2-*anti*
M = Li	62	60 / 40
Et_2AlCl	26	39 / 61
$TiCl_4/Ti(OiPr)_4$	62	45 / 55

43).[161] It should be noted that addition of diethylaluminum chloride is generally a method to enhance 1,2-chelation, but in this example the opposite result was obtained in only moderate yield.

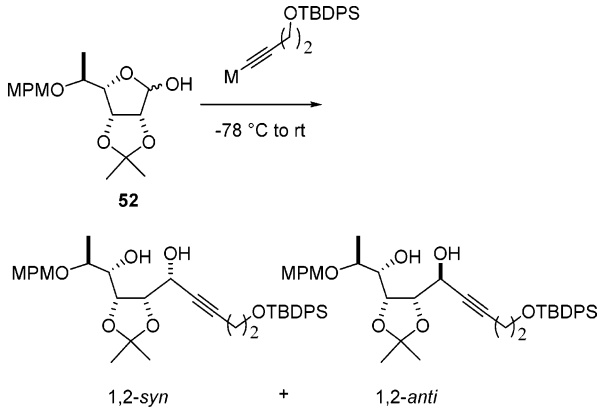
4.8.6. Case 6: Li/Mg/Ce

In their total synthesis of mucocin Takahashi and Nakata reported an interesting study of solvent and metal effects with aldehyde **52** and different alkynyllithium, magnesium, and cerium derivatives (Table 44).[45,162]

Surprisingly, the best stereoselectivity in favor of the 1,2-*syn* adduct was obtained when HMPA was added to the reaction mixture (Table 44; entry 5) but in low yield. A compromise was made between reaction selectivity and yield in a mixture of solvents, hexane/Et_2O (3:1), but no explanation was given to explain this selectivity increase or the excellent selectivity observed with HMPA. When the same reaction was performed with an alkynylmagnesium derivative generated in situ from the lithium species, the 1,2-*syn* selectivity dropped (Table 44; entry 6). When the corresponding Grignard reagent was used, inversion in stereoselectivity was observed with the 1,2-*anti* diastereoisomer becoming the major reaction product (Table 44; entry 7). Alkynylation with a cerium derivative did little to improve reaction selectivity (Table 44; entry 8).

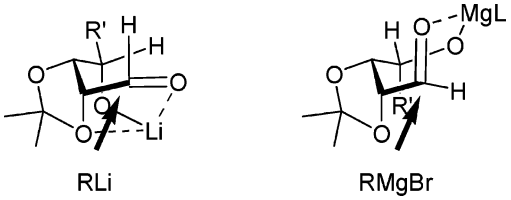
To explain their results the authors postulated that in Et_2O a highly chelated lithium species was responsible for the observed induction (Chart 3). In the case of the Grignard reagent a seven-membered cyclic chelation state was described which orients the selectivity toward a greater amount of the 1,2-*anti* diastereoisomer.

Table 44. Alkynylation of Aldehyde 52: Solvent and Metal Effects



Entry	Reaction conditions	Yield (%)	1,2-*syn* / 1,2-*anti*
1	*n*BuLi, Et_2O	73	80 / 20
2	*n*BuLi, Et_2O, LiI	79	71 / 29
3	*n*BuLi, hexane/Et_2O (3 :1)	78	86 / 14
4	*n*BuLi, toluene	66	67 / 33
5	*n*BuLi, Et_2O, HMPA	42	94 / 6
6	*n*BuLi, $MgBr_2$, Et_2O	21	55 / 45
7	EtMgBr, Et_2O	79	19 / 81
8	*n*BuLi, $CeCl_3$, Et_2O/HMPA	41	76 / 24

Chart 3



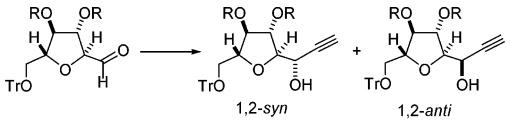
4.8.7. Case 7: Li/Mg/Zn

In the same article Takahashi and Nakata also investigated the stereoselective ethylnylation of three furan-derived aldehydes differing only in the oxygen protecting groups in positions 3 and 4 (Table 45).[45] Their results again confirmed that the stereochemical induction is a compromise between the metal used, steric interactions with other groups, and subsequent 1,2-chelation versus 1,3-chelation that is a result of the first two factors.

With a alkynyllithium derivative (Table 45; entry 1) the low selectivity observed with benzyl protecting groups may be the result of competition between 1,2- and 1,3-chelation. When the benzyl protecting groups were exchanged for bulkier TBS ones, 1,3-chelation was no longer favored and 1,2-chelation with the endocyclic oxygen gave more 1,2-*syn* adduct (Table 45; entry 2). With TBDPS protecting groups, the 1,2-*anti* diastereomer again became the major isolated product.

Use of the corresponding alkynylmagnesium derivative gave contradictory results, the 1,2-*syn* adduct being the major product in only one reaction with TBS protecting groups (Table 45; entry 5). With benzyl or TBDPS protecting groups the 1,2-*anti* adducts were favored, thus showing that chelation with magnesium is not systematic and depends on the steric interactions with the protecting groups.

Table 45. Protecting-Group Variations

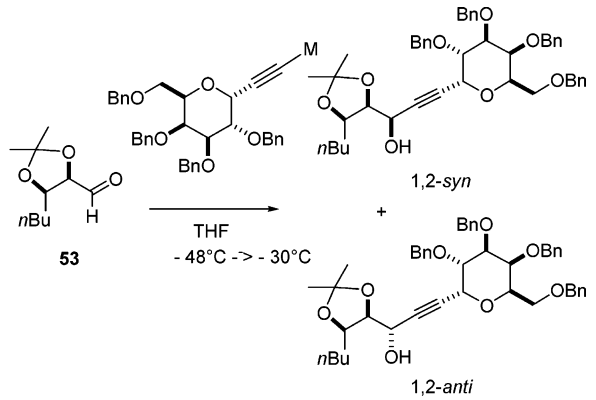


Entry	R	Reaction conditions	Yield (%)	1,2-syn / 1,2-anti
1	Bn	LiC≡CTMS, THF 0 °C	70	42 / 58
2	TBS	LiC≡CTMS, THF 0 °C	47	66 / 34
3	TBDPS	LiC≡CTMS, THF 0 °C	53	29 / 71
4	Bn	ClMgC≡CH, THF/Et_2O, 0 °C	83	25 / 75
5	TBS	ClMgC≡CH, THF/Et_2O, 0 °C	72	78 / 22
6	TBDPS	ClMgC≡CH, THF/Et_2O, 0 °C	69	36 / 64
7	Bn	ClMgC≡CH, $ZnCl_2$, THF/Et_2O, -78 °C	40	66 / 34
8	TBS	ClMgC≡CH, $ZnCl_2$, THF/Et_2O, -78 °C	63	89 / 11
9	TBS	ClMgC≡CH, $ZnCl_2$, CH_2Cl_2/THF/Et_2O, -78 °C	70	93 / 7
10	TBDPS	ClMgC≡CH, $ZnCl_2$, THF/Et_2O, -78 °C	47	58 / 42

1,2-*Syn* addition substantially increased with all three aldehydes when $ZnCl_2$ was added to the reaction mixture. The best results were obtained with the TBS derivative where 89% of the 1,2-*syn* product was isolated (Table 45; entry 8). Addition of methylene chloride enhanced the availability of the zinc cation and therefore made 1,2-chelation even easier, improving both the yield and the selectivity.

In another example Toba et al. recently reported a new approach to the synthesis of a C-glycoside analogue of the immunomodulating α-galactosylceramide OCH.[163] Addition of an alkynyl sugar derivative to the 2,3-isopropylidene-protected aldehyde **53** gave a mixture of adducts with poor selectivity (Table 46). No improvement was observed by changing the nature of the metal.

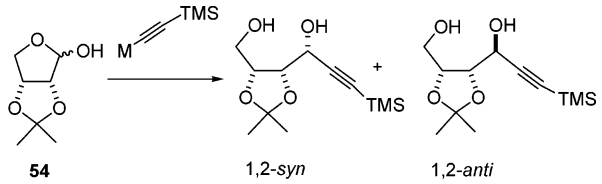
Table 46. Alkynyl Addition to Aldehyde 53



Entry	Reaction conditions	Yield (%)	1,2-*syn* / 1,2-*anti*
1	M = Li	77	61 / 39
2	M = MgX	39	≈ 61 / 39
3	M = ZnX	traces	nd

Current work in our laboratory has shown that alkynyl addition to the masked aldehyde **54** proceeds in good yield with good to excellent 1,2-*anti* selectivity in the presence of lithium, magnesium (Table 47).[164] With similar substrates substituted in position 4, Buchanan et al. hypothesized that the high 1,2-*anti* selectivity resulted from formation of a seven-membered ring by chelation of the organometallic reagent with the aldehyde and the free hydroxyl in position 4 (vide supra; Chart 1).[129] The nucleophile then attacks on

Table 47. Li, Mg, and Trimethylsilylacetylide Addition to Aldehyde 54



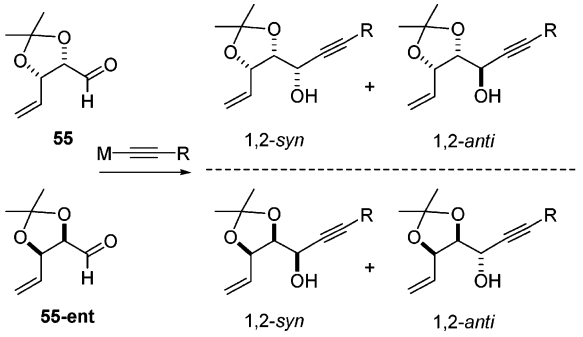
Entry	Metal/Conditions	Yield (%)	1,2-*syn* / 1,2-*anti*
1	Li, THF, -40°C	55	10/90
2	Li, THF, rt	69	0 / 100
3	Li, Et_2O, -78°C	87	50/50
4	Li, Et_2O, 0°C	66	40 / 60
5	BrMg, THF, -78°C	85	0/100

the less hindered face of the molecule. The presence of the isopropylidene protecting group actually enhances this effect by inhibiting 1,2-chelation.

4.8.8. Case 8: Li/B/Mg/Ce

In their study of the stereoselective cyclization of enynes mediated by metallocene reagents RajanBabu et al. reported addition of "various propynyl organometallic reagents" to aldehyde **55** (Table 48, entries 1−5).[165] The best results were

Table 48. Comparative Alkynyl Addition to Aldehyde 55 and Its Enantiomer

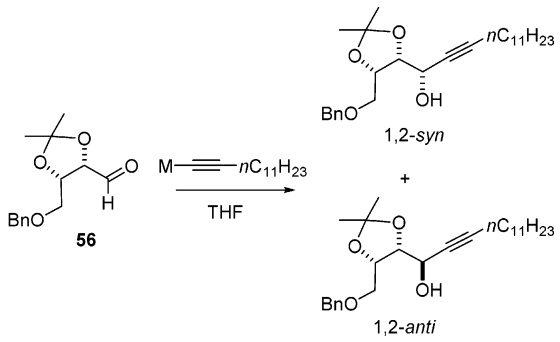


Entry	Aldehyde	Reaction conditions	R	Yield (%)	1,2-*syn* / 1,2-*anti*
1	**55**	M = Li, THF	CH_3	>73	76 / 24
2	**55**	M = BrMg, THF	CH_3	--	45 / 55
3	**55**	M =Li, Et_2O	CH_3	--	44 / 56
4	**55**	M = Li, Et_2O, TMEDA	CH_3	--	58 / 42
5	**55**	M = Li, BF_3, THF	CH_3	--	45 / 55
6	**55-ent**	M = BrMg, THF	H	26	34 / 66
7	**55-ent**	M = Cl_2Ce	TMS	68	30 / 70

obtained with an alkynyllithium derivative in THF at −20 °C to give the 1,2-*syn* product preferentially. More recently, alkynyl addition to the enantiomer of aldehyde **55** (**55-ent**) was reported by Poulsen and Madsen as part of a study of carbohydrate carbocyclization (entries 6 and 7).[166]

In the case of aldehyde **55-ent**, several different metals were tried in order to optimize the addition reaction (Li, $ZnBr_2$, Ce, or Zn triflate; with or without a protected alkynyl derivative), but only a complex mixture of products and/or aldehyde reduction was detected. Moderate 1,2-*anti* selectivity was observed with magnesium, and this result was further improved by use of trimethylsilylethynylcerium chloride.

