DISSERTATION

DIASTEREOSELECTIVE SYNTHESIS OF α-SUBSTITUTED PROPARGYLAMINES VIA DICOBALT COMPLEX METHODOLOGY

Submitted by

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In partial fulfillment of the requirements

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WE HEREBY RECOMMEND THAT THE DISSERTATION PREPARED UNDER OUR SUPERVISION BY SARRI S. SALMAN ENTITLED DIASTEREOSELECTIVE SYNTHESIS OF α-SUBSTITUTED PROPARGYLAMINES VIA DICOBALT COMPLEX METHODOLOGY BE ACCEPTED AS FULFILLING IN PART REQUIREMENTS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY.

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ABSTRACT OF DISSERTATION

DIASTEREOSELECTIVE SYNTHESIS OF α-SUBSTITUTED PROPARGYLAMINES VIA DICOBALT COMPLEX METHODOLOGY

Diastereoselective chromium carbene photochemistry afforded a cyclobutanone which was elaborated to a disubstituted butenolide bearing 4′-(benzyloxy)methyl and 4′-ethoxy groups. This template was converted to a 2′,3′-dideoxy-thymidine nucleoside analog.

Dicobalt hexacarbonyl complexes of propargyl *N,OTMS*-acetals were prepared, and the scope of their reactivity was studied. In the presence of $TiCl_4$, a mixture of $Co_2(CO)_6$-complex diastereomers was equilibrated to one, idicating a cationic intermediate. An equilibration/alkylation sequence allowed the preparation of propargylamides with high diastereocontrol. The absence of the cluster led to alkylation with decreased diastereoselectivity.

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ACKNOWLEDGEMENTS

Amid the raging civil war engulfing Lebanon, my parents committed to leaving Beirut during the spring of 1986. Moving us to Boston and foregoing a career, family, friends, and roots, they sacrificed their future for the sake of ours. I can never fully appreciate the magnitude of such a selfless act or the breadth of their courage. In recognition of their noble foresight, this dissertation is dedicated to my parents, Salah and Wadad Salman.

The encounter of one mentor in Life is a blessing; two, auspicious. My chemistry years were profoundly influenced by Profs. Bradford P. Mundy (Colby College) and Louis S. Hegedus (Colorado State University). Their teachings and counsel significantly contributed to my academic progress and personal development. I am indebted to Prof. Mundy for the fruitcake, and to Prof. Hegedus for the Burrowing Owls, Bald Eagles, and Sharp-tailed Grouse.

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Finally, as a trained scientist I owe a modicum of gratitude to *the great tragedy of Science - the slaying of a beautiful hypothesis by an ugly fact* (Thomas H. Huxley).

To the triumph of becoming over being

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LIST OF ABBREVIATIONS

(aq)	Aqueous
Ac_2O	Acetic anhydride
Acac	Acetyl acetonate
Bn	Benzyl
BSA	*N,O*-Bis(trimethylsilyl)acetamide
Bz	Benzoyl
CAN	Cerric ammonium nitrate
Cp	Cyclopentadienyl
Cp*	Pentamethylcyclopentadienyl
Cy	Cyclohexyl
Δ	Heat
dba	Dibenzylideneacetone
DCE	Dichloroethane
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	Diethyl azodicarboxylate
Dibal-H	Diisobutylaluminum hydride
DMF	Dimethylformamide
dppe	(Diphenylphosphino) ethane
dppm	(Diphenylphosphino) methane
dr	Diastereomeric ratio
ee	Enantiomeric excess
EtOAc	Ethyl acetate
hv	Light
L.A.	Lewis acid
LG	Leaving group
m-CPBA	*m*-Chloroperbenzoic acid
NBS	*N*-Bromosuccinimide
NMO	4-Methylmorpholine *N*-oxide
NMP	1-Methyl-2-pyrrolidinone
Nu	Nucleophile

LIST OF ABBREVIATIONS (continued)

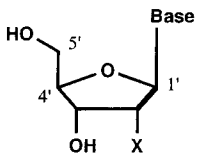
[O]	Oxidation reaction
Oxone	Potassium peroxymonosulfate
P	Protecting group
PivCl	Pivaloyl chloride
Py/Pyr	Pyridine
rt	Room temperature
(s)	Solid
T	Thymine
TBAF	Tetra-*n*-butyl ammonium fluoride
TBDPS	*tert*-Butyldiphenylsilyl
TES	Triethylsilyl
THF	Tetrahydrofuran
TMS	Trimethylsilyl
TMSOTf	Trimethylsilyl trifluoromethanesulfonate
Tp	Trispyrazolylborate
Ts	4-Toluenesulfonyl

Chapter 1: Synthesis of An 4′-Ethoxy Nucleoside Analogue

I. Introduction

4′-Disubstituted nucleoside analogues

Naturally occurring nucleosides, whether ribose or deoxyribose-based, are represented by the structure in Figure 1.

