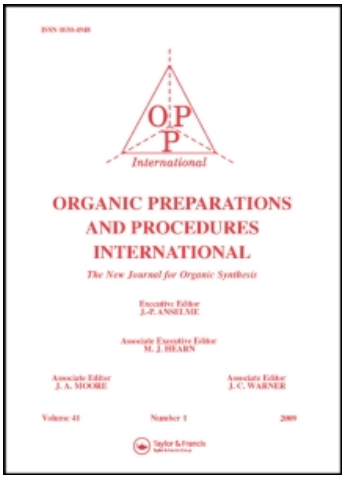


Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

RECENT PROGRESS IN THE ASYMMETRIC SYNTHESIS OF α-SUBSTITUTED PROPARGYLAMINES

J. Blanchet[a]; M. Bonin[a]; L. Micouin[a]
[a] Laboratoire de Chimie Thérapeutique, UMR 8638 associée au CNRS et à l'Université René Descartes Faculté des Sciences Pharmaceutiques et Biologiques, Pans cedex 06, France

To cite this Article Blanchet, J. , Bonin, M. and Micouin, L.(2002) 'RECENT PROGRESS IN THE ASYMMETRIC SYNTHESIS OF α-SUBSTITUTED PROPARGYLAMINES', Organic Preparations and Procedures International, 34: 5, 467 — 492
To link to this Article: DOI: 10.1080/00304940209355765
URL: http://dx.doi.org/10.1080/00304940209355765

ORGANIC PREPARATIONS AND PROCEDURES INT., 34 (5), 467-492 (2002)

RECENT PROGRESS IN THE ASYMMETRIC SYNTHESIS OF α-SUBSTITUTED PROPARGYLAMINES

J. Blanchet, M. Bonin* and L. Micouin*

Laboratoire de Chimie Thérapeutique UMR 8638 associée au CNRS
et à l'Université René Descartes
Faculté des Sciences Pharmaceutiques et Biologiques
4, av de l'Observatoire, 75270 Paris cedex 06, FRANCE

RECENT PROGRESS IN THE ASYMMETRIC SYNTHESIS OF α-SUBSTITUTED PROPARGYLAMINES

J. Blanchet, M. Bonin* and L. Micouin*

Laboratoire de Chimie Thérapeutique UMR 8638 associée au CNRS
et à l'Université René Descartes
Faculté des Sciences Pharmaceutiques et Biologiques
4, av de l'Observatoire, 75270 Paris cedex 06, FRANCE

INTRODUCTION

Enantiopure α-substituted propargylamines are useful synthetic intermediates which are often encountered as a part of biologically active compounds. Surprisingly, while the chemistry of enantiopure α-substituted propargyl alcohols is now well known and present in many synthetic strategies, the asymmetric preparation and use of their nitrogenated analogues is still in its infancy.[1] Important synthetic developments could be expected if a general and efficient method for the preparation of such intermediates in enantiomerically pure form was available. The use of a nitrogen directing group, as has been already demonstrated in numerous cases (α-aminoaldehydes chemistry for instance[2]), could lead to regio- and stereoselective transformations of the acetylenic group and deliver important synthetic intermediates, as well as biologically active derivatives.

The present article will emphasize the recent progress on this subject. Representative examples of biologically active compounds containing the α-aminopropargyl framework will be briefly summarized followed by synthetic methodology. The main focus will be on the asymmetric *preparation* of substituted amines, and their subsequent transformations. The chemical or enzymatic resolutions of racemic material will not be covered, and the preparation of hydroxylamines will be discussed only briefly.[3]

I. BIOACTIVITY OF NATURAL AND SYNTHETIC PROPARGYLAMINES

Among the wide variety of propargylic amines, the particular α-substituted alkyne motif is found in only a limited number of natural products and/or bioactive compounds. However, with the remarkable enediyne family, a very important series of new antitumor agents was discovered, all of which cleave DNA upon suitable triggering of core diradical-generating structures. The screening, isolation and biological activities of these microbial metabolites have been well documented in several

reviews.[4] Among these, the dynemicin **1** class shows structural characteristics of both the anthracyclin and the enediyne features with the particular aminopropargylic motif (*Fig. 1*).[5]

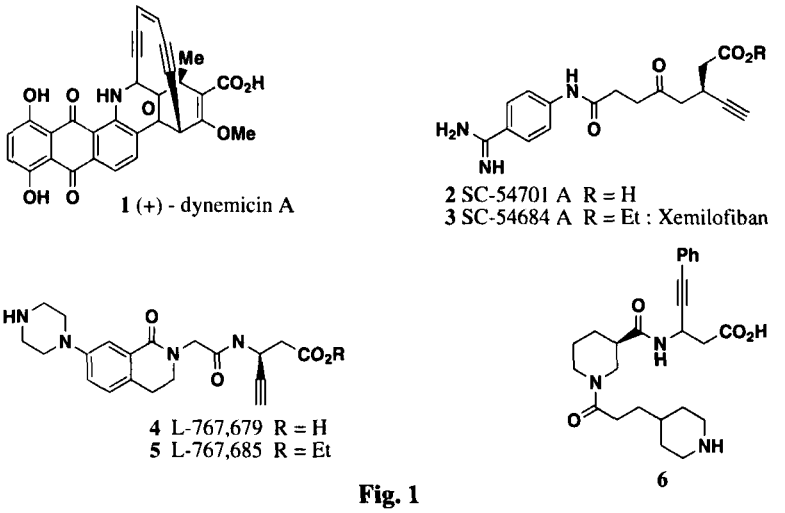


Fig. 1

In the medicinal chemistry area, three major classes of peptide mimetics were recently described as new fibrinogen receptor antagonists with an antithrombotic profile (*Fig. 1*).[6] Starting from the (aminobenzamidino) succidinyl Arg-Gly surrogate, Zablocki and co-workers discovered SC-54701 A, **2**, which displayed high anti-platelet aggregation activity.[7] The great number of hydrogen interactions established with the receptor is reported as key SAR feature. With an improved oral bioavailability and duration of action, the relative ethyl ester prodrug, xemilofiban **3**, was chosen as a lead compound for clinical development.[8]

Targeting the same biological system, the Merck group has also developed a series of 3,4-dihydroisoquinolinone-based GPIIb-IIIa antagonists exemplified by lactam L767,679 **4**. This compound utilizes the ethynyl β-amino acid subunit first identified by Searle and the low basicity of the arylpiperazine function to improve the potency and oral bioavailability. As in the previous series, the ethyl ester prodrug **5** shows the greatest activity by oral administration.[9] In addition, based on the same pharmacological profile, the related β-amino acid **6** was synthesized by the Johnson Pharmaceutical company and described as an excellent candidate for the treatment of arterial thrombotic disease.[10]

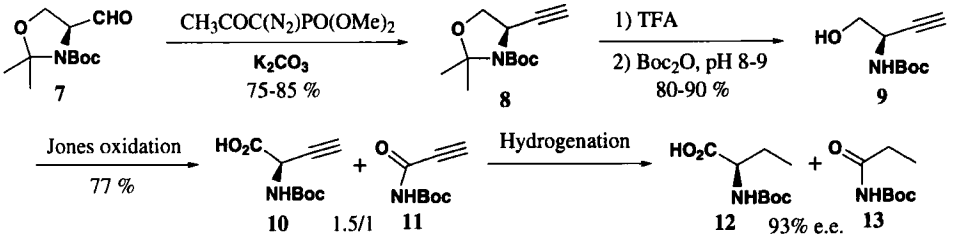
II. ASYMMETRIC SYNTHESIS OF PROPARGYLAMINES

1. Functional Group Transformation of α-Aminoaldehydes

a) From Serine

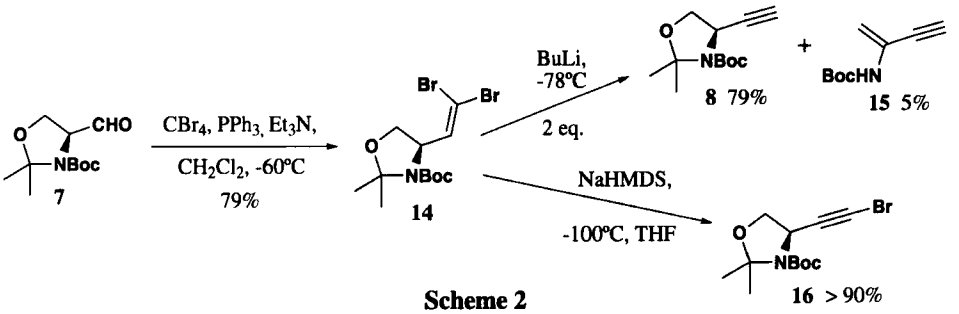
Since the conversion of an aldehyde to a terminal acetylenic function is an obvious reaction (*via* the methodology of Corey-Fuchs,[11] Wittig/Horner-Emmons,[12] Gilbert-Seyfert[13] or the recent Wang approach[14]), it is not surprising that this strategy has been used for the preparation of enantiomerically pure α-substituted propargylamines from chiral amino aldehydes.

Garner's aldehyde **7** (*Scheme 1*) has been used as starting material in the synthesis of optically active ethynyl glycine derivatives.[15] Conversion of protected serinal **7** into alkyne **8** was performed in good yield by the method developed by Ohira using dimethyl 1-diazo-2-oxopropyl phosphonate.[16] Oxidation of alcohol **9** proved to be the difficult step in this approach since an inseparable mixture of acid **10** and ketone **11** was obtained. The enantiomeric purity of compound **10** was checked after hydrogenation through derivative **12** which proved to be 93% e.e.