Table 49. 1,2-*Anti* Alkynylation of Aldehyde 56



Entry	Reaction conditions	Yield (%)	1,2-*syn* / 1,2-*anti*
1	M = ($OiPr)_3$Ti, -78 → 0 °C	98	<1 / >99
2	M = Li, -78 → 0 °C	43	73 / 27
3	M = BrMg, -78 → 0 °C	43	60 / 40
4	M = ClMg, -50 → 0 °C	66	76 / 24
5	M = Cl_2Ce, -78 → rt	66	77 / 23

4.8.9. Case 9: Li/Mg/Ce/Ti

Shimizu et al. reported a highly 1,2-*anti*-selective addition reaction with an alkynyltitanium derivative and the chiral aldehyde **56** (Table 49).[167]

Only moderate 1,2-*syn* selectivity was observed with magnesium or cerium compared to the corresponding lithium derivative. This was not surprising, however, because of the "anomeric effect" of the isopropylidene group (vide supra), which results in poor 1,2-chelation and consequently low inductions.

4.8.10. Case 10: Li/Mg/Ce/Cu/Zn

Michelet et al. carried out a detailed study on the alkynylation of the β-C-glycoside aldehyde **57** with five different metal derivatives (Table 50).[138] It should be noted that in entries 2−6 the aldehydes were all preequilibrated with the respective metal derivative before addition of the alkynyl reagent.

As expected, under nonchelation control, the 1,2-*anti* product was formed as the major reaction product when the reaction was carried out with lithium in the presence of HMPA (Table 50; entry 1). The selectivity was reversed with magnesium in a less coordinating solvent, and the 1,2-*syn* diastereoisomer was isolated in good yield (entry 2). Addition of cerium, copper, or zinc in the reaction mixture did little to improve the selectivity obtained with the original Grignard reagent. The authors stated that although the different diastereoisomers could not be separately identified by ^{1}H NMR spectroscopy, product ratios could be determined and the additions were assumed to follow Cram's chelation model.

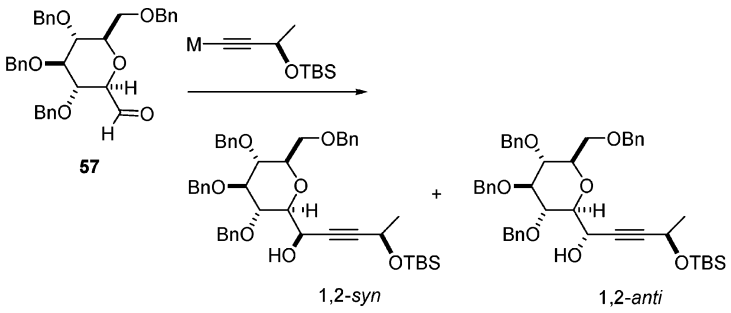
Application of the optimized reaction conditions was also efficient in coupling two other alkynyl derivatives to aldehyde **57** in good yield and selectivity (Table 51).

4.8.11. Case 11: Li/Mg/Ce/Cu/Sn/Ti/Zn

In the course of their recent studies concerning the stereoselective synthesis of C-glycosides, Guillarme and Haudrechy extensively explored the alkynylation of the open chain sugar aldehyde **58** through variations in solvent and metal reagents (Table 52).[168] It was envisioned that the asymmetric centers found in the sugar residue would be capable of effectively controlling reaction selectivity.

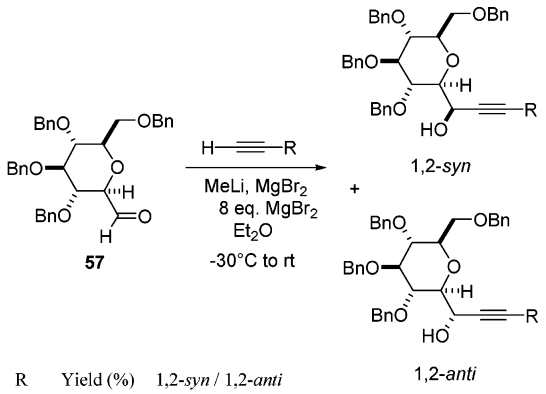
A definite solvent effect was observed with the lithium alkynyl reagent (Table 52; entries 1−3). Whereas a 1,2-*anti* selectivity was predominant in THF, the change to less chelating solvents favored the 1,2-*syn* diastereoisomer. Surprisingly, use of the more chelating magnesium derivative in THF also favored the 1,2-*anti* isomer but selectivity was reversed when the reaction was carried out in diethyl ether (Table 52; entries 4,5). Changing the metal component to cerium, copper, titanium, or aluminum did little to affect the

Table 50. Alkynylation of β-C-Glycoside Aldehyde 57



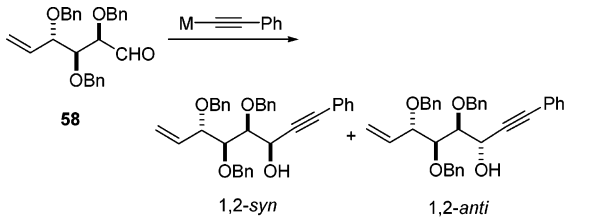
Entry	Reaction conditions	Yield (%)	1,2-*syn* / 1,2-*anti*
1	MeLi, HMPA, -78 °C→ rt	50	40 / 60
2	MeLi, $MgBr_2$, 8 eq. $MgBr_2$, Et_2O, -30 °C→ rt	75	75 / 25
3	MeLi, $CeCl_3$, 8 eq. $CeCl_3$, THF, -78 °C→ rt	20	58 / 42
4	MeLi, $MgBr_2$, 8 eq. CuI, THF/Me_2S, -78 °C→ rt	50	70 / 30
5	MeLi, $MgBr_2$, 8 eq. $ZnBr_2$, Et_2O, -78 °C→ rt	47	53 / 47
6	MeLi, $ZnBr_2$, 8 eq. $ZnBr_2$, Et_2O, 0 °C→ rt	No reaction	---

Table 51. Magnesium Alkynylation of Aldehyde 57



R	Yield (%)	1,2-*syn* / 1,2-*anti*
Ph	60	87 / 13
TMS	73	70 / 30

Table 52. Alkynylation of Aldehyde 58: Optimization of Solvent and Metal Reagents

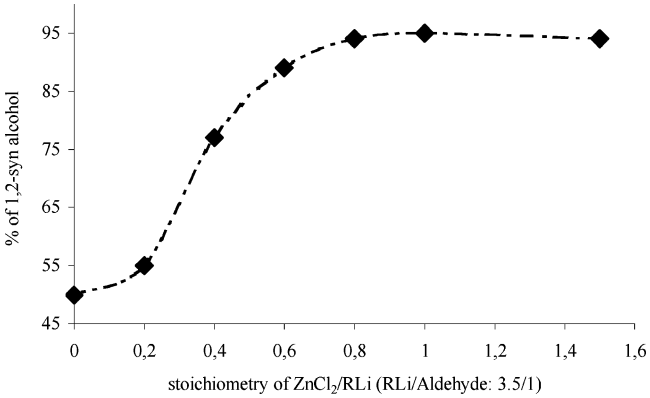


Entry	Reaction conditions	Yield (%)	1,2-*syn* / 1,2-*anti*
1	M = Li, THF, -78 → 0 °C	75	35 / 65
2	M = Li, Et_2O, -78 → 0 °C	75	50 / 50
3	M = Li, toluene, -78 → 0 °C	71	60 / 40
4	M = BrMg, THF, -78 → 0 °C	56	37 / 63
5	M = BrMg, Et_2O, -78 → 0 °C	74	58 / 42
6	M = Cl_2Ce, THF, -78 °C → rt	53	33 / 67
7	M = BrMg, CuBr•Sme_2, THF, -78 °C → rt	56	50 / 50
8	M = $(OiPr)_3Ti$, THF, -40 °C → rt	53	26 / 74
9	M = Li, $AlEt_2Cl$, THF, -78 °C → rt	No reaction	---
10	M = BrZn, THF, 0 °C → rt	23	77 / 23
11	M = BrZn, Et_2O, 0 °C → rt	37	83 / 17
12	M = ClZn, Et_2O, 0 °C → rt	79	93 / 7
13	M = Me_3Sn, THF, -78 → 0 °C	33	84 / 16

original stereoselectivity obtained with lithium (Table 52; entries 6−9). Use of zinc bromide (entry 11) gave good selectivity in favor of the 1,2-*syn* isomer but was low yielding. Changing the solvent to diethyl ether further increased the selectivity with only a slight increase in yield. In contrast to Mead's results with 2-alkoxyaldehydes,[38] the best selectivity was observed with a change in the counterion from zinc bromide to zinc chloride with a corresponding increase in yield (Table 52; entry 12). An organotin reagent was also tested in the absence of a Lewis acid, and while good selectivity was observed, the product was obtained in low yield.

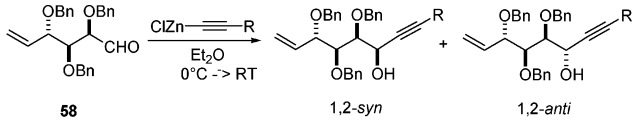
A study was then undertaken using various amounts of zinc chloride in the reaction mixture. The profile in Chart 4 shows that a certain zinc chloride concentration is crucial for a highly selective 1,2-*syn* addition with these 2,3-dialkoxyaldehydes.

Chart 4



Using these optimized conditions, the generality of the addition reaction to aldehyde **58** was then demonstrated with several zinc chloride derivatives giving good to excellent 1,2-*syn* selectivity (Table 53).

Table 53. Addition of Various Alkynylzinc Reagents to Aldehyde 58



R	Yield (%)	1,2-*syn* / 1,2-*anti*
Ph	79	93 / 7
nC_3H_7	47	83 / 17
nC_5H_{11}	32	86 / 14
TMS	85	>94 / <6
CH_2OTBS	55	86 / 14

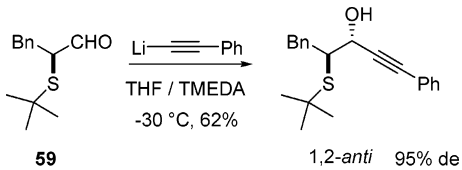
4.9. Miscellaneous Alkynylations of 2,3-Dialkoxyaldehydes

A compilation of alkynylations of 2,3-dialkoxyaldehydes is shown in Table 54.

5. 2- and 3-Thio-Substituted Aldehydes

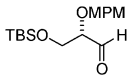
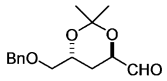
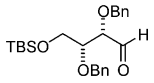
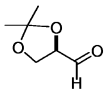
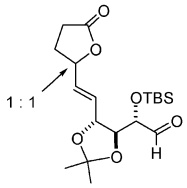
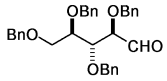
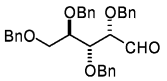
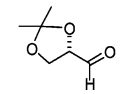
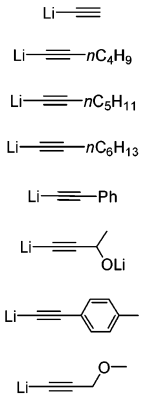
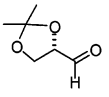
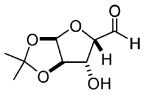
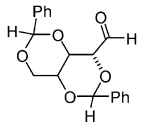
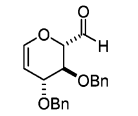
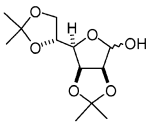
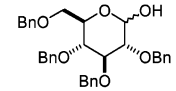
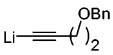
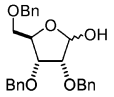
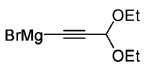
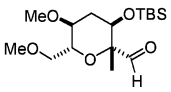
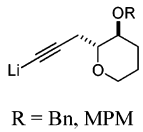
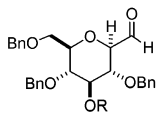
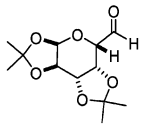
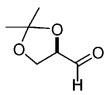
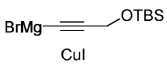
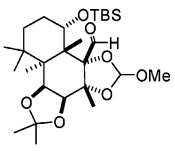
Reports of organometallic alkynyl addition to chiral 2- and 3-thio-substituted aldehydes are relatively rare in the literature, and in most cases the role of the sulfur atom is not discussed. In a study by Enders et al. of diastereoselective 1,2-additions to the chiral 2-thio-substituted aldehyde **59**, it was shown that addition of lithium phenylacetylide in the presence of TMEDA gave the 1,2-*anti* diastereoisomer almost exclusively (Scheme 24).[184]

Scheme 24



The presence of a bulky sulfur group in position 2 confers the same type of reactivity as a sterically hindered 2-alkoxy group, and the 1,2-*anti* diastereoisomer is predominant in a nonchelating environment.