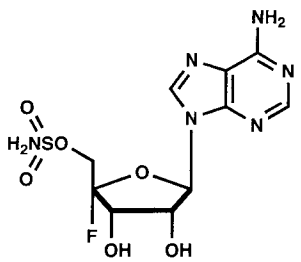


Base = Adenine (A), Thymine (T), Cytosine (C), Guanine (G), Uracil (U)

X = OH (ribose), H (deoxyribose)

Figure 1

In 1957, an antibiotic was isolated from the microorganism *Streptomyces calvus*.[1] Given the name nucleocidin, this 4′-fluoro-5′-O-sulfamoyladenosine **1** (Figure 2) exhibited broad antibacterial activity, particularly against *Trypanosoma protozoa*.[2] It was described as the first example of a 4′-disubstituted furanose moiety.

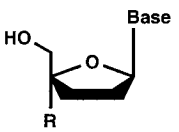


1

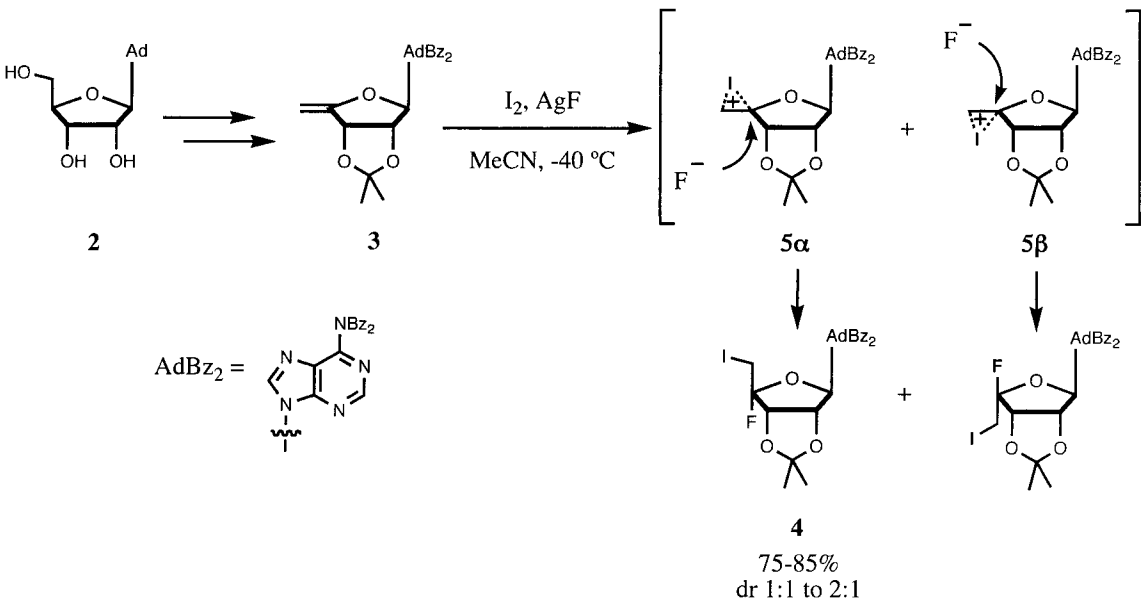
Figure 2

Subsequently, this class of compounds was also shown to exhibit anticancer properties.[3] The quest for more effective analogues, as well as the discovery of potent anti-HIV activity shown by AZT,[4] heralded efforts toward other members of this family (Table 1).[5]

Table 1: 4′-Disubstituted nucleoside analogues.