Scheme 1

A modification of the Corey-Fuchs procedure[17] has been reported to provide an efficient transformation of **7** to **14** (*Scheme 2*).[18] This dibromo derivative could lead to dehydrohalogenated



Scheme 2

compound **16** at low temperature or to **8** by treatment with 2 equiv. of BuLi and work-up. The latter

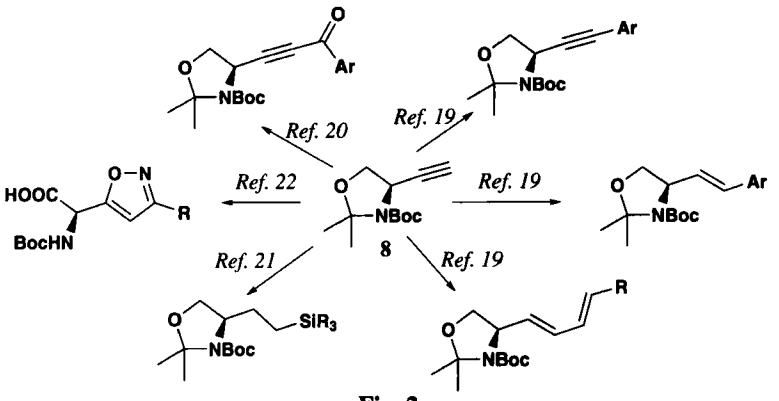
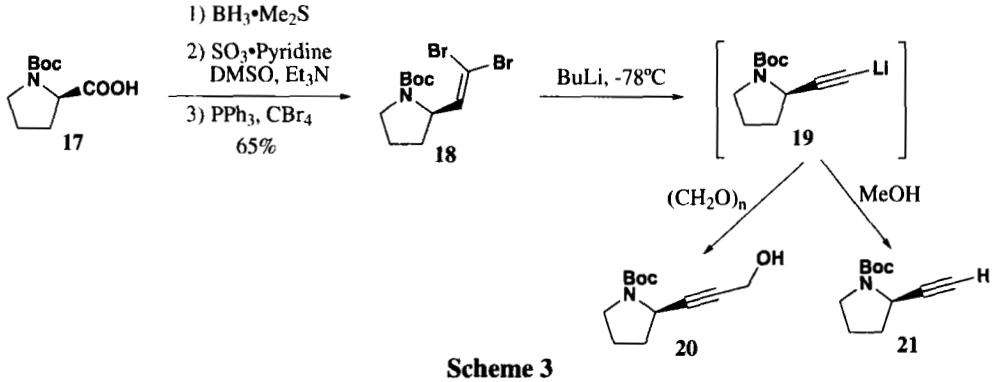


Fig. 2

transformation proved to be troublesome since the by-product **15** could be observed when a large excess of base was used for a prolonged reaction time. Compound **8** is a starting chiral building block for several transformations.[19-22]

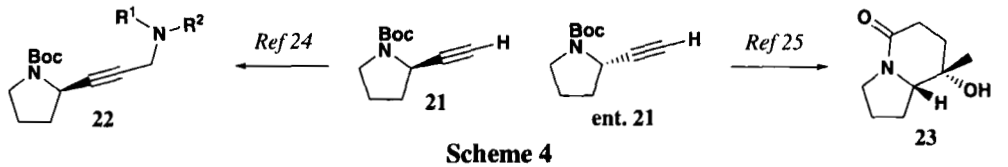
b) From Proline

Using Corey-Fuchs conditions, dibromo vinyl intermediate **18** can be synthesized from Boc-proline in good yield. This compound can then lead to the propargylpyrrolidine **21** or alcohol **20** if the lithiated intermediate is directly quenched with paraformaldehyde (*Scheme 3*).[23]



Scheme 3

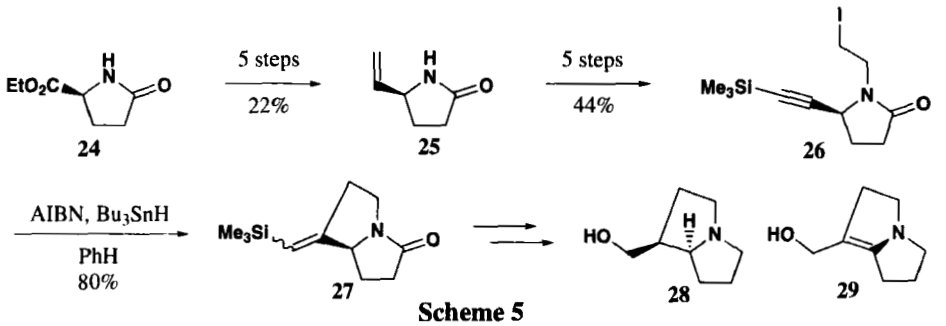
Compound **21** has served as a starting material for the preparation of derivatives **22** showing potential muscarinic properties[24] or as the key intermediate **23** in an enantioselective synthesis of pumiliotoxin 251D (*Scheme 4*).[25]



Scheme 4

c) From Glutamic Acid

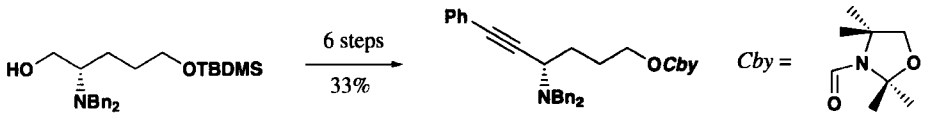
A general approach to pyrrolizidine alkaloids based on radical cyclizations has been described (*Scheme 5*).[26] The chiral non-racemic key intermediate **25** was prepared from ethyl pyrroglutamate in five steps in 22% yield. Its conversion to the N-substituted propargylic lactam **26** followed



Scheme 5

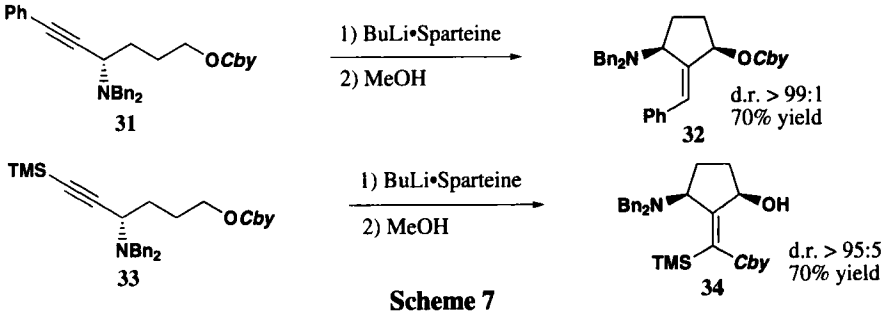
by the radical cyclization led to bicyclic lactam **27**, an intermediate for the synthesis of several pyrrolizidine alkaloids.

Enantiopure carbamate **31** (*Scheme 6*) has been prepared in 6 steps (in 33% overall yield) using the Corey-Fuchs procedure from alcohol **30** which was derived from (*S*)-glutamic acid.[27]



Scheme 6

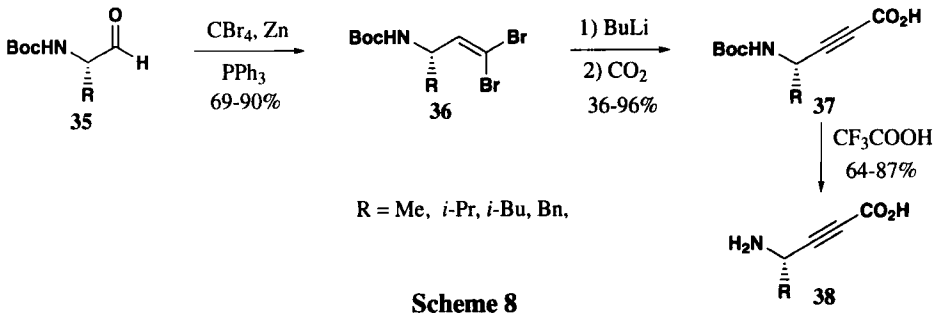
A tandem asymmetric deprotonation-intramolecular carbolithiation furnished the *cis* substituted cyclopentane **32** in a diastereoselective manner in 70% yield (*Scheme 7*). The tandem reaction using the trimethylsilyl-substituted propargylic amine **33** was followed by a trans-carbamoylation of the stabilized transient carbanionic species to yield **34**.[27]



Scheme 7

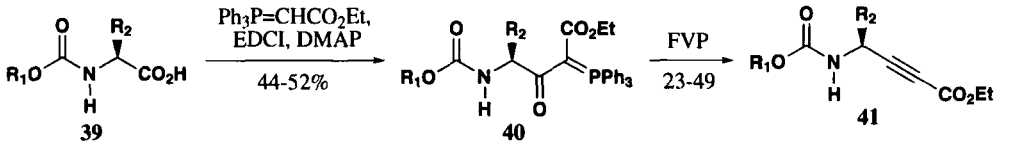
d) From Various Amino Acids

Two general methods for the preparation of chiral alkynylogous amino acids discussed below have been reported. Such derivatives could have some interesting properties when incorporated into peptidic frameworks, since they may influence secondary and tertiary structure of peptidomimetic drugs. The standard Corey-Fuchs transformation was used by Reetz and coworkers starting with N-Boc amino aldehydes (*Scheme 8*).[28] The enantiomeric purity of amino acids **38** was greater than 99%.



Scheme 8

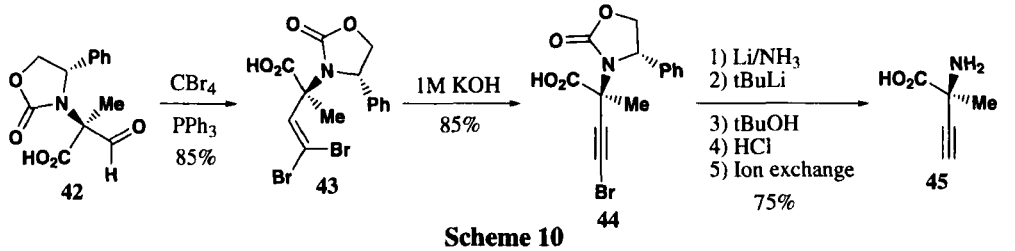
The same type of N-protected compounds have been prepared from amino acids *via* the flash vacuum pyrolysis of aminoacyl phosphorus ylides **40** (*Scheme 9*).[29] The enantiomeric purity of the final products was evaluated after hydrogenation and formation of their Mosher amide derivatives.