Table 54. Compilation of Alkynylations with No Given Stereoselectivity

Metal	Aldehyde	Alkynyl derivative	Yield (%)	Ref	Metal	Aldehyde	Alkynyl derivative	Yield (%)	Ref
Li			>81%	169	Mg			77	175
Li			> 80	170	Mg			nd 84	176 175
Li			40	114	Mg			60 98	177 178
					Mg			53	177
Li			≈ 80	171	Mg			71	179
					Mg			nd	126
					Mg			nd	128
Li			>82	172	Mg			65	180
Li			97	149	Mg			nd	181
Li		 R = Bn, MPM	88 (Bn) 76 (MPM)	173	Mg	 R = *t*Bu or Bn		41-73	182
Li			50	136	Cu			nd	183
Li			84	174	Zn			63	164

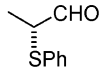
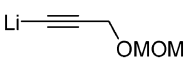
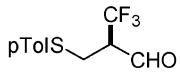
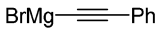
Of the two remaining literature examples, little or no information is given about reaction diastereoselectivity. These cases are included in Table 55.

6. 2-Aminoaldehydes

6.1. Linear 2-Aminoaldehydes

The stereochemical outcome of alkynyl additions to 2-aminoaldehydes is very similar to that of 2-alkoxyaldehydes. In general, if effective 1,2-chelation is possible, formation of the 1,2-*syn* diastereoisomer is favored. When chelation is monodentate or not possible, the nature of the protecting group in position 2 influences reaction selectivity and traditional Felkin−Anh rules are followed. Organometallic alkynyl addition to linear mono-Boc-protected 2-aminoaldehydes favors formation of the 1,2-*syn* diastereoisomers, but overall product ratios are moderate to disappointing (Table 56).

Table 55. Miscellaneous Alkynyl Addition to Chiral 2- and 3-Thio-Substituted Aldehydes

Aldehyde	Alkyne	Yield (%)	Ref.
		> 62	58
		38[a]	185

[a] An undefined 79/21 mixture of diastereoisomers was obtained.

The overall 1,2-*syn* selectivity can be explained through chelation with the Boc carbonyl group. It is interesting to note, however, that in the majority of examples an excess of base was used. Under these conditions the secondary amide is also deprotonated, and this metalated species is involved in chelation with the aldehyde, the adjacent Boc carbonyl, and/or the organometallic alkynyl derivative. Surprisingly, addition of HMPA to the reaction mixture (Table 56; entries 1 and 5) made no change in selectivity. Use of a silver/zirconium derivative improved the overall yield but gave the same product ratio as in the case of lithium alone (Table 56; entries 6 and 11).

In the cases where the 2-amino group is fully protected, inversion in selectivity occurs and the 1,2-*anti* product becomes the almost exclusive reaction product (Table 57).

The nitrogen and/or its protecting groups no longer participate in chelation, and the steric hindrance created in position 2 causes alkynyl addition to occur according to the Felkin−Anh model to give excellent 1,2-*anti* induction. In entry 5, the tosyl (Ts) group could potentially participate in chelation, but in light of the excellent reported selectivity, increased electrophilic activation of the aldehyde function is more probable.

In their synthesis of (−)-bestatin, Lee et al. reported a surprising 1,2-*syn* selectivity in the addition of ethynylmagnesium bromide to various monoprotected 2-aminoaldehydes (Table 58).[198]

Table 56. Organometallic Alkynyl Additions to Mono-Boc-Protected 2-Aminoaldehydes

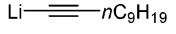
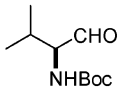
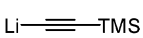
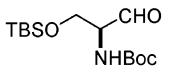
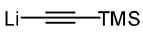
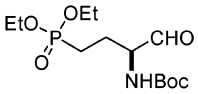
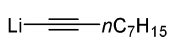
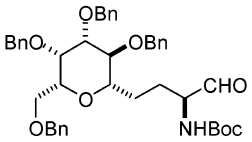
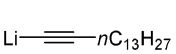
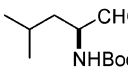
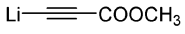
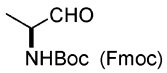
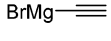
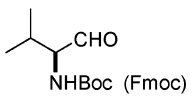
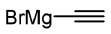
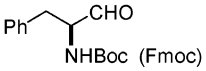
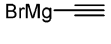
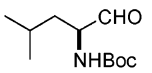
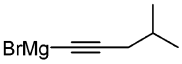
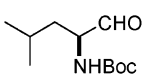
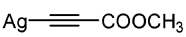
Entry	Aldehyde	Alkyne	Additives	Yield (%)	1,2-*syn* / 1,2-*anti*	Ref
1			HMPA	87	64 / 36	186
2			--	56	55 / 45	187
3			--	31	58 / 42	187
4			--	43	67 / 33	188
5			-- HMPA	65 35	70 / 30 70 / 30	189
6			--	42 38	85 / 15 82 / 18	190 53
7			--	95 89	87 / 13 80 / 20	191
8			--	97 85	83 / 17 81 / 19	191
9			--	93 90	78 / 22 75 / 25	191
10			--	80	67 / 33	192
11			Cp_2ZrCl_2 (1.2 eq) AgOTf (0.2 eq)	59	85 / 15	53

Table 57. Organometallic Alkynyl Additions to Fully Protected 2-Aminoaldehydes

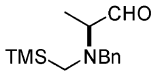
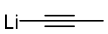
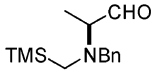
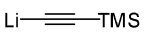
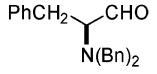
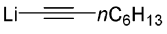
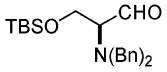
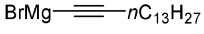
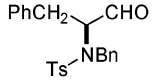
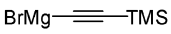
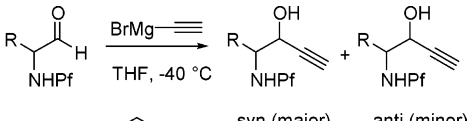
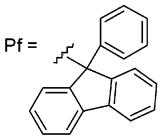
Entry	Aldehyde	Alkyne	Yield (%)	1,2-*syn* / 1,2-*anti*	Ref
1			90	0 / 100	193
2			79	0 / 100	194
3			82	4 / 96	195
4			82	0 / 100	196
5			81	0 / 100	197

Table 58. Ethynylmagnesium Bromide Addition to *N*-9-Phenylfluoren-9-yl-Protected Aldehydes

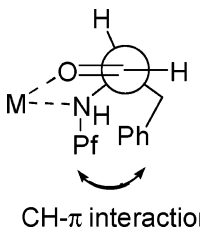




Entry	R	Yield (%)	1,2-*syn* / 1,2-*anti*
1	benzyl (*R*)	96	90 / 10
2	benzyl (*S*)	97	91 / 9
3	4-MPM (*R*)	94	90 / 10
4	4-MPM (*S*)	96	91 / 9
5	4-PNB (*R*)	97	91 / 9
6	4-PNB (*S*)	97	91 / 9
7	2-propyl (*S*)	94	64 / 36
8	*iso*-butyl (*S*)	95	71 / 29
9	Methyl (*S*)	93	69 / 31
10	$BnOCH_2$ (*S*)	94	60 / 40

Although the authors expected good 1,2-*anti* selectivity with the sterically hindered 9-phenylfluoren-9-yl (Pf) nitrogen protecting group, excellent 1,2-*syn* diastereoselectivity was observed with aromatic aminoaldehydes while only average 1,2-*syn* selectivity was seen with the aliphatic ones. A chelation-controlled cyclic transition state was postulated in which CH−π interactions between the aromatic aminoaldehyde and the Pf protecting group also strongly contribute to the excellent 1,2-*syn* diastereoselectivity observed (Chart 5).

Chart 5. Proposed Transition State for Alkynyl Addition with the Pf Protecting Group



^{1}H NMR and X-ray crystallography studies were carried out which further substantiated the proposed transition state.

6.2. Cyclic 2-Aminoaldehydes

Organometallic alkynyl addition to cyclic five-membered 2-aminoaldehydes is presented in Table 59, and no clear-cut tendency toward the 1,2-*syn* or 1,2-*anti* product can be observed.

In most cases, chelation between the aldehyde and the Boc carbonyl function should orient selectivity toward the 1,2-*syn* adduct, but 1,2-*anti* addition is predominant in entries 1 and 2, even with an alkynylmagnesium derivative. Surprisingly, in entry 4, use of a titanium derivative, normally known for inducing 1,2-*anti* additions, gave a majority of 1,2-*syn* addition. In entry 6, the excellent 1,2-*anti* induction observed can be attributed to lack of chelation and increased steric hindrance of the trityl protecting group.

Arndt et al. recently reported a study on alkynyl addition to aldehyde **60** as part of their synthetic studies toward trans−threo−trans oligopyrrolidines (Table 60).[203]

Diastereoselectivity was moderate with a lithium derivative (Table 60; entries 1−3) even in the presence of HMPA, and use of a cerium-based reagent only caused a further drop in selectivity (entry 4). The best 1,2-*anti* selectivity was obtained with an alkynyltitanium derivative, whereas excellent 1,2-*syn* selectivity was achieved with reagent control and use of NME as an external chiral inductor (see section 12 for a more detailed discussion of this reaction).

In the same article an alkynyllithium derivative was then prepared from the major addition product (1,2-*anti*, **61**) and added to aldehyde **60** to give a mixture of alcohols in excellent yield (Scheme 25). The authors noted that the

Scheme 25

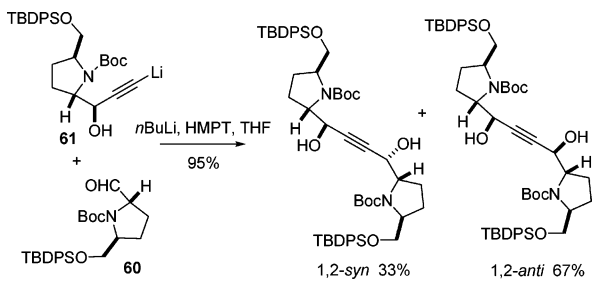


Table 59. Alkynyl Addition to Cyclic 2-Aminoaldehydes

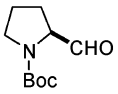
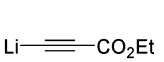
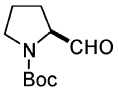
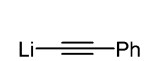
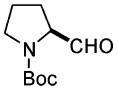
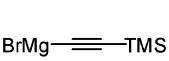
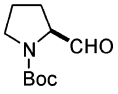
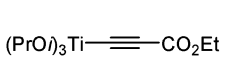
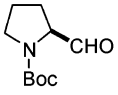
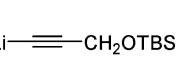
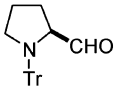
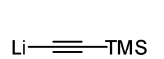
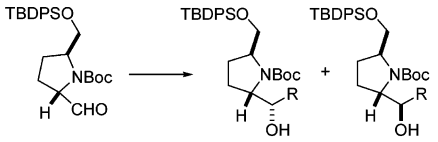
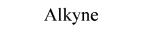
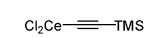
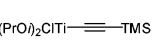
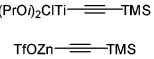
Entry	Aldehyde	Alkyne	Additive	Yield (%)	1,2-*syn* / 1,2-*anti*	Ref
1			--	80	45 / 55	199
			HMPA	78	28 / 72	
2			--	82	50 / 50	10
3			--	91	33 / 67	200
4			--	74	71 / 29	199
5			--	54	88 / 12	201
6			--	88	2 / >98	202

Table 60. Alkynyl Addition to Aldehyde 60



60 1,2-*syn* 1,2-*anti*

Entry	Alkyne	Additive	Yield (%)	1,2-*syn* / 1,2-*anti*
1		--	80	40 / 60
2		HMPA	84	30 / 70
3		--	49	38 / 62
4		--	95	45 / 55
5		--	88	25 / 75
6		NME (1S, 2R)	40	86 / 14
7		NME (1R, 2S)	90	99 / 1

presence of HMPA in the reaction mixture was essential for achieving the observed diastereoselectivity.