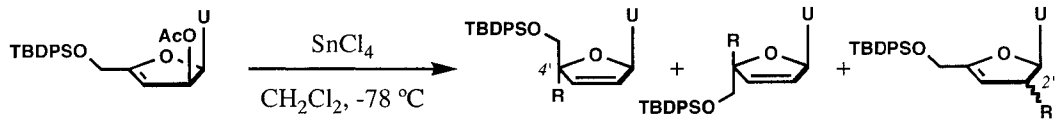
	R	Ref.
	SePh	6
	CH_2OH	7
	Allyl	8
	N_3	9
	CO_2Me	10
	$CONH_2$	11
	CN	6b
	CH_2COCH_3	6b
	F	12

Moffatt's synthesis of nucleocidin **1** began with adenosine **2** to generate unsaturated precursor **3** (Scheme 1).[12b] Concomitant electrophilic halogenation yielded **4** with poor diasteroselectivity. Perhaps the inability to modulate iodonium intermediate formation (**5α** versus **5β**) hampered the selectivity of this key reaction.



Scheme 1

Tanaka based his route to 4′-*C*-branched analogues on modified natural purine and pyrimidine nucleosides (Scheme 2).[8b] When subjected to various nucleophiles in the presence of $SnCl_4$, allylic acetate **6** produced **7** and **8** with moderate selectivity and yield. As the bulk of the nucleophile increased, a competing 2′-S_N2 mechanism was observed (**9**, Scheme 2).

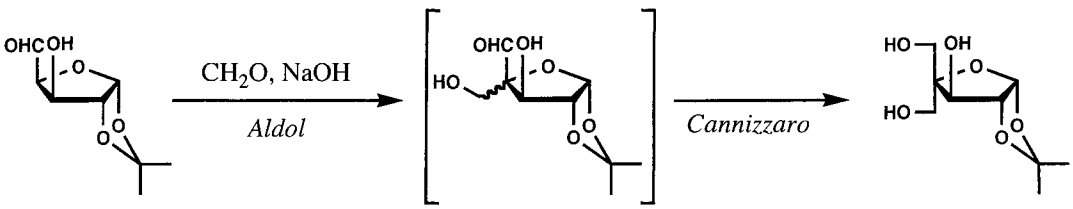


6 7 8 9

Reagent	R	**7**:**8** (yield)	**9** Yield
TMS		15:1 (79%)	
OTMS	O	6:1 (51%)	
NCTMS	CN	2:1 (64%)	
OTMS Ph	O Ph	6:1 (64%)	14%
OTMS	O	34:1 (70%)	17%

Scheme 2

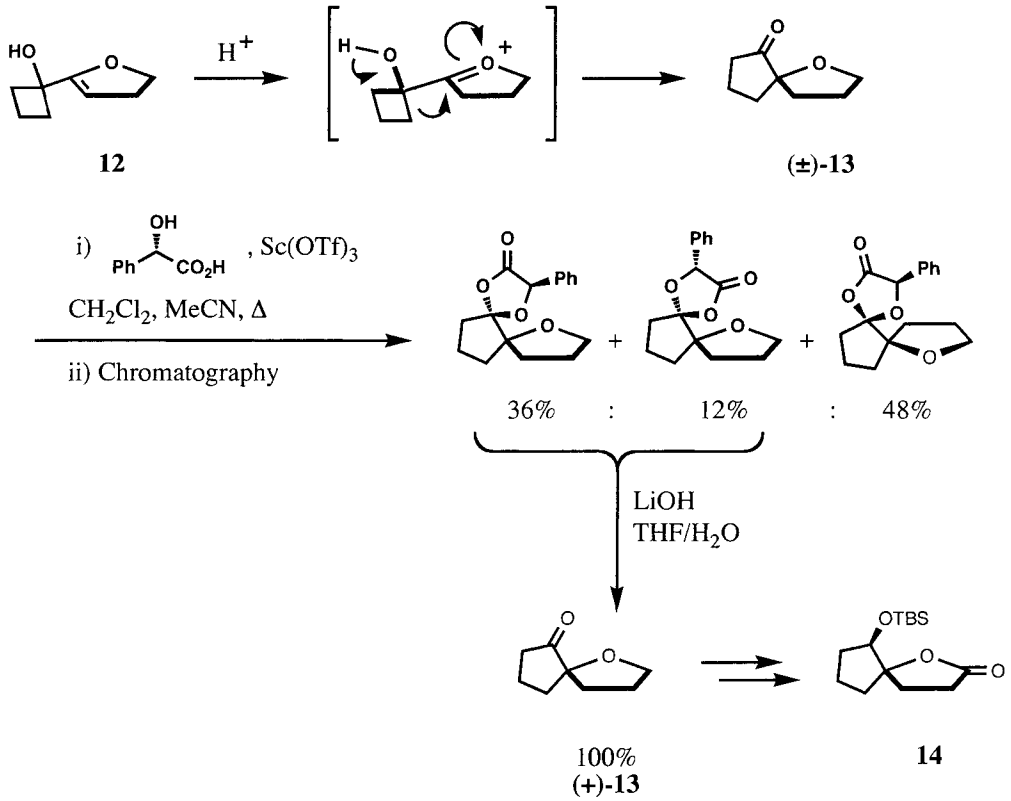
4′-Disubstituted nucleosides have also been synthesized from modified carbohydrates. Verheyden effected an Aldol/Cannizzaro reaction sequence on **10** to produce furanose **11** (Scheme 3).[13]