R_1 = Et, *i*Bu, Bn R_2 = Me, *i*Pr, *i*Bu, *s*Bu

Scheme 9

They were found to be between 70 and 95%, showing that some racemization might have occurred during the synthesis. Quaternary amino aldehydes can also serve as starting materials for the preparation of quaternary propargylamines. Conversion of **42** into propargylic oxazolidinone **44** (*Scheme 10*) was accomplished in a 72% yield.[30,31] Very careful reductive cleavage of the oxazolidinone and the acetylenic halide led to (+)-(*S*)-α-ethynylalanine **45** without over-reduction to 2-vinylalanine.

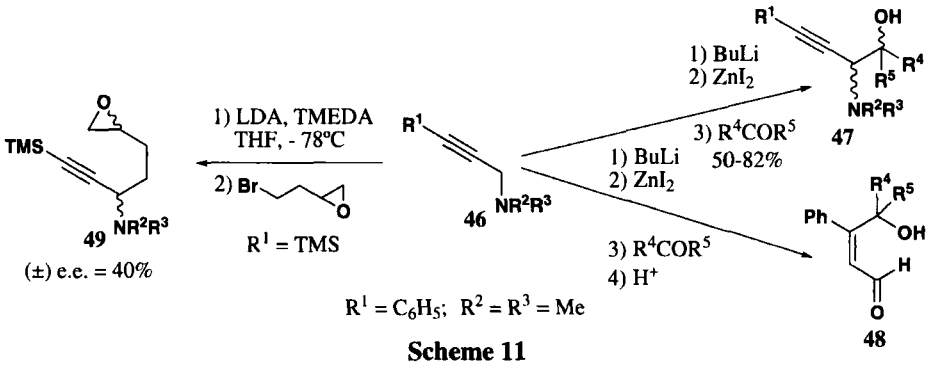


Scheme 10

Although the transformation of an aminoaldehyde into a terminal acetylenic compound is straightforward, this strategy is limited somewhat by the preparation of the enantiopure starting materials and, in some cases, by racemization problems.

2. Electrophilic Substitution of an Aminopropargylic Anion

Only limited examples of the use of aminopropargylic anion reactivity for the preparation of propargylamines have been reported. In the racemic series, Mercier and Epsztein [32] described the akylation of the lithiated derivatives with a bromo epoxide in a modest -but significant- diastereoselectivity (*Scheme 11*). Transmetalation to the corresponding organozinc compound followed by aldol

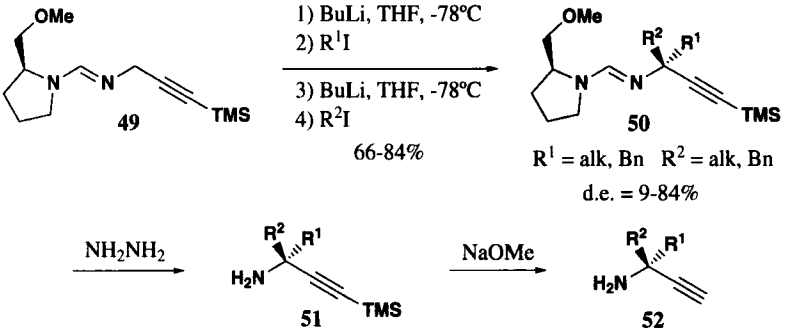


$R^1 = C_6H_5$; $R^2 = R^3 = Me$

Scheme 11

reaction led to in a mixture of *threo/erythro* alcohols **47**. The preparation of the organozinc intermediate allowed the regioselective formation of α-substituted propargylamines, except when compound **46** with R^1 = Ph was used; in that case, **46** reacted at the allenic position, leading to the conjugated aldehyde **48** after hydrolysis.

Kolb and Barth reported the only one application of this type in the chiral non-racemic series (*Scheme 12*).[33] The formation of quaternary asymmetric centers by two successive deprotonation-alkylation sequences of some derivatives **49** proved to be more stereoselective (d.e. = 67-84%) than mono alkylations reactions (d.e. = 9-15%).



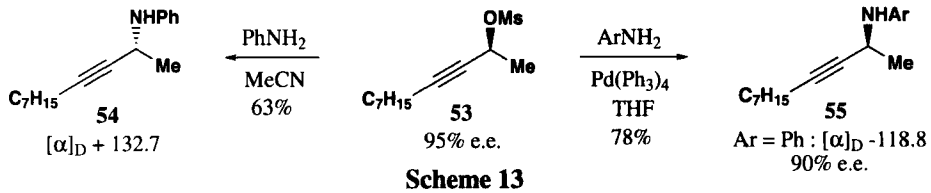
Scheme 12

3. Nucleophilic Substitution of a Propargylic Leaving Group

Creation of a C-N bond by nucleophilic substitution is an attractive and simple strategy since good methods for the asymmetric preparation of enantiopure propargyl alcohols are now available. This transformation can be performed in an inter- or intramolecular fashion.

a) Intermolecular Substitution

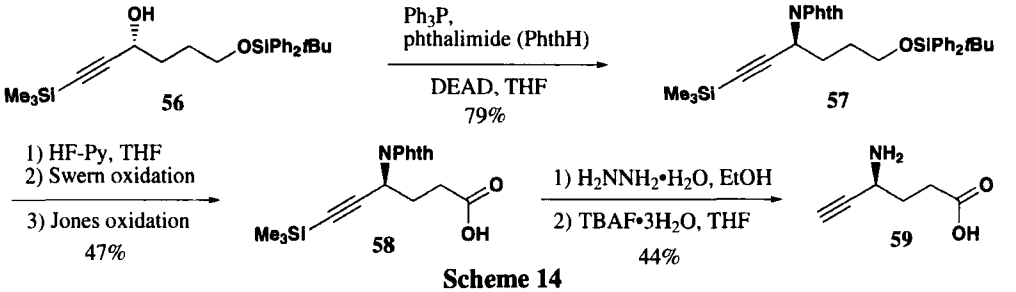
Marshall and coworkers developed an efficient enantiodivergent access to both enantiomers of amine **54** from an optically enriched propargyl alcohol (*Scheme 13*).[34] Treatment of mesylate **53** with aniline afforded amine **54** in 63% yield with inversion of configuration. On the other hand, in the presence of $Pd(Ph_3)_4$, amine **55** of opposite rotation was obtained, with a slight racemization.



Scheme 13

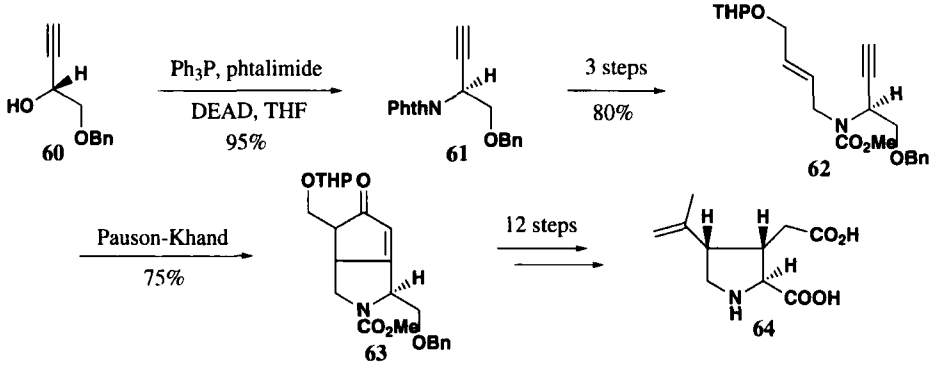
The overall retention of configuration was explained by a reactive pathway involving anti S_N2'-type oxidative addition of Pd(0) to the mesylate followed by an anti S_N2' attack by the amine on an allenyl Pd intermediate. Only aromatic amines were used as nucleophiles in the Pd-mediated substitution.

Classical Mitsunobu reaction[35] conditions were used for the preparation of propargylamines. Thus, (S)-γ-acetylenic GABA **59** (*Scheme 14*), with mammalian GABA-T inhibition properties, has



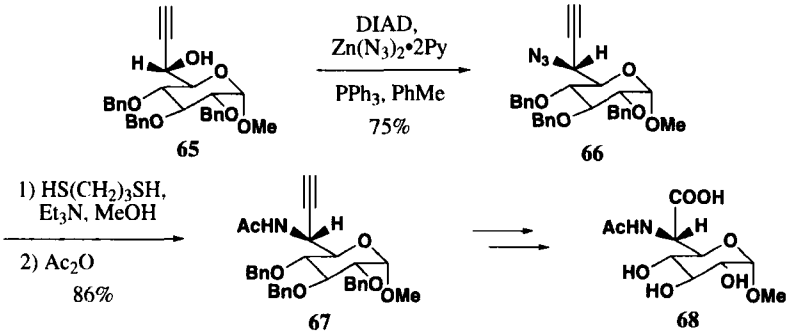
Scheme 14

been synthesized in an enantiomerically pure form from propargylic alcohol **56**.[36] A similar strategy afforded (-)-kainic acid **64** (*Scheme 15*).[37]