7. 3-Aminoaldehydes

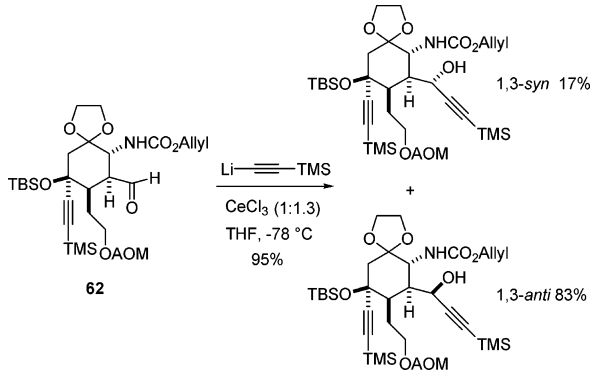
There are few reported examples of organometallic alkynyl addition to 3-aminoaldehydes in the literature. In their total synthesis of (±)-calicheamicinone, Clive et al. used an alkynylcerium reagent, generated from lithium trimethylsilyacetylide, which gave the best yield and selectivity when added to aldehyde **62** (Scheme 26).[204]

In another example using an alkynylcerium reagent, a 1:1 epimeric mixture of products was obtained (Scheme 27).[205] This lack of selectivity is most likely the result of the protected nitrogen function which is unable to participate in chelation.

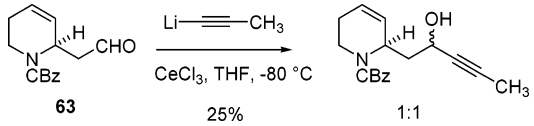
8. 3-Alkoxy-2-aminoaldehydes

Alkynylation of *N*-Boc-*N*-*O*-isopropylidene-L-serinal **64**, more commonly known as the Garner aldehyde, has received

Scheme 26



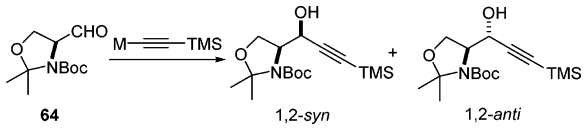
Scheme 27



considerable attention in recent years due to the multitude of activity directed toward the synthesis of sphingosine and ceramide derivatives. Three landmark papers were published in 1988 reporting the synthesis of D-(+)-erythro and L-(−)-threo sphingosine from L-serine.[206−208] In the first paper Herold clearly demonstrated that either 1,2-*syn* or 1,2-*anti* alkynylation of aldehyde **64** was possible simply by changing the reaction conditions and the type of metal used (Table 61). High 1,2-*anti* addition can be achieved with lithium in the presence of HMPA, whereas 1,2-*syn* addition is predominant with alkynylzinc or copper derivatives.

An important solvent effect can be seen with magnesium and zinc (Table 61; entries 8−10). The known chelating ability of these metals is diminished in THF, and the amount of 1,2-*syn* diastereoisomer is substantially increased by simply changing the solvent to diethyl ether (entry 10).

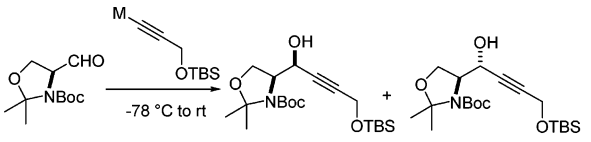
Table 61. Alkyne Addition to Aldehyde 64: Solvent and Metal Effects



64 1,2-*syn* 1,2-*anti*

Entry	Metal	Additive	Solvent	Yield (%)	1,2-*syn* / 1,2-*anti*
1	Li	--	THF	75	11 / 89
2	Li	HMPA	THF	85	5 / 95
3	Li	18-Crown-6	THF	70	7 / 93
4	Li	TMEDA	THF	75	9 / 91
5	Li	$ClTi(i\text{-}OPr)_3$	THF	90	25 / 75
6	Li	$ClZr(OBu)_3$	THF	90	8 / 92
7	Li	$ZnBr_2$	Et_2O	89	92 / 8
8	BrMg	--	THF	78	12 / 88
9	BrMg	$ZnBr_2$	THF	90	29 / 71
10	BrMg	$ZnBr_2$	Et_2O	89	85 / 15
11	BrMg	CuI	THF/SMe_2	86	95 / 5

Table 62. Alkyne Addition to Aldehyde 64: Solvent and Metal effects



64 1,2-*syn* 1,2-*anti*

Entry	Metal	Additive	Solvent	Yield (%)	1,2-*syn* / 1,2-*anti*
1	Li	-	Toluene	80	26 / 74
2	Li	-	Toluene[a]	75	40 / 60
3	Li	HMPA	Toluene	85	5 / >95
4	Li	$BF_3.Et_2O$	Toluene	60	85 / 15
5	Li	$MgBr_2.Et_2O$	$Toluene/Et_2O$	49	80 / 20
6	Li	Et_2AlCl	Toluene	56	21 / 79
7	Li	$EtAlCl_2$	Toluene	45	23 / 77
8	Li	$ZnCl_2$	$Toluene/Et_2O$	65	91 / 9
9	Li	$SnCl_4$	Toluene	46	>95 / 5

[a] Reaction performed at room temperature.

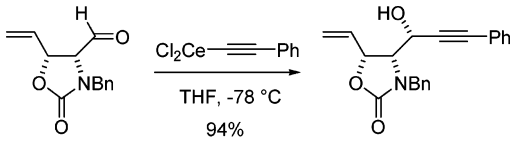
A similar alkynylation study with the Garner aldehyde was carried out almost 10 years later with a *tert*-butyldimethylsilylpropargyl ether by Gruza et al.,[209] which further confirmed the results reported by Herold (Table 62). While use of lithium was less selective when performed in toluene alone as compared to THF (vide supra), simple addition of HMPA in the reaction mixture led to excellent 1,2-*anti* selectivity. Increased 1,2-*syn* selectivity was observed when either boron trifluoride etherate was added to the reaction mixture or an alkynylmagnesium derivative was used. Alkynylzinc and tin derivatives gave the best 1,2-*syn* selectivity, albeit in lower yield as compared to reactions carried out in diethyl ether alone.

The transition states for nucleophilic additions to the Garner aldehyde are well documented in the literature,[2b] and it is clear that in a nonchelating environment the Felkin−Ahn approach is favored to give the 1,2-*anti* product. When chelation does occur with either the adjacent nitrogen or the Boc carbonyl, reaction stereoselectivity is inverted with the 1,2-*syn* isomer becoming the major reaction product.

All of the following examples in the literature follow the "general" reactivity rules presented above. Tables 63 and 64 are compilations of alkynyl additions to the Garner aldehyde, and close inspection shows that, in general, the reactivity of this 2-amino-3-alkoxyaldehyde follows that of a simple 2-alkoxyaldehyde.

Alkynyl additions to other 3-alkoxy-2-aminoaldehydes have also been reported in the literature. As part of a highly diastereoselective synthesis of 1,2-amino alcohols, Wee and Tang described the addition of an alkynylcerium derivative to the 4-oxazolidinone carboxaldehyde **65** which gave excellent 1,2-selectivity (Scheme 28).[237]

Scheme 28

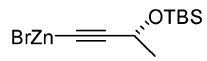


65 > 99 (syn) / 1 (anti)

The authors explained that observed selectivity was not a result of chelation control but rather introduction of the alkynyl nucleophile from the less hindered face of the preferred transition state as depicted in Chart 6.

As part of their synthetic studies on pactamycin, Tsujimoto et al. reported addition of lithium trimethylsilylacetylide to aldehyde **66** (Scheme 29).[238] The authors stated that the observed selectivity resulted from 1,3-chelation with the

Table 63. Alkynyl Addition to the (*S*)-Garner Aldehyde: Preferential 1,2-*Syn* Selectivity

Entry	Alkyne	additive	Yield (%)	1,2-*syn* / 1,2-*anti*	Ref
1[a]	BrMg—≡—TMS	CuI	>80	100 / 0	210
2	BrZn—≡—*n*Bu	--	95	95 / 5	211
3	BrZn—≡—C_7H_{15}	--	64	90 / 10	212
4	BrZn—≡—$C_{13}H_{27}$	--	87	95 / 5	206
5	BrZn—≡—Ph	--	80	94 / 6	212a, 212c
6		--	86	90 / 10	213

[a] (*R*)-Garner aldehyde.

Table 64. Alkynyl Addition to the (*S*)-Garner Aldehyde: Preferential 1,2-*Anti* Selectivity

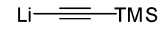
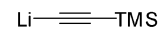
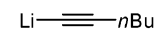
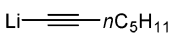
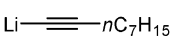
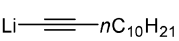
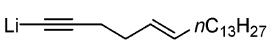
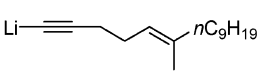
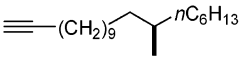
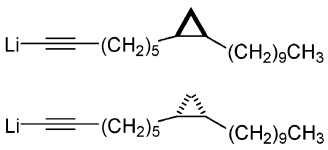
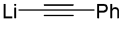
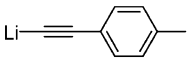
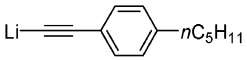
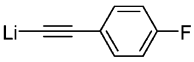
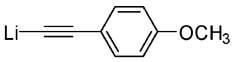
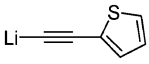
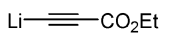
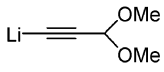
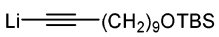
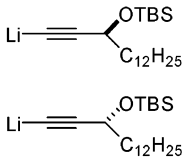
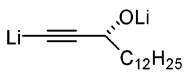
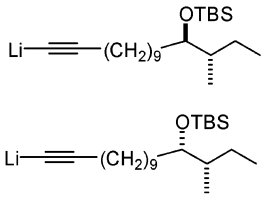
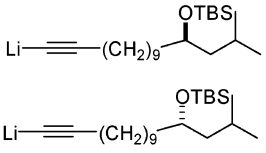
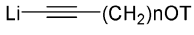
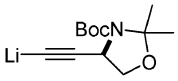
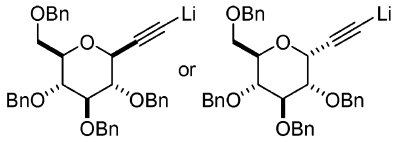
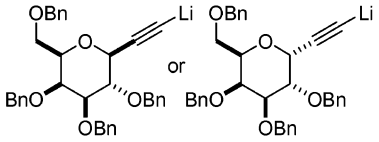
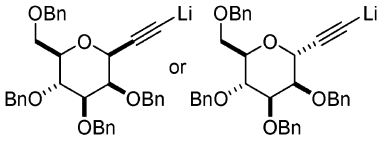
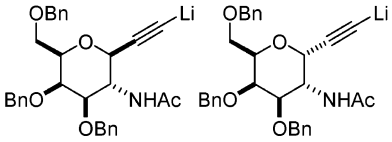
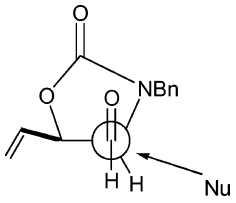
Entry	Alkyne	additive	Yield (%)	1,2-*syn* / 1,2-*anti*	Ref
1[a]		HMPA	>80	0 / 100	210
2		HMPA	88	0 / 100	214
3		HMPA	85	14 / 86	211
4		--	80	9 / 90	215, 216
5		HMPA	84	0 / 100	212
6		--	85	0 / 100	217
7		HMPA	71	5 / 95	206-208, 215, 216, 218, 219
8		--	49	4 / 96	220
9		--	85	0 / 100	221
10		--	75	0 / 100	222
11		HMPA	80 85	0 / 100	223
12		HMPA	84	10 / 90	212
13		HMPA	70	0 / 100	224
14		HMPA	76	0 / 100	224
15		HMPA	89	0 / 100	224
16		HMPA	23	0 / 100	224
17		HMPA	91	0 / 100	224
18[a]		HMPA	75	7 / 93	225
19		--	87	11 / 89	225a
20		HMPA	67	1 / >99	226
21		HMPA	87 78	5 / 95 0 / 100	227
22		--	nd	19 / 81	228

Table 64. (Continued)

Entry	Alkyne	additive	Yield (%)	1,2-*syn* / 1,2-*anti*	Ref
23		--	94	0 / 100	229,230
24		--	80	0 / 100	230
25		HMPA	n=3,10; nd	5 / >95	231
			n=12; 67	0 / 100	232,233
			n=13 ; 59	0 / 100	234
26		--	62	nd[b]	235
27[a]		--	68, 68	≈ 25 / 75 → 20 / 80	236
28[a]		--	56,58	≈ 25 / 75 → 20 / 80	236
29[a]		--	55,45	≈ 25 / 75 → 20 / 80	236
30[a]		--	75,52	≈ 25 / 75 → 20 / 80	236

[a] (*R*)-Garner aldehyde. [b] A 5/1 mixture of diastereoisomers was obtained with no further stereochemical information.