10 **11**

Scheme 3

Paquette elaborated the oxonium ion-initiated pinacol ring expansion of **12**, an unnatural precursor, to afford racemic spiro ketone **13** (Scheme 4).[14] Separation of enantiomers via chiral acetalization, followed by additional steps produced **14**, the scaffold for his conformationally restricted nucleoside analogues.

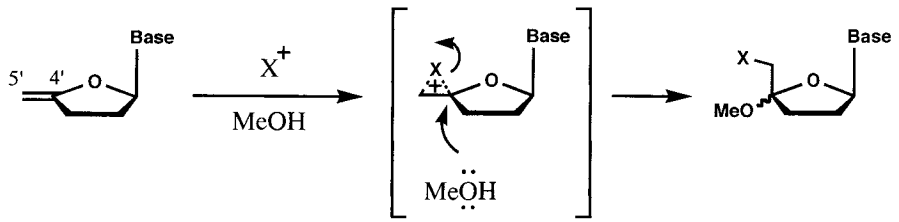


Scheme 4

Thus initial syntheses of 4′-disubstituted nucleoside analogues relied on the functionalization of existing D-nucleosides, but more recent contributions have begun to explore the use of non-nucleosidic starting materials.[Error! Bookmark not defined., 15]

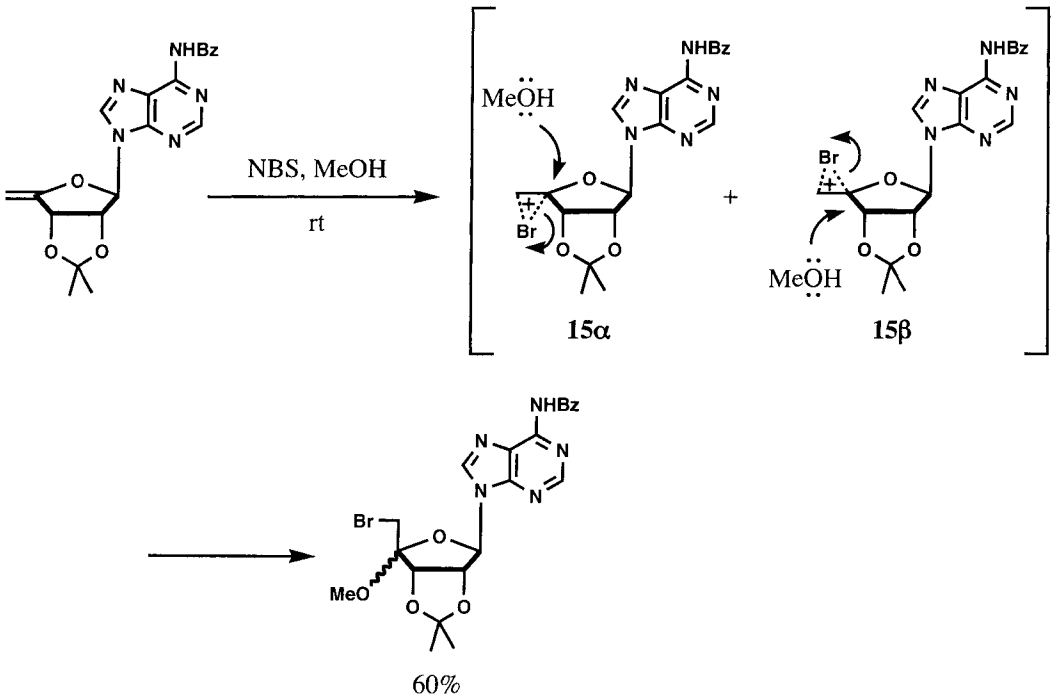
4′-Alkoxy nucleoside analogues

Most literature approaches to the preparation of 4′-alkoxy nucleoside analogues required 4′,5′-unsaturation to effect nucleophilic alkoxy addition (Scheme 5).