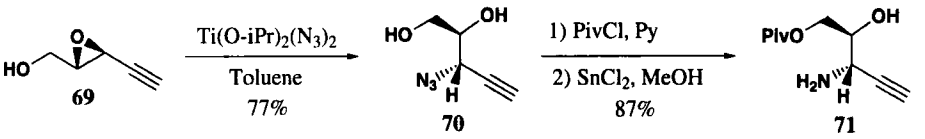
Scheme 15

Nucleophilic azide can replace phthalimide in the Mitsunobu reaction. The amino-propynilic compound **67** was employed as a key synthetic intermediate for the preparation of glycosyl amino acid **68** (*Scheme 16*). It could be prepared by a chemoselective reduction of azido derivative **66** with excess of 1,3-propanedithiol in the presence of triethylamine.[38]



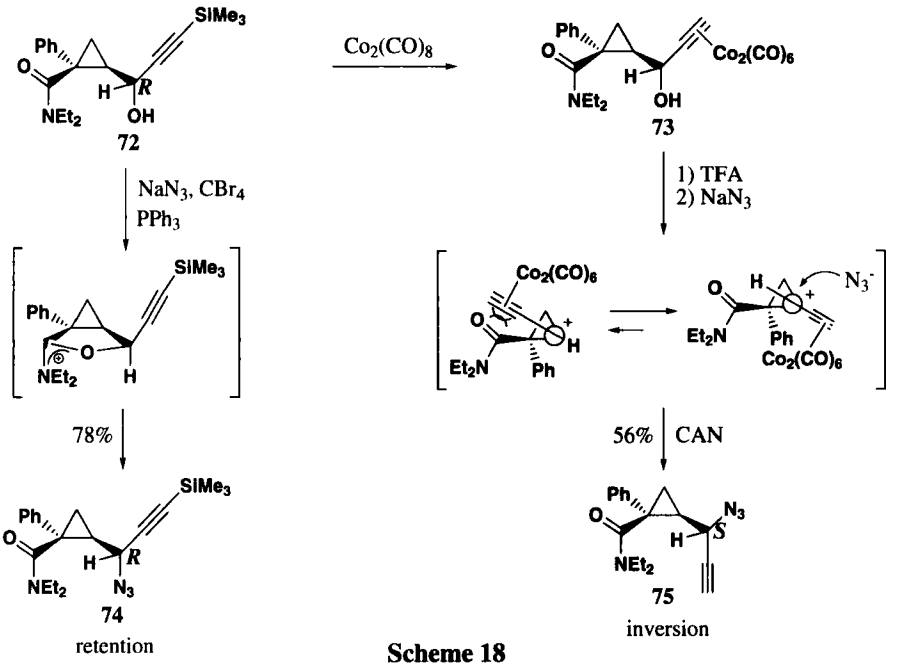
Scheme 16

Titanium mediated regioselective opening of propargylic epoxide **69** (*Scheme 17*), followed by protection of the primary alcohol and reduction of the azide group leads to ethynylamine **71**.[39] This compound is a key intermediate for the synthesis of aminonucleosides *via* a molybdenum-catalyzed



Scheme 17

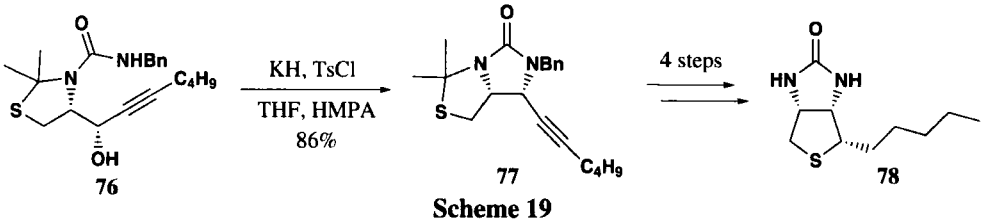
cycloisomerization. In a very elegant approach, both diastereomeric cyclopropyl derivatives **74** and **75** could be prepared in a diastereodivergent way starting from the same propargyl alcohol **72** (*Scheme 18*).[40] It is proposed that retention of configuration resulted from participation of the neighbouring amide group. Using the $Co_2(CO)_6$-alkyne complex, attack of an azide anion at the least hindered face of the most stable *s-trans* bisected conformation led to compound **75** with inversion of configuration.



Scheme 18

b) Intramolecular Substitution

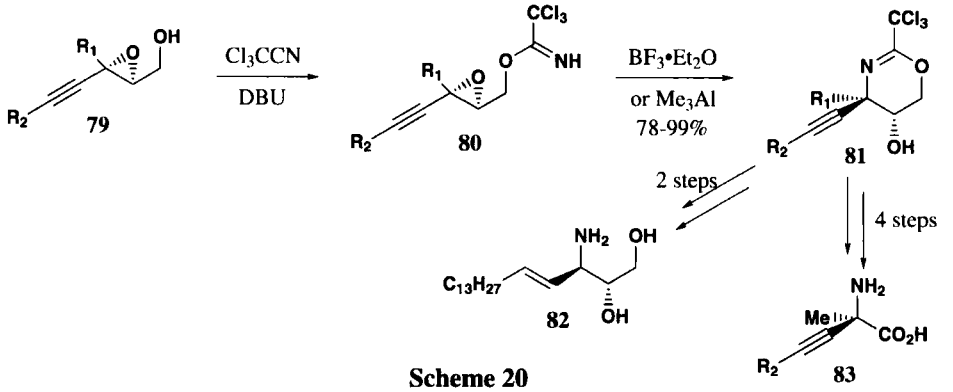
An intramolecular nucleophilic substitution has been used for the synthesis of the *syn* urea part of (+)-deoxybiotin **78** (*Scheme 19*).[41] This cyclisation is not trivial and could only be accomplished under carefully controlled conditions (KH, TsCl, HMPA 30 eq.).



76 77 78

Scheme 19

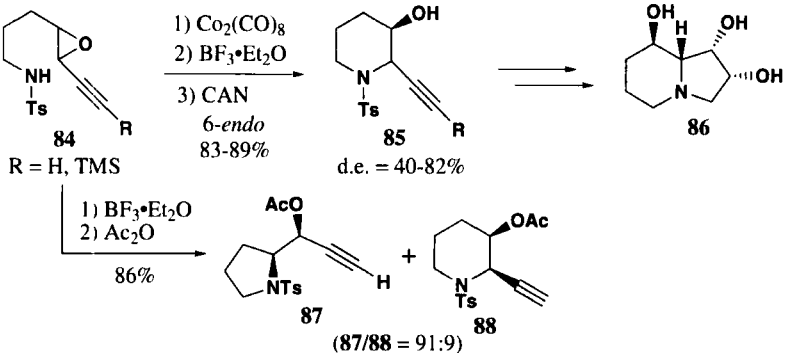
Lewis acid catalysed regioselective epoxide opening could be achieved starting from the trichloroacetimidate **80** (*Scheme 20*). Dihydrooxazine **81** led to amino diol **82**, an isomer of D-*erythro*-sphingosine,[42] and the quaternary acetylenic amino acids **83**.[43] Regioselective intramolecular



79 80 81 82 83

Scheme 20

opening of the epoxide **84** was observed under Nicholas reaction conditions (*Scheme 21*).[44] A moderate retention of configuration of the propargylic center was obtained.[45] In the absence of the cobalt complex, a classical 5-*exo* cyclisation takes place in a highly stereoselective manner with a small amount of the *endo* mode product.



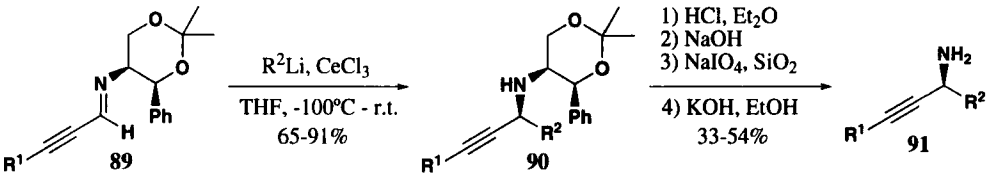
84 R = H, TMS 85 86 87 88

(**87/88** = 91:9)

Scheme 21

4. Nucleophilic Attack on Propargylic Imines

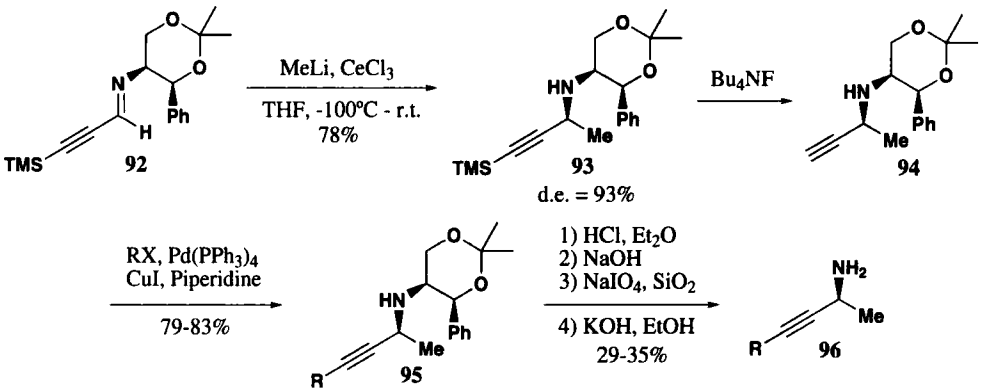
A general method for the preparation of α-substituted propargylamines has been proposed by Enders and co-workers. It is based on the diastereoselective reaction of organocerium reagents with chiral aldimines **89** (*Scheme 22*).[46] Oxidative treatment and hydrolysis of the transient formamide



R^2 = Me, Et, Bu, $TBSO(CH_2)_3$, allyl
R^1 = Ph, *t*Bu, TMS

Scheme 22

affords primary propargylamines **91** (*Scheme 23*).