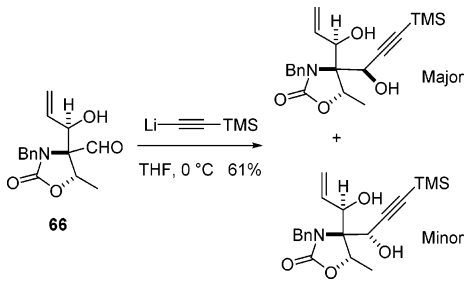
Chart 6



deprotonated hydroxyl group and addition of the alkynyl reagent from the less hindered side to give the (*R*)-alcohol as the major reaction product.

Guanti et al. reported addition of lithium trimethylsilylacetylide to two unusual diastereoisomeric 3-alkoxy-2-aminoaldehydes (**67**, **68**) in which reaction selectivity was dependent on the configuration of the starting aldehyde (Table 65).[239]

Scheme 29



In each case the observed diastereoselectivity can be explained by both the different chair transition states adopted by the starting aldehyde and chelation between the aldehyde and the Boc protecting group followed by attack on the less hindered face of the aldehyde (Chart 7).

Table 65. Alkynyllithium Addition to Aldehydes 67 and 68

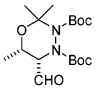
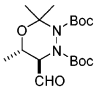
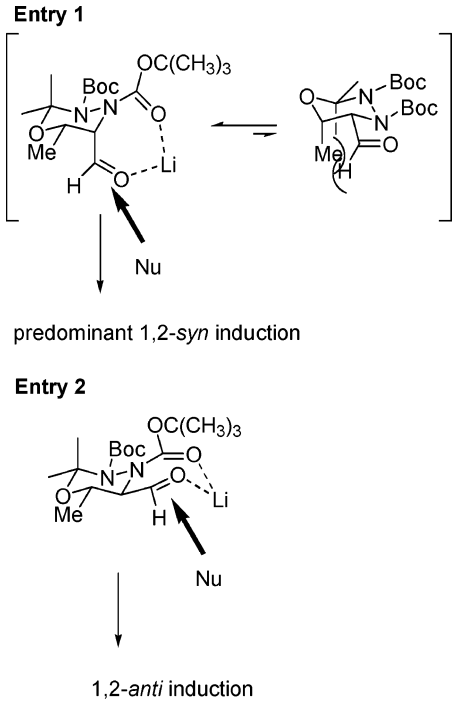
Entry	Aldehyde	Reaction conditions	Yield (%)	1,2-*syn* / 1,2-*anti*
1	 **67**	LiC≡CTMS, THF	70	64 / 36
		LiC≡CTMS, THF/HMPA	78	69 / 31
2	 **68**	LiC≡CTMS, THF	62	7 / 93

Chart 7



8.1. 4-Oxoazetidine-2-carboxaldehydes

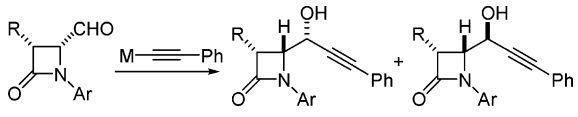
Alkynyl addition to 4-oxoazetidine-2-carboxaldehydes has been an effective strategy used by several groups to gain access to fused bicyclic β-lactams as well as highly functionalized γ-lactams. The unique structure of these aldehydes confers a reactivity which is difficult to compare with other 2-aminoaldehydes, especially when an alkoxy group is in position 3 of the β-lactam. When this occurs, the aldehyde is both a "2-amino" and a "3-alkoxy" simultaneously, and all of the different possible transition states must be considered to explain reaction selectivity.

In a first series of examples Turos et al. reported addition of lithium or magnesium phenylacetylide to a 3-substituted-4-oxoazetidine-2-carboxaldehyde (Table 66).[240,241]

While reaction diastereoselectivity was not exceptional in the case of the lithium derivative, use of the corresponding magnesium one gave exclusive 1,2-*syn* induction in moderate yield. More recently, Alcaide et al. explored acetylene addition to a variety of different 3-alkoxy-4-oxoazetidine-2-carboxaldehydes (Table 67).[242]

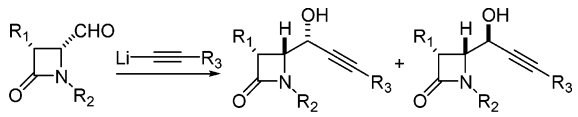
The authors tentatively explained the excellent 1,2-*syn* diastereoselectivity observed by Felkin−Anh approach of the incoming acetylide from the less hindered face (Chart 8). It should be noted that this is also the preferred transition state when chelation is involved, both models leading to the same diastereoisomer.

Table 66. Phenylacetylide Addition to 3-Alkoxy- and 3-Amino-4-oxoazetidine-2-carboxaldehydes



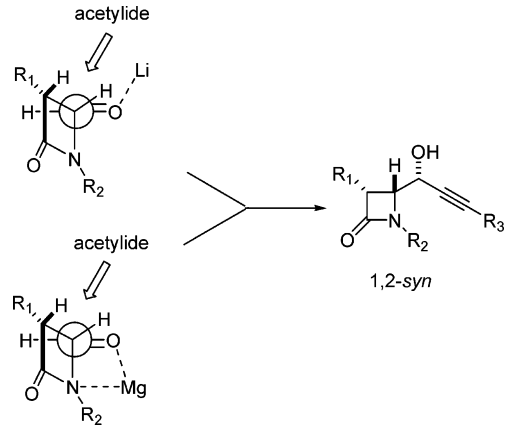
Entry	R	Metal	Yield (%)	1,2-*syn* / 1,2-*anti*
1	PhtN	Li—≡—Ph	69	67 / 33
2	CH_3O	Li—≡—Ph	55	83 / 17
3	PhtN	BrMg—≡—Ph	> 68	100 / 0
4	CH_3O	BrMg—≡—Ph	> 55	100 / 0

Table 67. Alkynyl Addition to Various 4-Oxoazetidine-2-carboxaldehydes



Entry	R_1	R_2	R_3	Yield (%)	1,2-*syn* / 1,2-*anti*
1	PhO	PMP	Ph	79	100 / 0
2	PhO	PMP	TMS	81	100 / 0
3	PhO	allyl	Ph	66	100 / 0
4	PhO	allyl	TMS	70	100 / 0
5	BnO	PMP	Ph	77	100 / 0
6	MeO	PMP	Ph	64	100 / 0
7	MeO	PMP	TMS	56	100 / 0
8	MeO	3-butenyl	Ph	54	70 / 30
9	MeO	3-butenyl	TMS	42	70 / 30

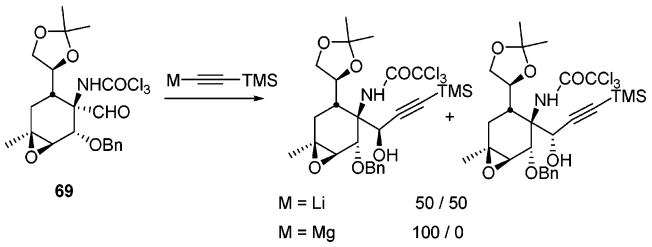
Chart 8. Felkin−Anh and Chelation-Controlled Transition States for Addition to 4-Oxoazetidine-2-carboxaldehydes



8.2. 1-Aminocyclohexane Carboxaldehydes: Tetrodotoxin and Analogs

Another example of alkynyl addition to several unusual 3-alkoxy-2-aminoaldehydes was reported by Isobe et al. in their syntheses of tetrodotoxin and various analogues from complex 1-amino-cyclohexane carboxaldehydes. Although the additions in themselves were relatively straightforward, the diastereoselectivity of the reaction varied immensely with minor changes in substrate. The focus of this discussion is to try to explain these differences by taking a closer look at the different possible transition states.

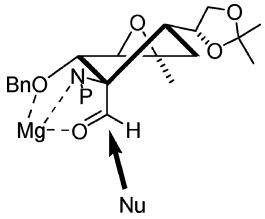
Scheme 30



In the first example, as part of the synthesis of (−)-5,11-dideoxytetrodotoxin,[243] reaction of lithium trimethylsilylacetylide with the aminocarboxaldehyde **69** was totally unselective. Use of the corresponding magnesium derivative, a more efficient chelating agent, gave only one product in good yield (Scheme 30).

These results can be explained by looking at the preferred conformation of the cyclohexane ring (Chart 9). All of the

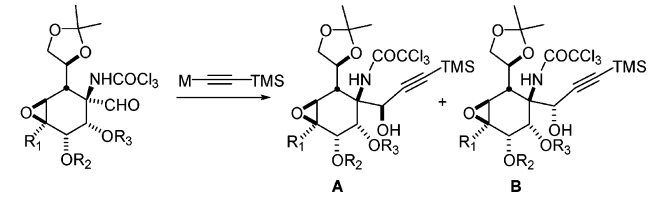
Chart 9



bulkier groups are in a pseudoequatorial position, and the magnesium efficiently chelates with the oxygen in position 2, the amide, and the aldehyde function.

In their stereocontrolled synthesis of 8,11-dideoxytetrodotoxin,[244] 11-deoxytetrodotoxin,[245] and optically active tetrodotoxin,[246] three almost identical aminoaldehydes were used, differing only in the absence or presence of protected hydroxyl groups in positions 2, 3, and 4 of the cyclohexane ring. The reaction was only completely stereoselective in entry 1 (Table 68). In entry 5, the opposite diastereoselectivity was observed in the major reaction product.

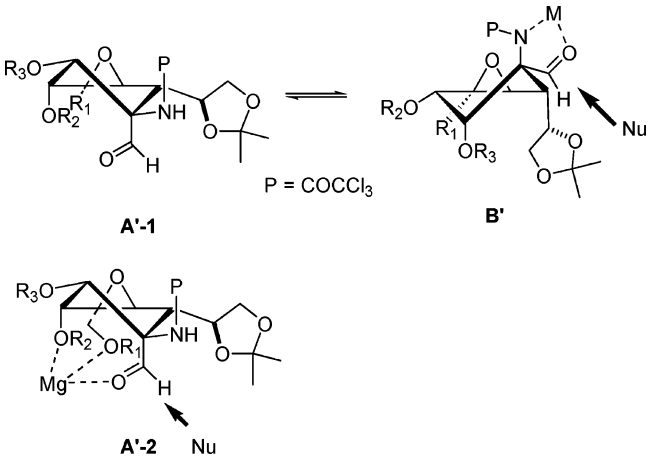
Table 68. Alkynyl Addition to Differently Protected 1-Amino-cyclohexane Carboxaldehydes



Entry	R_1	R_2	R_3	Metal	Yield (%)	**A / B**
1	CH_3	TMS	H	Li	>71	0 / 100
2	CH_3	TMS	H	Mg	nd	20 / 80
3	CH_3	TMS	TMS	Li	nd	37 / 63
4	CH_3	TMS	TMS	Mg	80	15 / 85
5	CH_2OTES	TES	TES	Mg	88	80 / 20

The preferred conformation for the cyclohexane ring when $R_1 = CH_3$ and $R_3 = H$ places the bulky OTMS group in a pseudoequatorial position (Chart 10, **B′**). Nucleophilic attack would then occur from the less hindered face of the molecule to give diastereoisomer **B**. When $R_1 = CH_3$ and R_2 and R_3 = OTMS, there is no longer one preferred conformation

Chart 10. Proposed Transition States for Alkynyl Addition

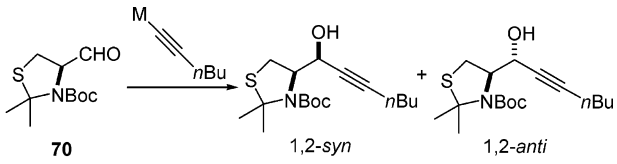


because of the two sterically hindered silyl groups and selectivity drops (Table 68; entries 3 and 4). In entry 5, **A′-2** can be considered the preferred conformer because of the presence of an additional hydroxyl group in position 4 and the possibility of better chelation with magnesium. Nucleophilic attack then occurs from the less hindered side of the molecule to give diastereoisomer **A** preferentially.