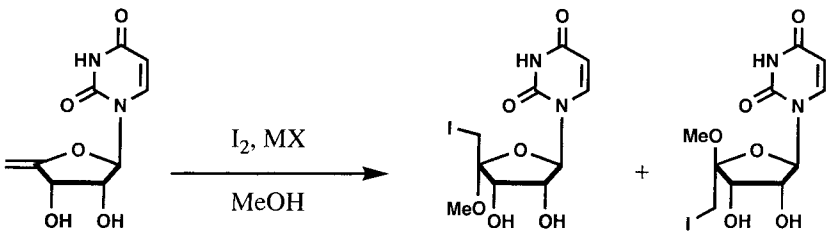
Scheme 5

Sasaki first reported the Markovnikov addition of hypobromous acid, generated in situ, to unsaturated nucleosides (Scheme 6).[16] The addition occurred with no diastereoselection, an outcome reminiscent of Moffatt's synthesis of nucleocidin (see Scheme 1) and a possible indication of the inability to control bromonium ion intermediate formation (**15α** vs **15β**).



Scheme 6

This selectivity problem was also encountered by Moffatt (Scheme 7).[17] However, upon switching to lead carbonate, the β-anomer **16** was the exclusive product. Concomitant precipitation of PbI_2 drove formation of the iodonium ion intermediate (vide supra).



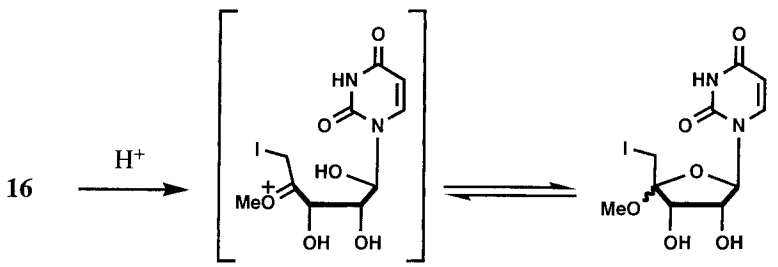
16

MX = AgOAc 2 : 1

$PbCO_3$ >99 : 1

Scheme 7

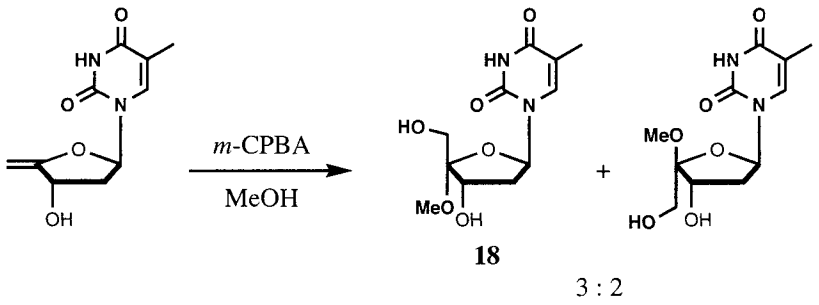
It was postulated that with the former reagent the subsequent acetic acid formed catalyzed the equilibration of **16** via **17** (Scheme 8).



17

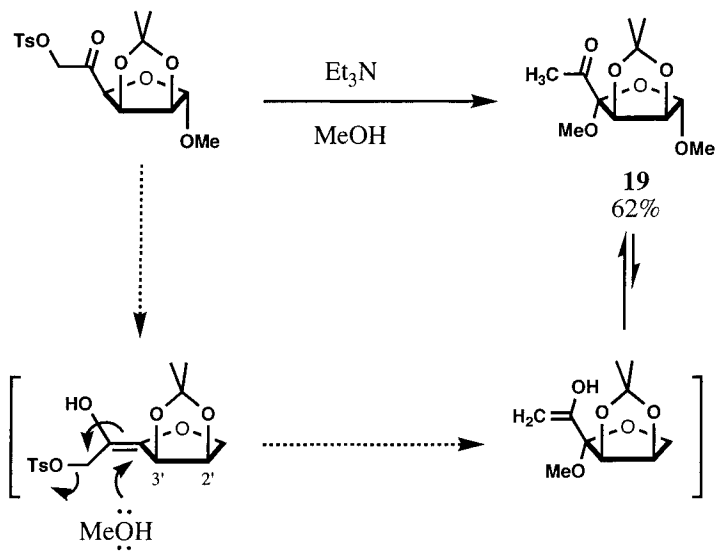
Scheme 8

More recently, researchers at Syntex relied on an epoxidation/epoxide opening strategy to prepare thymidine derivative **18**, albeit with poor selectivity (Scheme 9).[4c]