R = CHCl=CH, Thien-2-yl

Scheme 23

Starting from silylated acetylenic amine **93**, functionalization of the triple bond could be performed *via* the Sonogashira coupling of the deprotected compound **94**. Despite the need for very low temperature conditions and excess (4-5 eq.) of organoceric reagents, this method is probably one of the most general and versatile for the preparation of propargylic amines at a laboratory scale.

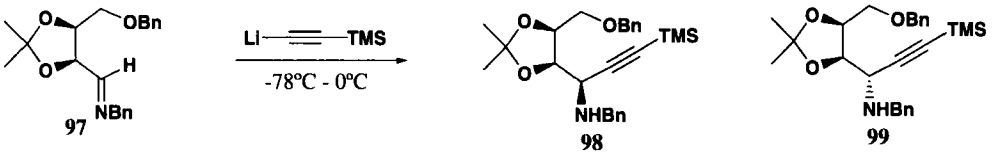
5. Nucleophilic Attack on Imines and Related Functions

Although the Mitsunobu reaction and its variants have been broadly used for the preparation of propargylic amines, this strategy is not versatile since it cannot deliver molecular diversity from a single precursor. Nucleophilic addition on imines or related functional groups (nitrones, iminiums..) is usually the method of choice for the rapid and general preparation of α-substituted amines.[47] Moreover, the relatively low acidity of acetylenic protons (pK = 25) enables the facile preparation of various metallic salts of alkynes.[48] The reactivity of the electrophile and nucleophile can therefore be tuned in order to get an efficient reaction with good yield and diastereoselectivity.

a) Lithium Alkynilides

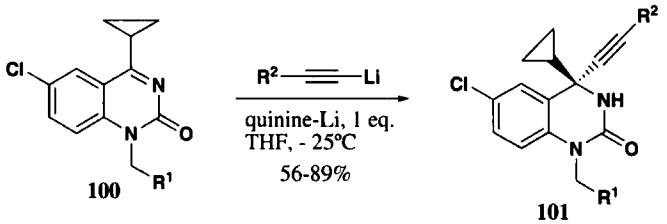
i. With Imines

The addition of lithium trimethylsilylacetylide on imine **97** derived from tartaric acid has been reported by Shimizu and co-workers (*Scheme 24*).[49] Addition of lithiated trimethylsilyl acetylene



Scheme 24

to compound **97** proceeded in a completely *syn* fashion, albeit in a low yield. In the presence of $BF_3.Et_2O$, a reversal of the diastereoselectivity could be obtained, leading to the exclusive formation of the *anti* adduct. Enantioselective addition of lithium alkynides in the presence of one equivalent of lithium alkoxide of quinine has been used by Huffman and co-workers in their synthesis of various H.I.V. reverse transcriptase inhibitors (*Scheme 25*).[50] Enantioselectivities ranging from 37 to 97% were obtained, depending on the side-chain substitution. Optimization of temperature and concentration proved to be critical, and best results were obtained using the bulky 9-anthrylmethyl protecting group, with 2-ethynylpyridine as nucleophile.

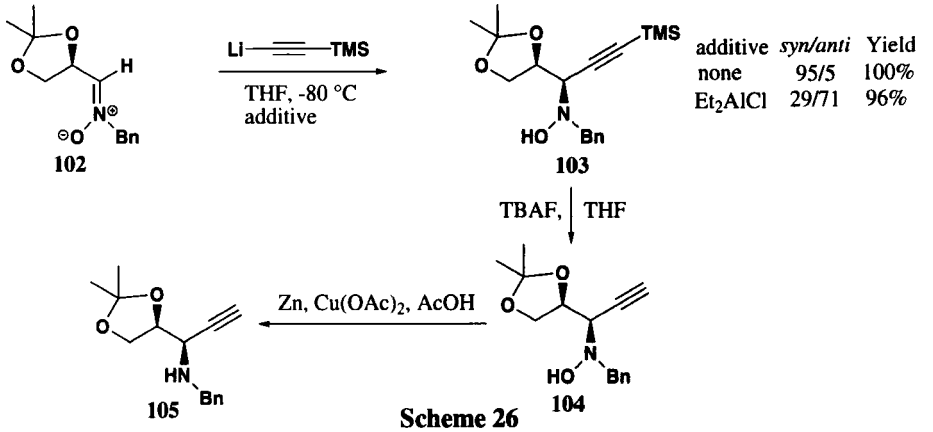


R^1 = H, Ph, 4-MeOPh, 4-ClPh, 2,6-ClPh, 9-anthryl
R^2 = 2-pyr, 3-pyr, 4-pyr, Ph, 4-MeOPh, 4-ClPh, Bu, TMS

Scheme 25

ii. With Nitrones

Nucleophilic additions of lithium alkynilides on chiral non-racemic nitrones have been used by many groups, but only one example of this strategy for the preparation of propargylamines has been reported.[51] The addition of lithium trimethylsilylacetylide on nitrone **102** derived from glyceraldehyde at very low temperature afforded *syn* hydroxylamine **103** in a quantitative yield (*Scheme 26*).

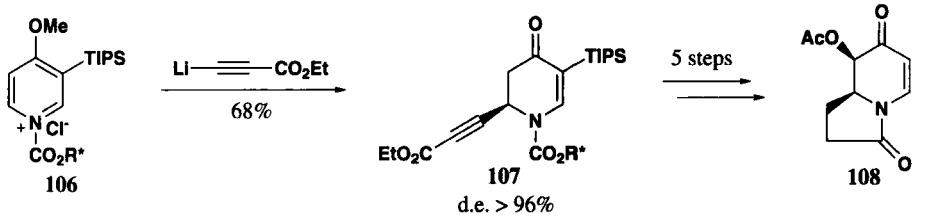


Scheme 26

The addition of one equivalent of Lewis acid to precomplexed nitrone led to the *anti* compound as the major product. Although the deprotection and the reduction of hydroxylamine **103** was also described yielding propargylamine **105**, no yield was reported for these two transformations.

iii. With Acyliminium Salts

As a part of a program to expand the synthetic utility of N-acyl-2,3-dihydropyridones, nucleophilic attack of chiral acyliminium salt **106** was performed with lithiated ethyl propiolate (*Scheme 27*).[52] The addition occurred in a diastereoselective fashion, providing a useful synthetic intermediate for polyhydroxylated indolizidines.



d.e. > 96%

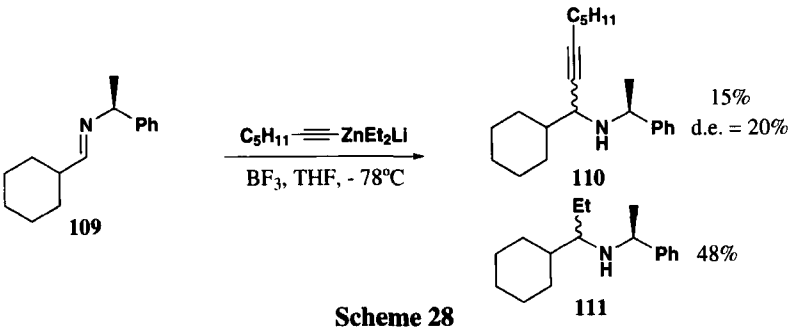
R* = (+)-trans-2-(α-cumyl)-cyclohexyl

Scheme 27

b) Zinc Alkynilides

i. With Imines

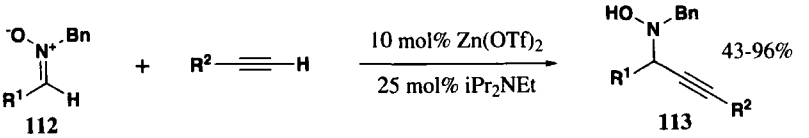
Addition of organozincates to aliphatic aldimines derived from (*S*)-phenylethylamine has been investigated by Savoia and co-workers. Propargylamine **110** (*Scheme 28*) was obtained in a very low yield and stereoselectivity, with amine **111** resulting from the transfer of an ethyl group as major side-product.[53]



Scheme 28

ii. With Nitrones

Very important results have been recently reported by Carreira and co-workers on the catalytic *in situ* mild generation of zinc alkynilides.[1a] Terminal acetylenes react with nitrones and tosylimines in the presence of a *sub*-stoechiometric amount of zinc triflate and Hünig's base to give products in good to excellent yields (*Scheme 29*).[54]



R^1 = *c*-Hex, Ph, Pent, *t*-Bu, *i*-Pr
R^2 = $SiMe_3$, CH_2SiMe_3, Bu, $PhCH_2CH_2$, $TBSOCH_2$, *t*-Bu, $BrCH_2$

Scheme 29

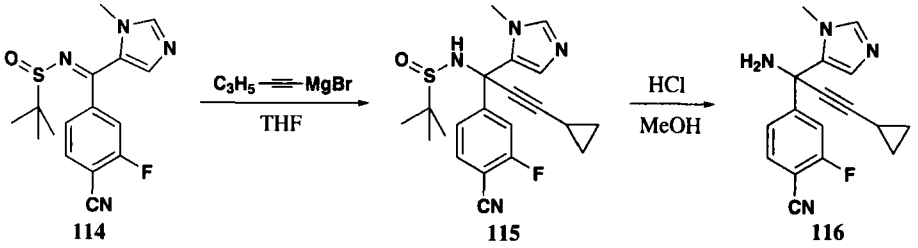
Preliminary results have shown that the use of a chiral nitrone derived from 4-phenyl-4-hydroxyaminobutane and *iso*butyraldehyde with tri-*iso*propylsilylacetylene as a nucleophile affords the corresponding adduct in 76% d.e. Promising results were also obtained when using (+)-N-methyl-pseudoephedrine as an external chiral adjuvant with an achiral nitrone.