8.3. 2-Amino-3-thio-substituted Aldehydes

The "thio" version of the Garner aldehyde **70** has also been used in asymmetric synthesis with results that are essentially identical to the corresponding oxygenated series. Fujisawa et al. used this aldehyde as a chiral precursor in their synthesis of (+)-deoxybiotin (Table 69).[211] Once again,

Table 69. Alkynyllithium or Alkynylzinc Addition to Aldehyde 70



metal	solvent	additive	Yield (%)	1,2-*syn* / 1,2-*anti*
Li	THF	--	88	40 / 60
Li	THF	HMPA	71	17 / 83
BrZn	Et_2O	--	48	95 / 5
ClZn	Et_2O	--	86	>99 / 1

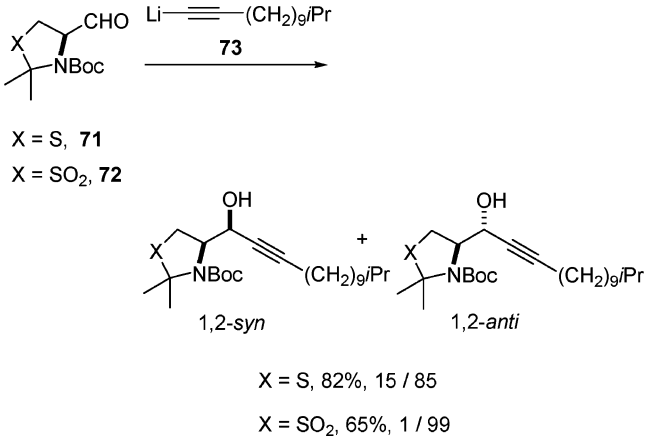
good to excellent 1,2-*syn* or 1,2-*anti* selectivity was obtained depending on the organometallic reagent and reaction conditions used.

In the synthesis of sulfobacin A and B, Mori et al. reported addition of the lithium acetylide **73** to aldehyde **71** and its fully oxidized counterpart **72** (Scheme 31).[247] Good to excellent 1,2-*anti* selectivity was achieved in both cases.

9. 2-Alkoxy-3-aminoaldehydes

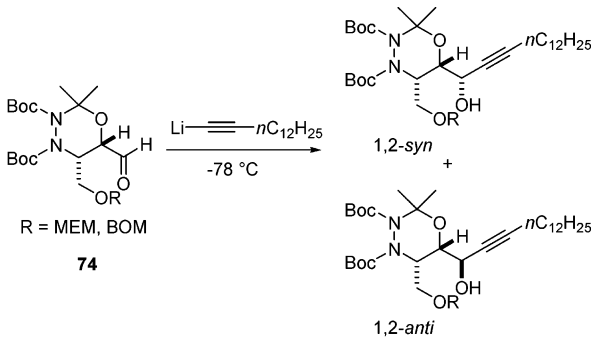
Reaction diastereoselectivity in organometallic alkynyl addition to 2-alkoxy-3-aminoaldehydes is highly substrate dependent, and there is no set rule to predict the major reaction product.

Scheme 31



In a first example, alkynyllithium addition to aldehyde **74**, a synthon in the synthesis of D-ribo-C_{18}-phytosphingosine, proceeded in moderate to good selectivity depending on the absence or presence of HMPA in the reaction mixture (Table 70).[248]

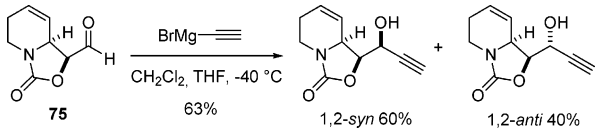
Table 70



R	Solvent	Yield (%)	1,2-*syn* / 1,2-*anti*
MEM	THF	69	26 / 74
MEM	THF/HMPA	71	15 / 85
BOM	THF	75	23 / 77
BOM	THF/HMPA	71	15 / 85

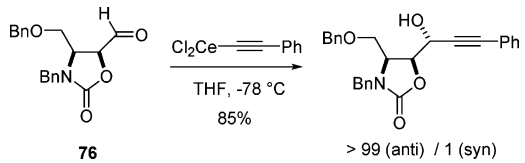
In a second example, ethynylmagnesium bromide was added to the 2-alkoxy-3-aminoaldehyde **75** to give a majority of the 1,2-*syn* addition product (Scheme 32).[249]

Scheme 32



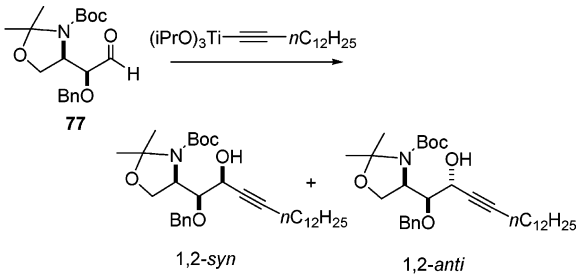
Excellent selectivity was reported by Wee and Tang involving alkynylcerium addition to the 5-oxazolidinone carboxaldehyde **76** (Scheme 33).[237] The 1,2-*anti* diastereoselectivity was explained as being the result of a controlled addition through formation of a seven-membered cerium(III) chelate.

Scheme 33



Shimizu et al. reported a very interesting study with the 2-alkoxy-3-aminoaldehyde **77** where excellent 1,2-*anti* selectivity was achieved with titanium derivatives (Table 71).[250]

Table 71. Alkynyl Addition to Aminoaldehyde 77

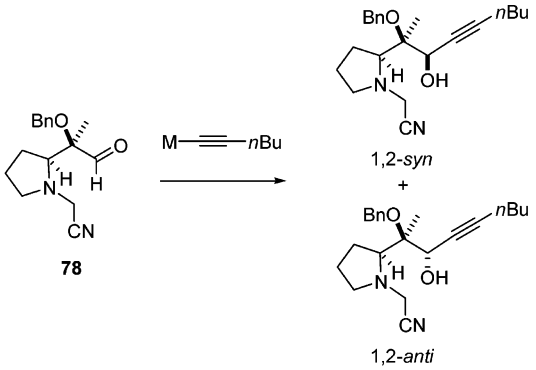


Temperature	Yield (%)	1,2-*syn* / 1,2-*anti*
-78 °C → 23 °C	94	14 / 86
-100 °C → 23 °C	90	7 / 93
-105 °C → 23 °C	93	5 / 95
-110 °C → 23 °C	40	<1 / >99

Lowering the temperature substantially increased reaction selectivity in favor of the 1,2-*anti* isomer but was, however, detrimental to the product yield.

Overman et al. reported addition of various alkynyl derivatives to the 2-alkoxy-3-aminoaldehyde **78** in their synthesis of allopumiliotoxins (Table 72).[251,252] The cya-

Table 72. Alkynyl Addition to the 2-Alkoxy-3-aminoaldehyde 78



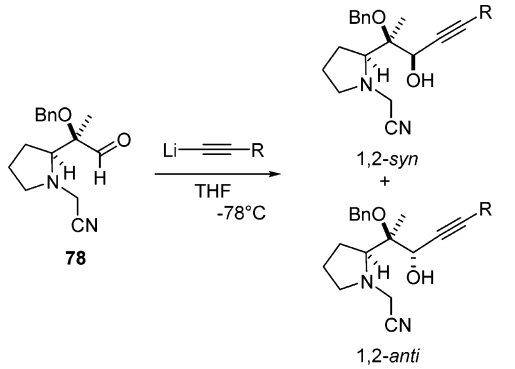
Reaction conditions	Yield (%)	1,2-*syn* / 1,2-*anti*
$ZnBr_2$, Et_2O, -78°C	nd	no reaction
$ZnBr_2$, Et_2O/THF (15:1), -78°C	nd	no reaction
M = Cl_2Ce, THF, -78°C	nd	no reaction
M = Li, THF, -78 °C	85	76 / 24
M = Li, Et_2O, -20°C	90	69 / 31
M = Li, toluene, -40°C	86	50 / 50
M = Li, nC_6H_{14}, -40°C	81	69 / 31
M = BrMg, THF, -78°C	61	64 / 36
M = $(OiPr)_3Ti$, THF, -50 °C	80	>91 / 9

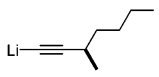
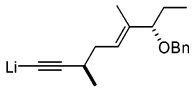
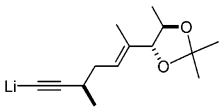
nomethyl protecting group was chosen to disfavor competitive chelation of the carbonyl oxygen and the pyrrolidine nitrogen during the metal acetylide addition step.

In a model study using a 1-hexynylmetal compound, use of zinc or cerium gave no reaction (Table 72). Overall 1,2-*syn* addition was observed in the case of lithium and magnesium and explained through 1,2-chelation. Surprisingly, the best results were achieved with titanium, giving 1,2-*syn* addition with greater than 90% selectivity. This selectivity is difficult to explain as titanium normally orients toward the *anti* adducts. The cyanomethyl protecting group may have an influence on reaction stereoselectivity.

When titanium addition was performed with more elaborate alkynyl side chains the stereoselectivity was markedly reduced. As a result, the corresponding lithium derivatives were used giving the 1,2-*syn* diastereoisomers as the major reaction products with moderate to good diastereoselectivity (Table 73).

Table 73. Addition of Lithium Alkynyl Derivatives to Aldehyde 78



R	Yield (%)	1,2-*syn* / 1,2-*anti*
	41	74 / 26
	71	75 / 25
	85	80 / 20

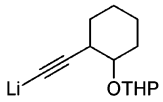
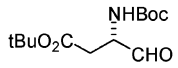
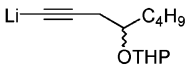
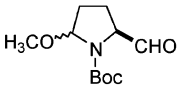
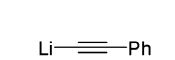
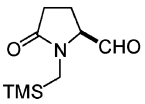
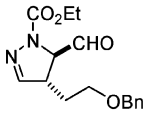
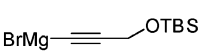
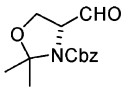
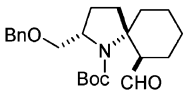
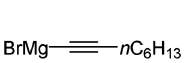
10. Miscellaneous Alkynyl Addition to Cyclic and Linear Amino and Alkoxyaminoaldehydes

A compilation of alkynyl additions to amino and alkoxyaminoaldehydes is shown in Table 74.

11. Alkynyl Halide Addition to Alkoxyaldehydes

Only a few examples exist in the literature where an alkynyl halide was directly added to an alkoxyaldehyde via a nickel(II)/chromium(II) mediated coupling reaction (Table 75). Organochromium species are known for their highly nucleophilic but weakly basic character. In general, reaction conditions are very mild and allow the use of highly functionalized coupling partners. Unfortunately, the majority of the reported inductions are low except for entry 6, where good 1,2-*syn* selectivity was observed.

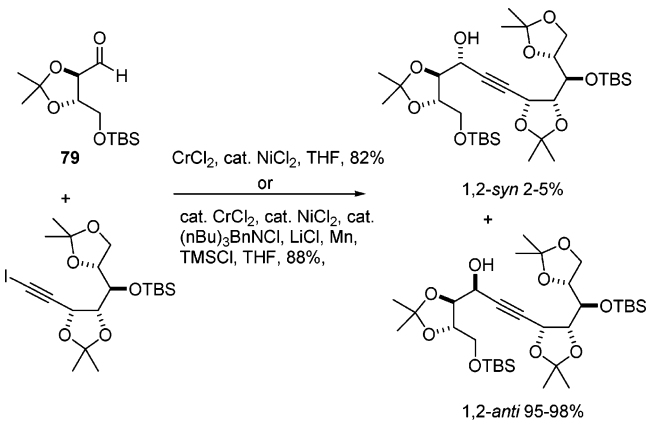
Table 74. Miscellaneous Alkynyl Addition to Amino and Alkoxyaminoaldehydes

Aldehyde	Alkyne	Yield (%)	Ref
		69	253
		67	253
		90	254
		63[a]	193
		>68	255
	 X = Cl, Br	88	256
		88	257

[a] An undetermined 4.5:1 mixture of diastereoisomers was obtained.