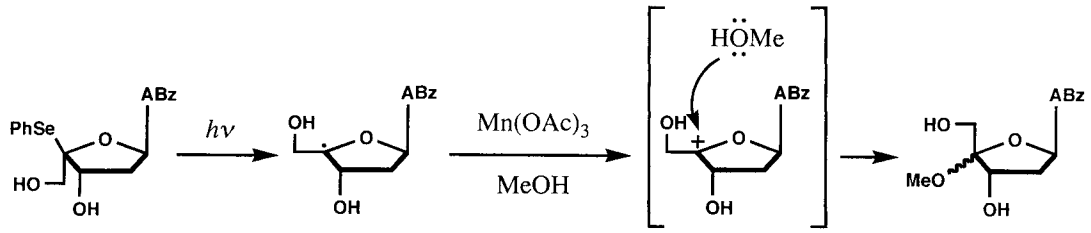
Scheme 9

An analogous alkene addition was proposed by Dmytraczenko et. al for the synthesis of **19** (Scheme 10).[18] The exclusive α attack was attributed to steric direction by the β 2′-3′-diol ketal.



Scheme 10

An interesting route was published by Giese in which manganese-mediated oxidation of the 4′-deoxyribonucleoside radical **20** to cation **21** afforded acetal **22** after MeOH quench, also with low selectivity (Scheme 11).[19]



20 **21** **22**

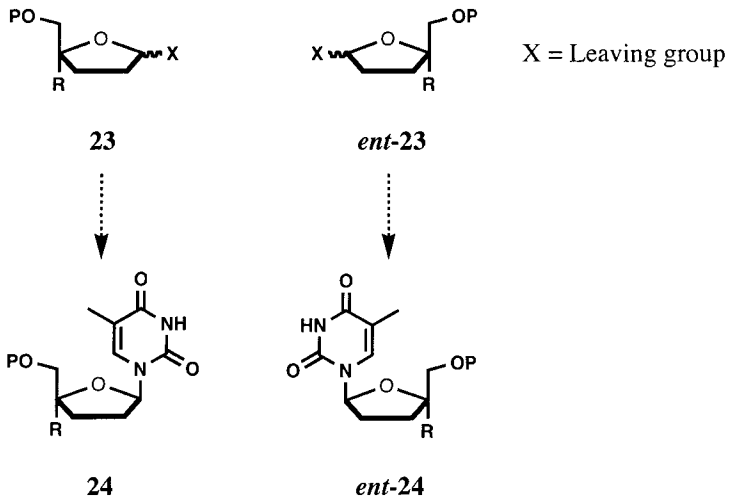
91%
56 : 44

Scheme 11

Analogous to other 4′-disubstituted nucleosides, syntheses of 4′-alkoxy analogues were restricted to the use of natural D-nucleosides. Therefore a novel 4′-disubstituted nucleoside synthesis not limited by natural starting materials would add to the art form. It should be noted that recent syntheses of L-ribose,[20] and its commercial availability, should provide access to the unnatural L-nucleoside analogue series. The discovery that L-nucleosides exhibited antiviral activity with reduced toxicity,[21] and their recent application to L-RNA synthesis,[22] further adds to the value of their synthesis.

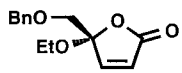
II. Rationale

A de novo synthesis of 4′-disubstituted nucleoside analogues, relying on a convergent approach of incorporating a nucleoside base onto carbohydrate derivate **23** and ***ent*-23**, would overcome long and nonstereoselective precedents (vide supra) and permit the preparation of both enantiomers (**24** and ***ent*-24**, Scheme 12).