If general, this strategy would provide a simple and efficient access to α-substituted propargylamines, provided that reduction of the nitrones into the corresponding amines can be performed chemoselectively.

c) Magnesium Alkynilides

i. With Imines

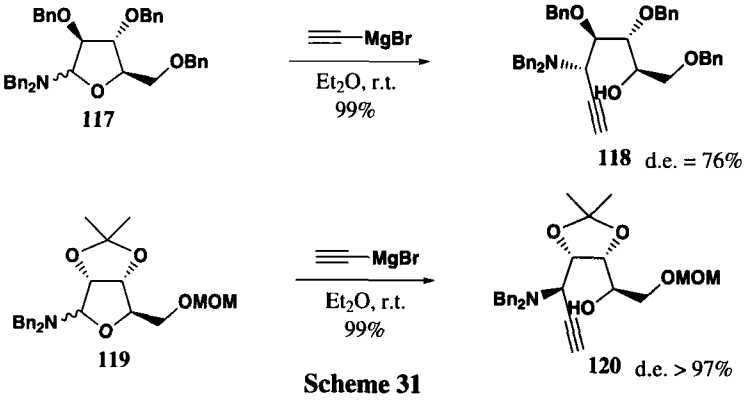
Addition of an excess (6 eq.) of pentynylmagnesium bromide to sulfinyl ketimine **114** (*Scheme 30*) has been recently reported to occur in excellent yield and with 58% d.e.[55] Quantitative cleavage of the sulfinyl group under acidic conditions afforded propargylamine **116** as a possible FPTase inhibitor.



Scheme 30

ii. With Iminium Salts

The stereochemical outcome of the reaction of Grignard reagents with dialkylaminofuranosides derived from pentoses has been investigated (*Scheme 31*). In the ribose or arabinose series, good



Scheme 31

to excellent diastereoselectivities were obtained. The rate of the reaction was highly dependent on the presence of an oxygenated side chain in the 5-position on the pentose. The preference for the *erythro* configuration was explained by the approach of the nucleophile from the side opposite to the electronegative α-substituent on the most stable rotamer **Ib**.[56]

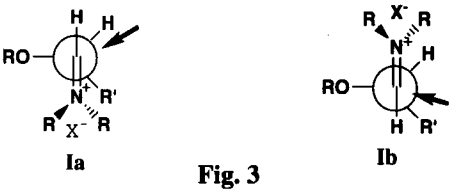
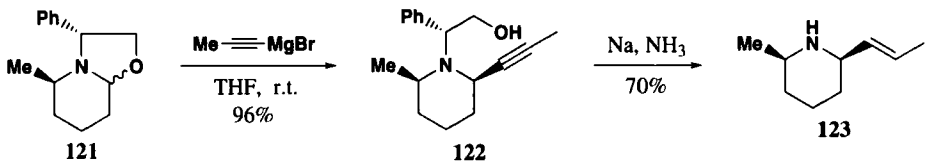


Fig. 3

As part of their work on the diastereoselective reaction of Grignard reagents with oxazolidines, Higashiyama and co-workers reported the preparation of propargylamine **122** from compound **121** (*Scheme 32*). The propargylamine **122**, obtained in excellent diastereoselectivity and yield with 4 eq. of propynylmagnesium bromide, could be transformed in one step into (-)-pinidine **123**.[57]

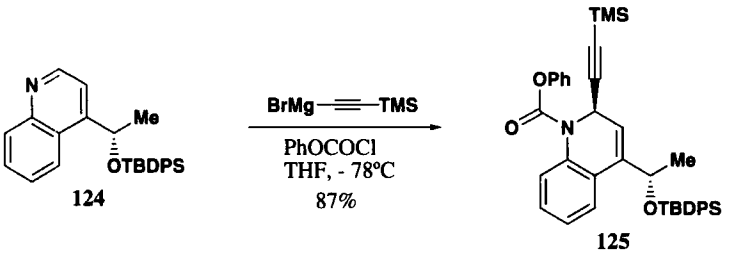


121 122 123

Scheme 32

iii. With Acyliminium Salts

In the course of the asymmetric synthesis of antitumor dynemicin A, the reaction of organomagnesium bromides with chiral N-acylquinolinium intermediates has been investigated by several groups. In a model study, the influence of 1,4-asymmetric induction has been studied by Isobe and coworkers (*Scheme 33*).[58] Good diastereoselectivity could be obtained when the secondary alcohol was protected by a large group, leading to an attack from the less hindered face of the reactive intermediate.

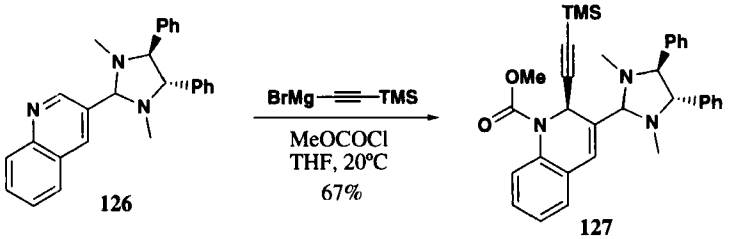


124 125

d.e. = 86%

Scheme 33

1,3- Asymmetric induction has been observed starting with chiral 3-quinolinyl aminal **126** by Mangeney and co-workers (*Scheme 34*).[59] The 1,2- adduct was obtained in excellent (98:2) regioselectivity, and in good diastereomeric excess. This strategy proved to be efficient since it has been

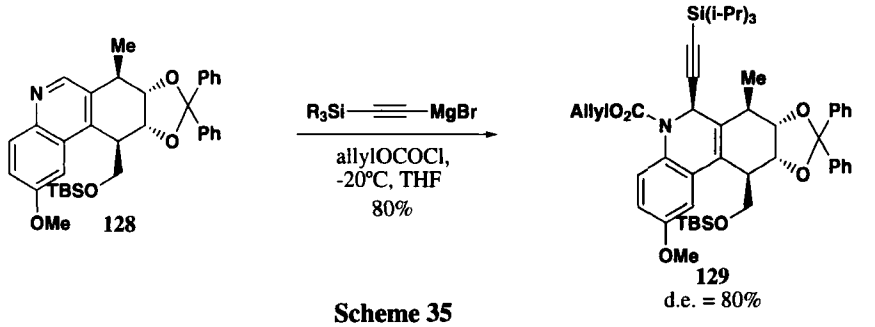


126 127

d.e. = 80%

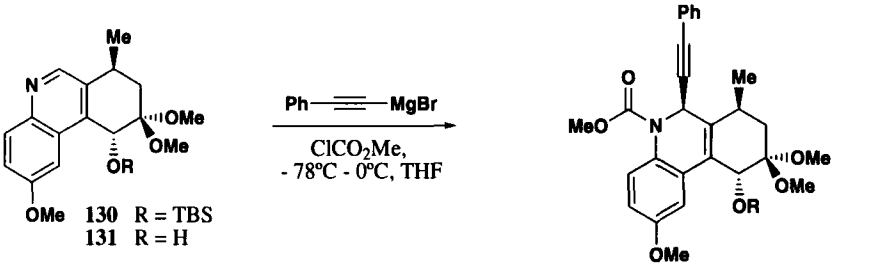
Scheme 34

used in the total synthesis of the natural compound. Danishefsky and co-workers used the benzophenone ketal **128** as a device to shield the α face and direct the attack of the tri-*iso*propylsilylacetylene magnesium bromide on the desired side.[60]



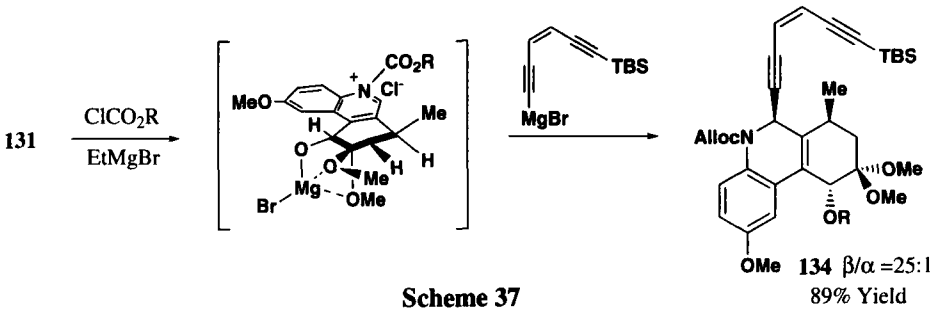
Scheme 35

The control of the selectivity of this addition was also a key point in the synthesis shown in *Scheme 36* by Myers and co-workers.[61]



Scheme 36

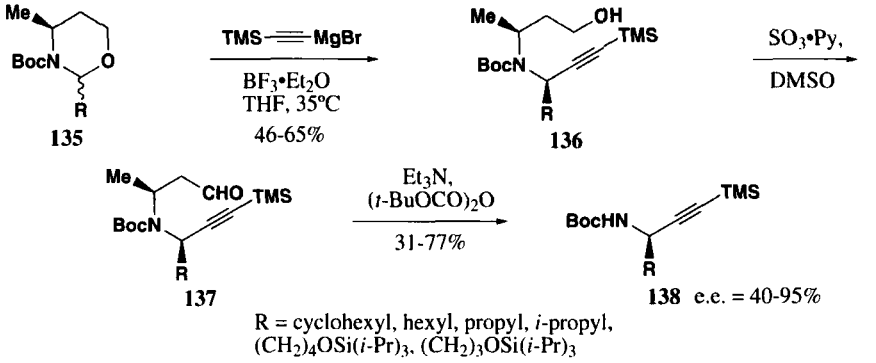
In an initial model study, The O-TBS ether **130** reacted with phenylacetylide in the presence of methylchloroformate in a poorly diastereoselective way, affording the unwanted product of acetylide addition *trans* to the methyl group as the slightly enhanced isomer. However, when the same reaction was performed with the free alcohol **131**, the *cis* addition product **133** was greatly favoured. This stereochemical outcome was explained by the formation of an intermediate alkoxide chelate (*Scheme 37*), placing the methyl group in a pseudo equatorial position and leading to the *cis* compound *via* an axial attack of the β face of this reactive conformer.