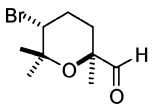
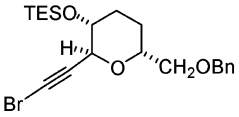
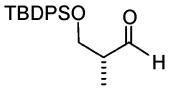
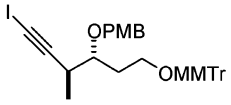
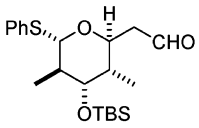
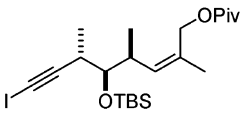
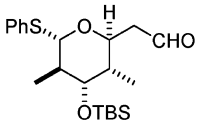
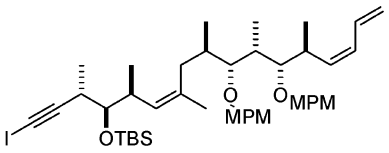
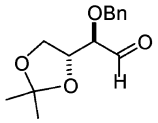
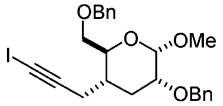
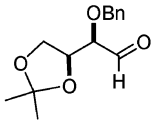
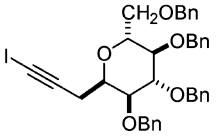
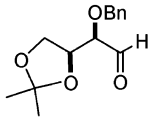
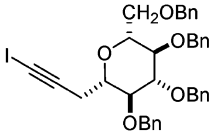
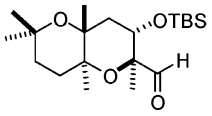
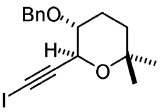
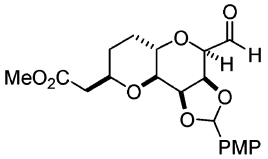
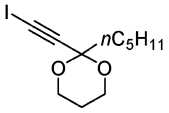
In a recent article a highly efficient nickel/chromium coupling was reported by Fürstner and Wuchrer in their synthesis of the nucleoside antibiotic hikizimycin (Scheme 34).[265] The authors explained that the observed diastereoselectivity was expected in the case of chiral aldehydes having polar substituents α and/or β to the carbonyl group; as a result, the alkynyl halide addition followed a nonchelation-controlled pathway.

Scheme 34



The reaction was performed using traditional methods with a large excess of $CrCl_2$ (de > 95%) as well as with the process developed by the authors (de ≈ 90%) in which only catalytic amounts of the chromium salts are necessary and

Table 75. Addition of Alkynyl Halides to Chiral Alkoxy Aldehydes

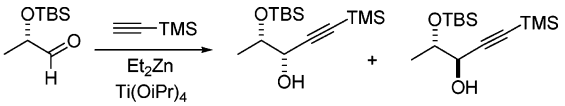
Entry	Aldehyde	Alkynyl halide	Yield	1,2-*syn* / 1,2-*anti*	Ref
1			75	nd	258
2			75-90	50 / 50	259
3			65	25 / 75 (1,3-*syn*/1,3-*anti*)	260
4			65	33 / 67	260
5			74	67 / 33	261
6			72	80 / 20	262
7			65	50 / 50	262
8	 racemic		nd	Two diastereoisomers out of four possible	263
9			65	89 / 11	264

recycled in the reaction mixture by the redox couple of Mn powder and TMSCl.

12. Alkynylation with the Addition of an External Chiral Inductor

In the sections that follow zinc is the metal of choice for all alkynylation reactions performed in the presence of an external chiral inductor. The subject of asymmetric alkynyl zinc additions to aldehydes and ketones has been treated in several recent reviews by Pu[266] and Cozzi et al.[267] We wish to specifically develop this subject for chiral alkoxy aldehydes and present the latest data in this area.

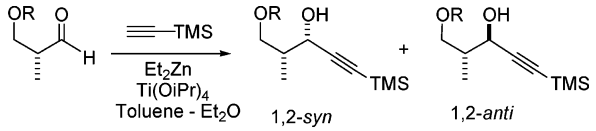
Table 76. Alkynyl Addition to Aldehyde 80 Catalyzed by a Ti(O*i*Pr)$_4$−BINOL Complex



80 1,2-*syn* 1,2-*anti*

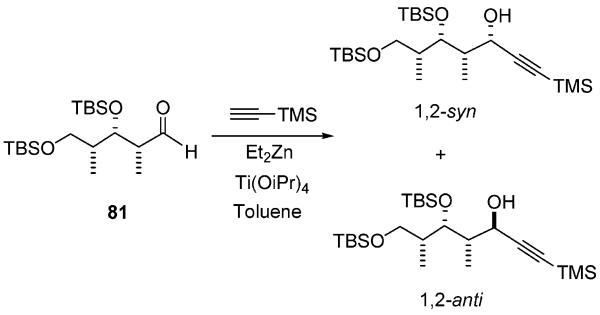
Conditions	Yield (%)	1,2-*syn* / 1,2-*anti*
No chiral inductor	45	15 / 85
(*S*)-BINOL	55	55 / 45
(*R*)-BINOL	60	8 / 92

Table 77. Ti(O*i*Pr)$_4$−BINOL-Catalyzed Addition to Chiral 3-Alkoxyaldehydes

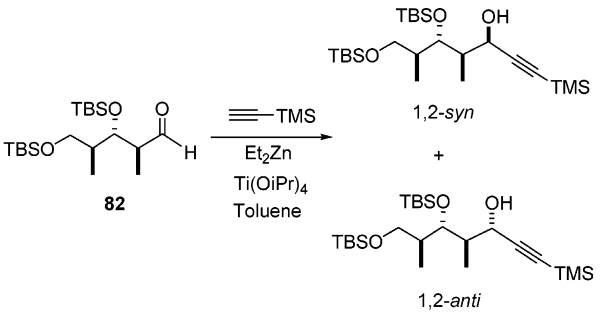


R	Conditions	Yield (%)	1,2-*syn* / 1,2-*anti*
TBS	No chiral inductor	45	60 / 40
TBS	(*S*)-BINOL	73	10 / 90
TBS	(*R*)-BINOL	67	95 / 5
MPM	(*S*)-BINOL	73	15 / 85
MPM	(*R*)-BINOL	63	88 / 12

Table 78. Ti(O*i*Pr)$_4$−BINOL-Catalyzed Addition to 3-Alkoxyaldehydes 81 and 82



Conditions	Yield (%)	1,2-*syn* / 1,2-*anti*
No chiral inductor	56	67 / 33
(*R*)-BINOL	85	88 / 12



Conditions	Yield (%)	1,2-*syn* / 1,2-*anti*
No chiral inductor	71	45 / 55
(*S*)-BINOL	59	75 / 25
(*R*)-BINOL	59	15 / 85

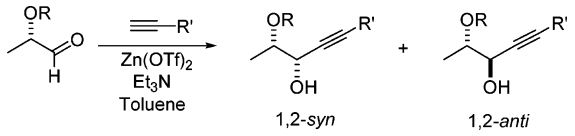
12.1. Binaphthol-type Ligands

Marshall and Bourbeau recently reported the synthesis of enantioenriched propargylic alcohols catalyzed by a Ti(O*i*Pr)$_4$–BINOL complex.[268] Their results showed that additions of trimethylsilylacetylide to chiral 2-alkoxyaldehydes were diastereoselective but substrate dependent. The best selectivity was obtained in the "matched" cases in which the Ti(O*i*Pr)$_4$–BINOL complex oriented the alkynyl addition toward the same product as that observed in the absence of an external ligand. For example, in the simple case of the lactic aldehyde **80**, the 1,2-*anti* addition product is favored when no external ligand is present, consistent with a Felkin−Anh transition state (Table 76). Addition of the Ti(O*i*Pr)$_4$−(*R*)-BINOLcomplex further improved the selectivity in favor of the 1,2-*anti* isomer, thus showing a "matched" effect.

When the same reaction conditions were applied to simple chiral 3-alkoxyaldehydes, excellent 1,2-*syn* or 1,2-*anti* diastereoselectivities could be obtained with either (*S*)- or (*R*)-BINOL (Table 77).

Additions to more complex aldehydes proved to be less selective, even in cases where a matched effect was expected to give excellent diastereoselectivity (Table 78).

Table 79. Alkynyl Zinc Addition Catalyzed by (1*R*,2*S*)- or (1*S*,2*R*)-*N*-Methyl Ephedrine



Entry	R	R'	NME	Yield (%)	1,2-*syn* / 1,2-*anti*	Ref
1	TBS	CH_2OAc	(1*R*,2*S*)	69	9 / 91	272
2	TBS	CH_2OAc	(1*S*,2*R*)	70	96 / 4	272
3	TBS	CH_2OBn	(1*R*,2*S*)	92	20 / 80	273
2	TBS	CH_2OBn	(1*S*,2*R*)	86	92 / 8	273
3	TES	CH_2OBn	(1*R*,2*S*)	52	31 / 69	273
4	TES	CH_2OBn	(1*S*,2*R*)	82	80 / 20	273
5	TIPS	CH_2OBn	(1*R*,2*S*)	79	47 / 53	273
6	TIPS	CH_2OBn	(1*S*,2*R*)	76	82 / 18	273
7	Bn	CH_2OBn	(1*R*,2*S*)	85	39 / 61	273
8	Bn	CH_2OBn	(1*S*,2*R*)	85	76 / 24	273
9	MEM	CH_2OBn	(1*R*,2*S*)	70	41 / 59	273
10	MEM	CH_2OBn	(1*S*,2*R*)	58	81 / 19	273
11	MPM	*n*Bu	(1*S*,2*R*)	84	> 97 / < 3	39

12.2. *N*-Methyl Ephedrine (NME)

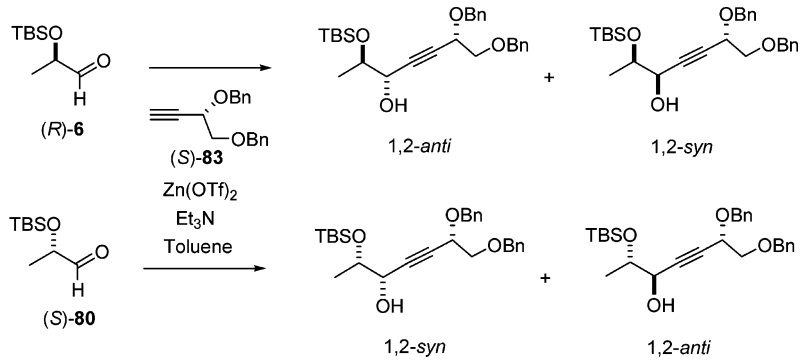
The principle of an external chiral additive was also developed by Carreira and co-workers for the synthesis of optically active propargylic alcohols via direct enantioselective addition of terminal alkynes to aldehydes.[269−271] Their procedure, using zinc trifluoromethanesulfonate, triethylamine, and *N*-methyl ephedrine, has proven to be extremely efficient and is largely illustrated in the literature.

Carreira et al. first reported addition of an alkynyl zinc reagent to a simple chiral 2-alkoxyaldehyde (Table 79, entry 1).[272] Their initial results indicated that the stereochemical outcome is reagent and not substrate controlled, as excellent *opposite* selectivities were achieved using (1*R*,2*S*)- or (1*S*,2*R*)-*N*-methyl ephedrine. This was further confirmed by the work of Kojima et al. with several differently protected aldehydes (Table 79; entries 3−10).[273]

The results in Table 79 indicate that, in general, addition of (1*R*,2*S*)-*N*-methyl ephedrine favors formation of a secondary alcohol with an *R* configuration and that (1*S*,2*R*)-*N*-methyl ephedrine favors formation of the *S* alcohol.