Scheme 12

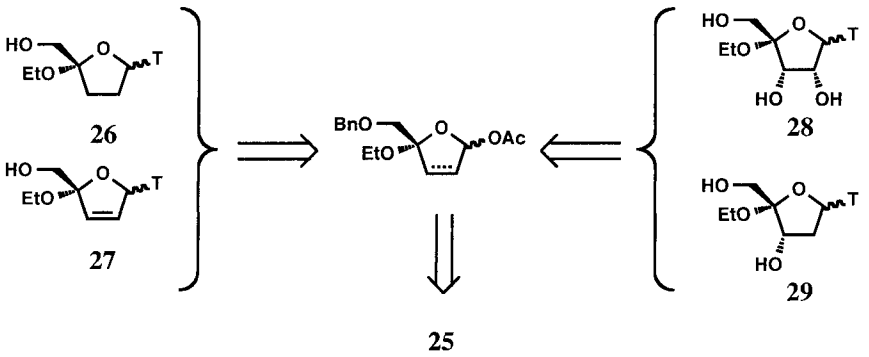
The Hegedus group recently reported the synthesis of chiral butenolide **25** (Figure 3).[23]



25

Figure 3

It was envisioned that further manipulations of this template would afford access to analogue targets **26**, **27**, **28**, and **29** (Scheme 13).

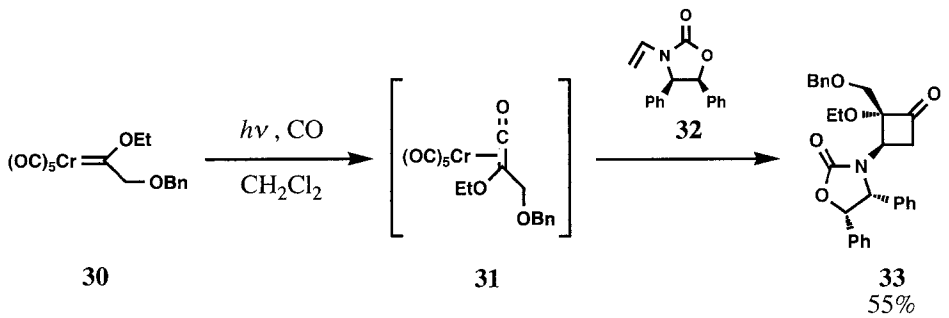


Scheme 13

III. Results & Discussion

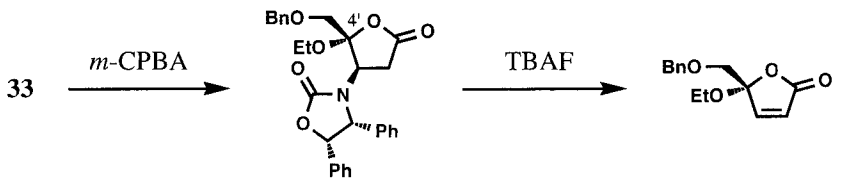
Template synthesis

Although lacking experimental confirmation, it is believed that photolysis of carbene complex **30** generates a chromium-bound ketene **31** which reacted with optically active ene carbamate **32** to produce cyclobutanone **33** as the sole diastereomer (Scheme 14). The absolute stereochemistry of the product is determined by the configuration of the ene carbamate, thus both enantiomers of **33** are within reach. This strategy overcomes the limitation imposed by relying on natural carbohydrates (vide supra). It should be noted that the photochemical step produces the thermodynamically less-stable product, in which the two large groups are *syn* (vide infra).



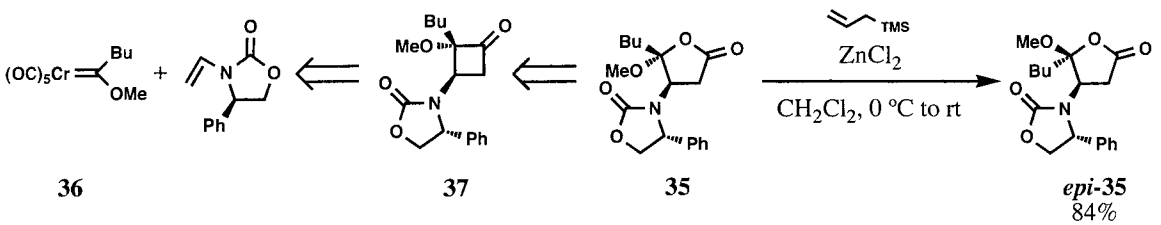
Scheme 14

Subsequent Baeyer-Villiger ring expansion, with retention of 4′-stereochemistry, afforded lactone **34**; treatment of which with TBAF eliminated the oxazolidinone to give butenolide **25** in high yield (Scheme 15).