Scheme 37

Using this strategy, compound **134** could be obtained in 89% yield, with a β/α selectivity greater than 25:1. In addition to the enhanced reactivity of the acyliminium species with Grignard reagents for the synthesis of functional quinolines, a more systematic study by Tabor and co-workers

was aimed at developing a general access toward α-substituted propargylamines (*Scheme 38*).[62]

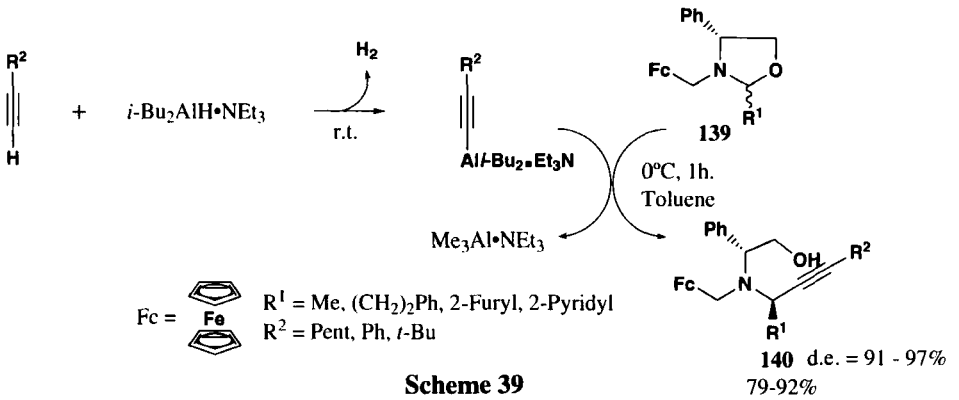


Scheme 38

This approach involved the ring-opening of tetrahydrooxazines **135** with acetylenic Grignard reagent under Lewis acid catalysis. Aminoalcohols **136** could be obtained in moderate to good yield, and led to protected propargylamines **138** after oxidation and a retro-Michael reaction. The e.e. of final amines appeared to be unrelated to the d.e. of the starting tetrahydrooxazine and were below 86%, except for R = $(CH_2)_4OSi(i\text{-}Pr)_3$ where an e.e. of 95% was obtained. The role of $BF_3{\bullet}Et_2O$, which is essential for the reaction, is unclear. The moderate diastereomeric excesses obtained in some cases could be due to the choice of the nucleophile and electrophile in this strategy. The formation of the reactive acyliminium species requires the presence of a Lewis acid, and cannot be generated solely in the presence of the Grignard reagent. Moreover, the nucleophilic organomagnesium halide could react in the presence of Lewis acid in an S_N2-manner, as already observed with acetals.[63] This competitive reactive pathway could be responsible for the decrease of diastereoselectivity in some cases. Despite some strong dependence of the final e.e. on the variation of substrate, this strategy provides a simple method for the preparation of protected α-substituted propynyl amines.

d) Aluminum Alkynilides

The study of the nucleophilic opening of chiral oxazolidines **139** (*Scheme 39*) with mixed

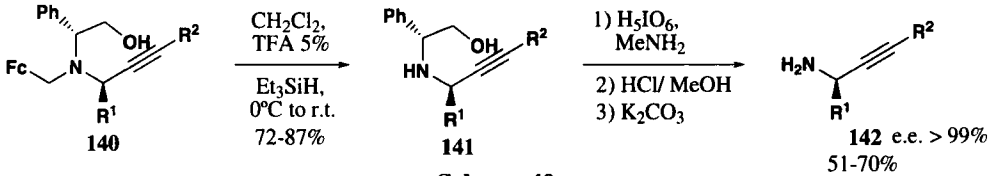


Scheme 39

alkynylaluminum compounds was started by our group.[64] These species are known to be good

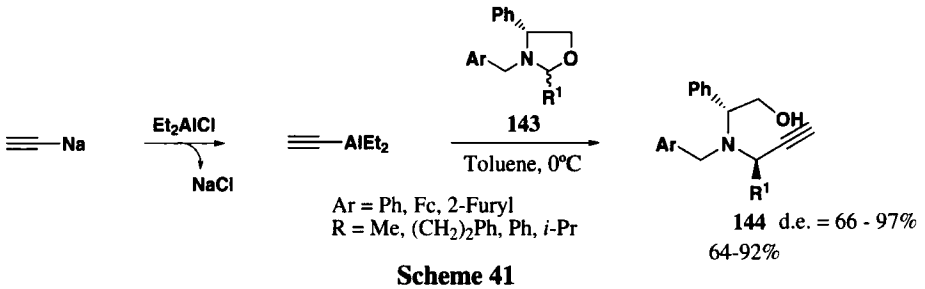
oxophilic Lewis acids, poor nucleophiles, and usually react by preferentially transferring their alkynyl group.[65]

Alkyne metalation was performed with a DIBAH-Et_3N complex at room temperature.[65] The resulting tertiary amine complex reacted with several N-protected oxazolidines in the presence of one equivalent of trimethyl- or triethylaluminum leading to very good diastereoselectivities and yields. Only alkynyl group transfer was observed, without any competitive reduction or alkylation of the oxazolidine. Secondary propargylamines could be obtained, after chemioselective acidic cleavage of the ferrocenylmethyl protective group, as single a diastereomer after chromatographic purification. Oxidative cleavage of the chiral appendage afforded final compounds whose optical purity was determined by chiral HPLC to be greater than 99% (*Scheme 40*).



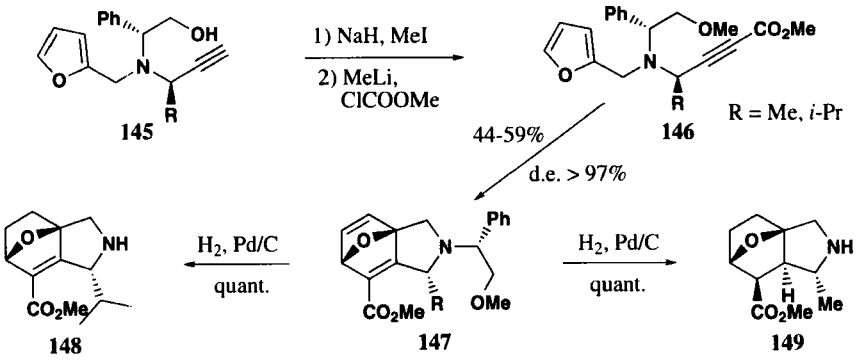
Scheme 40

Diethylaluminum acetylides also react with oxazolidines. This reagent was prepared *in situ* by transmetalation of commercially available sodium acetylide with diethylaluminum chloride at room temperature.[66]



Scheme 41

Propargylamines such as **145** have been used for the preparation of polyfunctionnal dihydroisoindolines in a simple fashion by intramolecular Diels-Alder reaction (IMDAF) (*Scheme 42*).[67] The combination of oxazolidine and mixed organoaluminum chemistry provides an efficient and general access to α-substituted propargylamines, using inexpensive standard commercially available organoaluminum solutions and simple experimental procedures.



Scheme 42

III. CONCLUSION

Numerous examples of the use of α-susbtituted propargylamines in synthetic strategies are presented in this article, showing the great synthetic value of such intermediates. However, most of them are "target oriented" and do not use simple and versatile methods for the preparation of these reagents in enantiomerically pure form. Recent progress in this field, mainly based on the addition of nucleophiles on imines or related functions, show promising results. Simple and practical methods are now available, using relatively under-exploited zinc or aluminum acetylide chemistry to afford α-substituted propargylamines under scalable reaction conditions. However, a practical enantioselective preparation of these useful intermediates, based on the use of a small amount of an available enantiopure catalytic species, is still to be discovered and remains an important synthetic challenge.

REFERENCES

1. For recent asymmetric catalytic synthesis of propargyl alcohols : (a) D. E. Frantz, R. Fässler, C. S. Tomooka and E. M. Carreira, *Acc. Chem. Res.*, **33**, 373 (2000); (b) D. E. Frantz, R. Fässler and E. M. Carreira, *J. Am. Chem. Soc.*, **122**, 1806 (2000); (c) K. Matsumura, S. Hashigushi, T. Akariya and R. Noyori, *J. Am. Chem. Soc.*, **119**, 8738 (1997); (d) C. J. Helal, P. A. Magriotis and E. J. Corey, *J. Am. Chem. Soc.*, **118**, 10938 (1996).

2. M. T. Reetz, *Chem. Rev.*, **99**, 1121 (1999).

3. In spite of our efforts to gather all relevant publications, we want to apologize to research groups whose work is not mentioned in this paper. We would be pleased if they could informed us about missing papers.

4. (a) "*Enediyne Antibiotics as Antitumor Agents*", T. W. Doyle and D. B. Borders, Eds., Marcel-Dekker: New York (1994); (b) K. C. Nicolaou and E. J. Sorensen, "*Classics in Total Synthesis*", VCH: Weinheim (1996).

5. (a) M. Konishi, H. Ohkuma, K. Matsumoto, T. Tsuno, H. Kamei, T. Meyaki T. Oki, H. Kawaguchi, G. D. VanDuyne and J. Clardy, *J. Antibiot.* **42**, 1449 (1989); (b) A. G. Myers, S. B. Cohen, N. J. Tom, D. J. Madar and M. E. Fraley, *J. Am. Chem. Soc.*, **117**, 7574 (1995); (c) M. E. Maier, F. Bosse and A. J. Niestroj, *Eur. J. Org. Chem.*, 1 (1999).