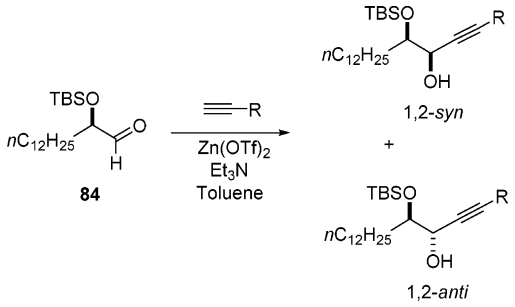
Maezaki et al. used this reaction extensively in their synthetic studies toward *Annonaceous* acetogenins.[273−275] They showed that for these particular substrates the chirality of the aldehyde and/or the alkyne had little to no influence

Table 80. Terminal Alkynyl Addition to (*R*)-Aldehyde 6 and (*S*)-Aldehyde 80



Aldehyde	NME	Yield (%)	1,2-*syn* / 1,2-*anti*
(*R*)-**6**	(1*R*,2*S*)	66	92 / 8
	(1*S*,2*R*)	25	27 / 73
(*S*)-**80**	(1*R*,2*S*)	58	16 / 84
	(1*S*,2*R*)	15	61 / 39

Table 81. NME-Catalyzed Alkynyl Addition to Aldehyde 84



Entry	R	NME	Yield (%)	1,2-*syn* / 1,2-*anti*
1	CH_2OBn	(1*R*,2*S*)	54	>97 / <3
		(1*S*,2*R*)	25	36 / 64
2		(1*R*,2*S*)	trace	nd
		(1*S*,2*R*)	trace	nd
3		(1*R*,2*S*)	93	>97 / <3
		(1*S*,2*R*)	43	15 / 85
4		(1*R*,2*S*)	74	>97 / <3
5		(1*R*,2*S*)	86	95 / 5
6		(1*R*,2*S*)	96	>97 / <3
		(1*S*,2*R*)	Quant	6 / 94

on the stereochemistry of the addition product. Combination of the (*S*)-alkyne **83** with the (*R*)-aldehyde **6** provided better yield and selectivity than the corresponding combination of the (*S*)-alkyne **83** and the (*S*)-aldehyde **80** (Table 80).

The same authors then explored asymmetric alkynylation with the long chain aldehyde **84** (Table 81). The sluggish reaction of the dibenzyl alkyne derivative (entry 2) led to a change in protecting groups. The benzylidene acetal was found to give the best yield and selectivity, even when a mixture of the endo and exo acetals was used (Table 81, entry 6).

The resulting propargylic alcohols were then transformed into the corresponding THF cores frequently found in natural acetogenins. Subsequent asymmetric alkynylation of these aldehydes with trimethylsilylacetylide then gave access to eight diastereoisomeric isomers with predictable selectivity simply by changing the chiral ligand (Table 82). Use of a more elaborate alkyne (Table 82; entry 5) gave the same stereochemical outcome as with trimethylsilylacetylene in excellent yield.

Only one example was found in the literature in which Carreira's alkynyl addition method was used with a 2-aminoaldehyde (Table 83).[203] Predicting reaction selectivity was not as straightforward as with a 2-alkoxyaldehyde. Apparently, chelation of the zinc ion with aminoaldehyde **60** is extremely efficient, and the authors found that changing the chiral auxiliary did not change the stereochemical outcome of the reaction.

Finally, a few last examples show that this reaction is applicable to other aldehyde and alkyne substrates in an overall high yielding and a selective manner (Table 84).

13. Conclusion

As can be seen by the numerous literature examples dealing with organometallic alkynyl addition to chiral 2- and/or 3-alkoxy-, amino-, and thio-substituted aldehydes, this reaction remains important in the preparation of functionalized organic molecules. Although predicting the stereochemical outcome of these additions still remains problematic in some cases, there are others where certain "rules" can be followed to achieve a desired diastereoselectivity.

In the simple case of 2-alkoxyaldehydes, chelating metals such as magnesium or zinc are reagents of choice in orienting the reaction toward the 1,2-*syn* adduct. On the other hand, when 1,2-*anti* selectivity is desired, the choice of a noncoordinating countercation, such as lithium, boron, or titanium, is more appropriate. The nature of the alkynylboron or titanium reagent is equally important because different ligands can affect reaction selectivity. For example, titanium reagents which contain alkoxy instead of chloro ligands are weakly Lewis acidic and give nonchelation control. A bulky (silyl) protecting group on the oxygen in position 2 and the

Table 82. NME-Catalyzed Alkynyl Additions to Tetrahydrofuran Carboxaldehydes

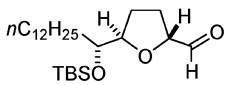
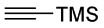
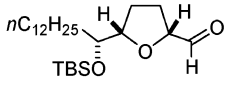
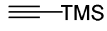
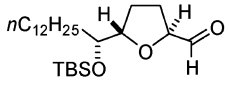
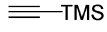
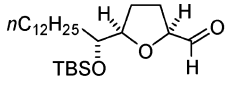
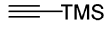
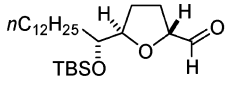
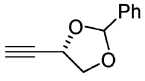
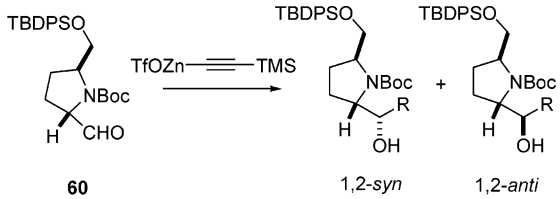
Entry	Aldehyde	Alkyne	NME	Yield (%)	1,2-*syn* / 1,2-*anti*
1			(1*R*,2*S*)	70	> 97 / < 3
			(1*S*,2*R*)	72	< 3 / > 97
2			(1*R*,2*S*)	61	> 97 / < 3
			(1*S*,2*R*)	71	< 3 / > 97
3			(1*R*,2*S*)	75	< 3 / > 97
			(1*S*,2*R*)	69	> 97 / < 3
4			(1*R*,2*S*)	79	> 97 / < 3
			(1*S*,2*R*)	66	< 4 / > 96
5			(1*R*,2*S*)	97	> 97 / < 3
			(1*S*,2*R*)	87	< 3 / > 97

Table 83. NME-Catalyzed Alkynyl Addition to the 2-Aminoaldehyde 60



60 1,2-*syn* 1,2-*anti*

Entry	NME	Yield (%)	1,2-*syn* / 1,2-*anti*
1	(1S, 2R)	40	86 / 14
2	(1R, 2S)	90	99 / 1

use of a coordinating solvent also strongly orients the reaction toward the 1,2-*anti* product.

The same general tendencies can be extended to reactions of 2-aminoaldehydes. While excellent 1,2-*syn* selectivity is more difficult to achieve with these substrates, monoprotection of the nitrogen with a "participating" group such as a Boc orients the reaction toward a majority of the 1,2-*syn* adduct. Excellent 1,2-*anti* diastereoselectivity can be obtained with alkynyllithium and magnesium derivatives using a fully protected bulky nitrogen substrate.

For addition to 3-alkoxyaldehydes, use of an alkynyltin reagent with various Lewis acids is the most efficient method for obtaining excellent 1,3-*anti* selectivity. Obtaining 1,3-*syn* selectivity is more problematic, and this particular challenge is cleanly resolved by reagent control and use of an external chiral inductor as discussed in section 10.

Predicting reaction diastereoselectivity can be more difficult with 2,3-hetero-disubstituted aldehydes because of competing 1,2- and 1,3- bidentate metal chelation processes. In most cases, however, 2,3-dialkoxyaldehydes have the same reactivity as 2-alkoxyaldehydes. Use of chelating metals such as magnesium or zinc are most efficient in orienting the reaction toward the 1,2-*syn* adduct, although care must be taken in the choice of solvent and protecting groups. When 1,2-*anti* selectivity is desired, use of an alkynyltitanium derivative is the best choice with a sterically hindered protecting group in position 2.

The reactivity of 3-alkoxy-2-aminoaldehydes, in particular that of the Garner aldehyde and its corresponding "thio" counterpart, is also similar to that of 2-alkoxyaldehydes. Chelation with the Boc protecting group and addition of alkynylzinc, copper, or tin derivatives give good to excellent 1,2-*syn* diastereoselectivity. Use of an alkynyllithium derivative and addition of HMPA in the reaction mixture preferentially give the 1,2-*anti* addition product.

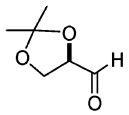
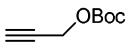
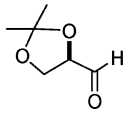
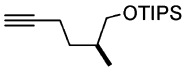
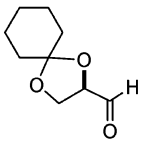
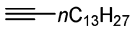
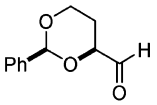
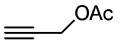
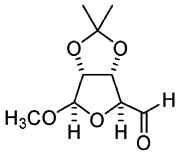
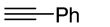
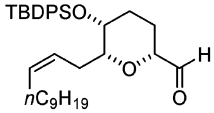
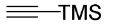
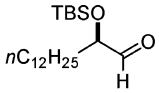
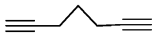
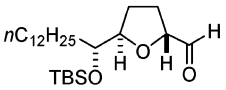
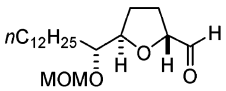
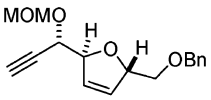
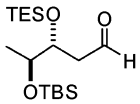
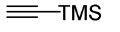
Examples of alkynyl addition to 2-alkoxy-3-aminoaldehydes are relatively few in the literature. These reactions are highly substrate dependent, and no clear-cut tendencies can be observed. The reported results vary from excellent (although unexplained) 1,2-*syn* selectivity with a titanium derivative to excellent 1,2-*anti* additions with both alkynyltitanium and cerium reagents, although results with the latter metal were clearly substrate dependent. Alkynyllithium derivatives also gave contradictory results, the 1,2-*syn* or 1,2-*anti* adducts being the major reaction products depending on substrate and reaction conditions.

For 2- and 3-thio-substituted aldehydes, good diastereoselectivity was observed in only one case. High 1,2-*anti* addition was achieved when the sulfur group in position 2 was protected with a sterically hindered group.

The nickel−chromium coupling reaction of an alkynyl halide to a chiral alkoxy-aldehyde is among the less traditional methods of alkynyl addition. In general, reported inductions are not very high, but this reaction is extremely mild and can thus give access to complex molecules through the use of highly functionalized coupling partners.

In the last section it was shown that reagent control, or use of an external chiral inductor such as BINOL or NME, can be an extremely efficient way of controlling reaction diastereoselectivity. Although excellent opposite selectivities can be obtained in many cases by simply changing the chiral inductor, the reaction remains substrate dependent when more complex aldehydes are used. Examples of "matched" and "mismatched" stereoselectivity are common in the literature,

Table 84. NME-Catalyzed Alkynyl Additions to Various Aldehydes

Entry	Aldehyde	Alkyne	NME	Yield (%)	1,2-*syn* / 1,2-*anti*	Ref
1			(1*S*,2*R*)	78	0 / 100	276
2			(1*R*,2*S*)	75	94 / 6	277
3			(1*R*,2*S*)	61	95 / 5	278
4			(1*S*,2*R*)	89	91 / 9	279
5			(1*R*,2*S*)	> 87%	0 / 100	280
6			(1*R*,2*S*)	75	> 95 / 5	281
7			(1*R*,2*S*)	84	97 / 3	282
8			(1*R*,2*S*)	84	97 / 3	282
9			(1*R*,2*S*)	> 70%	100 / 0	283
10			(1*S*,2*R*)	> 58	100 / 0	284

the best inductions being obviously obtained in the matched cases.

In conclusion, it is clear that the subject of alkynyl addition to chiral 2- and/or 3-alkoxy-, amino-, and thio-substituted aldehydes is not as simple as could first be imagined. One purpose of this review has been to show that a great amount of effort has been, and still is, directed toward making these types of addition reactions as selective as possible. By bringing all of these reactions together, we hope that this review will help fellow chemists to find "the best reagent" for the "best stereoselectivity" for any given alkynyl addition.

14. Abbreviations

AOM	*p*-anisyloxymethyl
BOC	*tert*-butoxycarbonyl
Bn	benzyl
Bz	benzoyl
DIMS	diisopropylmethylsilyl
HMPA	hexamethylphosphoramide
MEM	2-methoxyethoxymethyl
MOM	methoxymethyl
MPM	4-methoxyphenylmethyl
MTM	methylthiomethyl
Pf	9-phenylfluoren-9-yl

TBS	*tert*-butyldimethylsilyl
TBDPS	*tert*-butyldiphenylsilyl
TES	triethylsilyl
TIPS	triisopropylsilyl
TMEDA	*N*,*N*,*N*′,*N*′-tetramethylethylenediamine
TMS	trimethylsilyl
Ts	*p*-toluenesulfonyl
Tr	triphenylmethyl

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