6. R. M. Scaborough and D. D. Gretler, *J. Med. Chem.*, **43**, 3453 (2000).

7. J. A. Zablocki, J. G. Rico, R. B. Garland, T. E. Rogers, K. Williams, L. A. Schretzman, S. A. Rao, P. R. Bovy, F. S. Tjoeng, R. J. Lindmark, M. V. Toth, M. E. Zupec, D. E. Mcmackins, S. P. Adams, M. Miyano, C. S. Markos, M. N. Milton, S. Paulson, M. Herin, P. Jacqmin, N. S. Nickolson, S. G. Panzer-Knodle, N. F. Haas, J. D. Page, J. A. Szalony, B. B. Taite, A. K. Salyers, L. W. King, J. G. Campion and L. P. Feigen, *J. Med. Chem.*, **38**, 2378 (1995).

8. *Drugs Fut.*, **24**, 588 (1999).

9. J. H. Hutchinson, J. J. Cook, K. M. Brashear, M. J. Breslin, J. D. Glass, R. J. Gould, W. Halczenko, M. A. Holahan, R. J. Lynch, G. R. Sitko, M. T. Stranieri and G. D. Hartman, *J. Med. Chem.*, **39**, 4583 (1996).

10. W. J. Hoekstra, B. E. Maryanoff, B. P. Damiano, P. Andrade-Gordon, J. H. Cohen, M. J. Costanzo, B. J. Haertlein, L. R. Hecker, B. L. Hulshizer, J. A. Kauffman, P. Keane, D. F. McComsey, J. A. Mitchell, L. Scott, R. D. Shah and S. C. Yabut, *J. Med. Chem.*, **42**, 5254 (1999).

11. E. J. Corey and P. L. Fuchs, *Tetrahedron Lett.*, **13**, 3769 (1972).

12. L. Horner, H. Hoffmann and H. G. Wippel, *Chem. Ber.*, **91**, 61 (1958).

13. J. C. Gilbert and U. Weerasooriya, *J. Org. Chem.*, **47**, 1837 (1982).

14. Z. Wang, J. Yin, S. Campagna, J. A. Pesti and J. M. Fortunak, *J. Org. Chem.*, **64**, 6918 (1999).

15. P. Meffre, L. Gauzy, C. Perdigues, F. Desanges-Levêque, E. Branquet, P. Durand and F. Le Goffic, *Tetrahedron Lett.*, **36**, 877 (1995).

16. S. Ohira, *Synth. Comm.*, **19**, 561 (1989).

17. D. Grandjean, P. Pale and J. Chuche, *Tetrahedron Lett.*, **35**, 3529 (1994).

18. G. Reginato, A. Mordini, A. Degl'Innocenti and M. Caracciolo, *Tetrahedron Lett.*, **36**, 8275 (1995).

19. G. Reginato, A. Mordini and M. Caracciolo, *J. Org. Chem.*, **62**, 6187 (1997).

20. G. Cabarrocas, S. Rafel, M. Ventura and J. M. Villalgordo, *Synlett*, **5**, 595 (2000).

21. G. Reginato, A. Mordinia and M. Valacchi, *Tetrahedron Lett.*, **39**, 9545 (1998).

22. M. Falorni, G. Giacomelli and E. Spanu, *Tetrahedron Lett.*, **39**, 9241 (1998).

23. J. Y. L. Chung and J. T. Wasicak, *Tetrahedron Lett.*, **31**, 3957 (1990).

24. E. J. Trybulski, R. H. Kramss, R. M. Mangano and A. Rusinko, III, *J. Med. Chem.*, **33**, 3190 (1990).

25. J. Cossy, M. Cases and D. Gomez Pardo, *Bull. Soc. Chim. Fr.*, **134**, 141 (1997).

26. P. F. Keusenkothen and M. B. Smith, *J. Chem. Soc., Perkin Trans. 1*, 2485 (1994).

27. M. Oestreich, R. Fröhlich and D. Hoppe, *J. Org. Chem.*, **64**, 8616 (1999).

28. M. T. Reetz, T. J. Strack, J. Kanand, R. Goddard, *J. Chem. Soc., Chem. Commun.*, 733 (1996).

29. R. A. Aitken, N. Karodia, *J. Chem. Soc., Chem. Commun.*, 2079 (1996).

30. P.-J. Coulson, L. S. Hegedus, *J. Org. Chem.*, **58**, 5918 (1993).

31. C. Cativiela, M. D. Diaz-de-Villegas, *Tetrahedron: Asymm.*, **9**, 3517 (1998).

32. R. Epsztein, F. Mercier, *Synthesis*, 183 (1977).

33. M. Kolb, J. Barth, *Angew. Chem.*, **92**, 753 (1980).

34. J. A. Marshall, M. A. Wolf, *J. Org. Chem.*, **61**, 3238 (1996).

35. O. Misunobu, *Synthesis*, 1 (1981).

36. A. B. Holmes, A. B. Tabor, R. Baker, *J. Chem. Soc., Perkin Trans. 1*, 3301 (1991)

37. S. Takano, K. Inomata, K. Ogasawara, *J. Chem. Soc., Chem. Commun.*, 169 (1992).

38. S. Czernecki, S. Horns, J.-M. Valery, *J. Org. Chem.*, **60**, 650 (1995).

39. F. E. McDonald, M. M. Gleason, *J. Am. Chem. Soc.*, **118**, 6648 (1996).

40. S. Shuto, S. Ono, H. Imoto, K. Yoshii, A. Matsuda, *J. Med. Chem.*, **41**, 3507 (1998).

41. T. Fujisawa, M. Nagai, Y. Koike, M. Shimizu, *J. Org. Chem.*, **59**, 5865 (1994).

42. B. Bernet, A. Vasella, *Tetrahedron Lett.*, **24**, 5491 (1983).

43. U. Schmidt, M. Respondek, A. Lieberknecht, J. Werner, P. Fischer, *Synthesis*, 256 (1989).

44. K. M. Nicholas, *Acc. Chem. Res.*, **20**, 207 (1987).

45. C. Mukai, Y-I Sugimoto, K. Miyazwa, S. Yamaguchi, M. Hanaoka, *J. Org. Chem.*, **63**, 6281 (1998).

46. (a) D. Enders, J. Schankat, *Helv. Chem. Acta*, **76**, 402 (1993); (b) D. Enders, J. Schankat, *Helv. Chem. Acta*, **78**, 970 (1995).

47. D. Enders, U. Reinhold, *Tetrahedron: Asymm.*, **8**, 1895 (1997).

48. P. J. Garratt, *"Comprehensive Organic Synthesis"*, B. M. Trost, I. Flemming Eds, Pergamon Press, New York, **3**, 271 (1991).

49. M. Shimizu, M. Kawamoto, Y. Niwa, *J. Chem. Soc., Chem. Commun.*, 1151 (1999).

50. M. A. Huffman, N. Yasuda, A. E. De Camp, E. J. J. Grabowski, *J. Org. Chem.*, **60**, 1590 (1995).

51. P. Merino, S. Anoro, E. Castillo, F. Merchan, T. Tejero, *Tetrahedron: Asymm.*, **7**, 1887 (1996).

52. D. L. Comins, D. A. Stolze, P. Thakker, C. L. McArdle, *Tetrahedron Lett.*, **39**, 5693 (1998).

53. G. Alvaro, P. Pacioni, D. Savoia, *Chem. Eur. J.*, **3**, 726 (1997).

54. D. E. Frantz, R. Fässler, E. M. Carreira, *J. Am. Chem. Soc.*, **121**, 11245 (1999).

55. A. W. Shaw, S. J. deSolms, *Tetrahedron Lett.*, **42**, 7173 (2001).

56. M. Nagai, J. J. Gaudino, C. S. Wilcox, *Synthesis*, 163 (1992).

57. H. Poerwono, K. Higashiyama, H. Takahashi, *J. Org. Chem.*, **63**, 2711 (1998).

58. T. Nishikawa, M. Yoshikai, K. Obi and M. Isobe, *Tetrahedron Lett.*, **35**, 7997 (1994).

59. F. Rezqui, P. Mangeney and A. Alexakis, *Tetrahedron Lett.*, **40**, 6241 (1999).

60. M. D. Shair, T. Young Yoon, K. K. Mosny, T. C. Chou and S. J. Danishefsky, *J. Am. Chem. Soc.*, **118**, 9509 (1996).

61. A. G. Myers, N. J. Tom, M. E. Fraley, S. Cohen and D. J. Madar, *J. Am. Chem. Soc.*, **119**, 6072 (1997).

62. (a) A. Rae, J. Ker, A. B. Tabor, J. L. Castro and S. Parsons, *Tetrahedron Lett.*, **39**, 6561 (1998); (b) A. Rae, J. L. Castro and A. B. Tabor, *J. Chem. Soc., Perkin Trans. 1*, 1943 (1999).

63. A. Alexakis and P. Mangeney, *Tetrahedron: Asymm.*, **1**, 477 (1990).

64. (a) J. Blanchet, M. Bonin, A. Chiaroni, L. Micouin, C. Riche and H.-P. Husson, *Tetrahedron Lett.*, **40**, 2935 (1999); (b) J. Blanchet, M. Bonin, L. Micouin and H.-P. Husson, *J. Org. Chem.*, **65**, 6423 (2000).

65. (a) G. Zweifel and J. A. Miller *Org. React.*, **34**, 375 (1984); (b) E.-I. Negishi *"Organometallics of Main Group Metals in Organic Synthesis"*, John Wiley, New York, 286 (1980).

66. J. Blanchet, M. Bonin, L. Micouin and H.-P. Husson, *Tetrahedron Lett.*, **42**, 3171 (2001).

67. C. O. Kappe, S. S. Murphree and A. Padwa, *Tetrahedron*, **53**, 14179 (1997).

(Received November 7, 2001; in final form February 22, 2002)