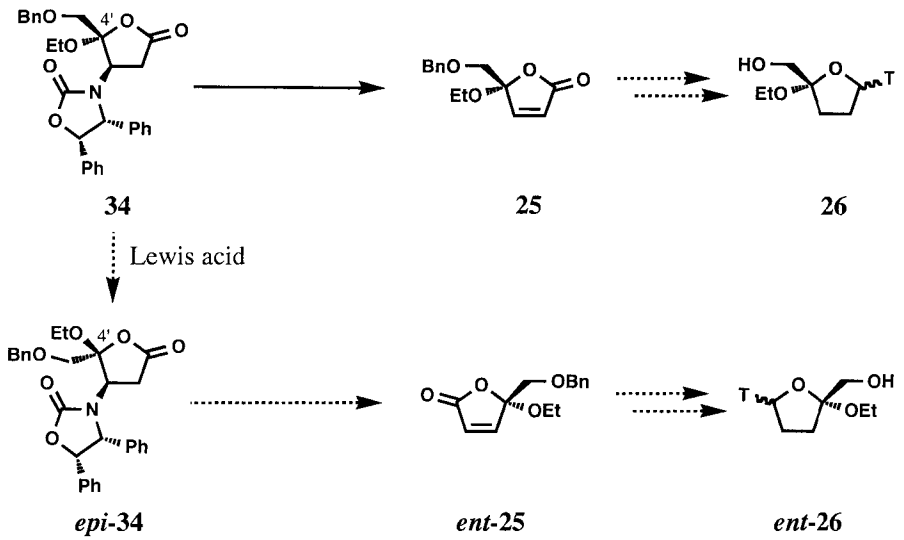
Scheme 15

Prior serendipitous results from the Hegedus group had epimerized lactone **35** at the 4′-position in the presence of zinc chloride, indicating a kinetic pathway for the photochemical step (**36** to **37**, Scheme 16),[24]



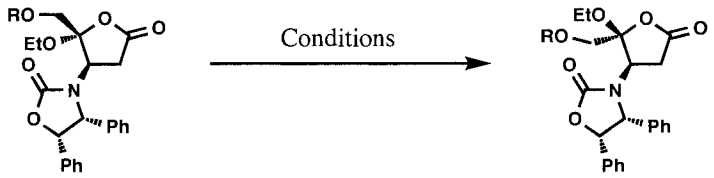
Scheme 16

Therefore, this discovery potentially allows for the synthesis of both butenolide enantiomers (**25** and ***ent*-25**) and subsequent nucleoside analogues from a common precursor, lactone **34** (Scheme 17).



Scheme 17

Epimerization studies were undertaken on the system (Scheme 18). Although compound **31** would only partially invert, complete conversion was achieved with **38**. Again, these results are consistent with cyclobutanone **30** being a kinetic product.



31 R = Bn
38 R = TBS

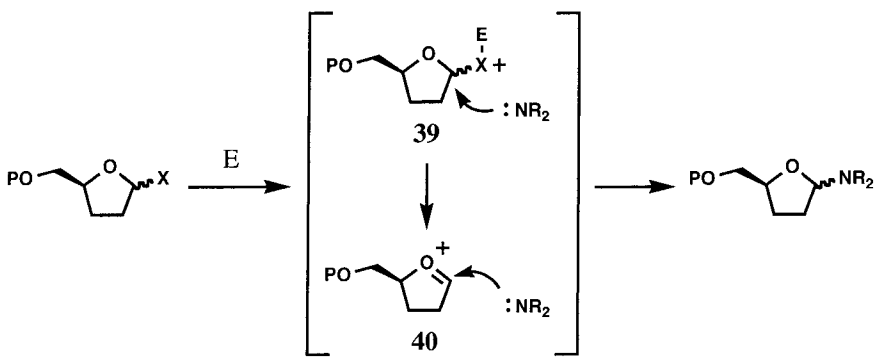
***epi*-31**
***epi*-38**

Substrate	Lewis acid (eq.)	Result
31	$ZnCl_2$ (1)	3:1 dr
31	$ZnCl_2$ (5)	6:1 dr
31	$ZnCl_2$ (20)	Decomposition
31	$BF_3 \cdot OEt_2$ (1.2)	9:1 dr
31	$BF_3 \cdot OEt_2$ (3.5)	10:1 dr
38	$SnCl_4$ (0.5)	>95:5 dr

Scheme 18

2′,3′-Dideoxy analogue synthesis

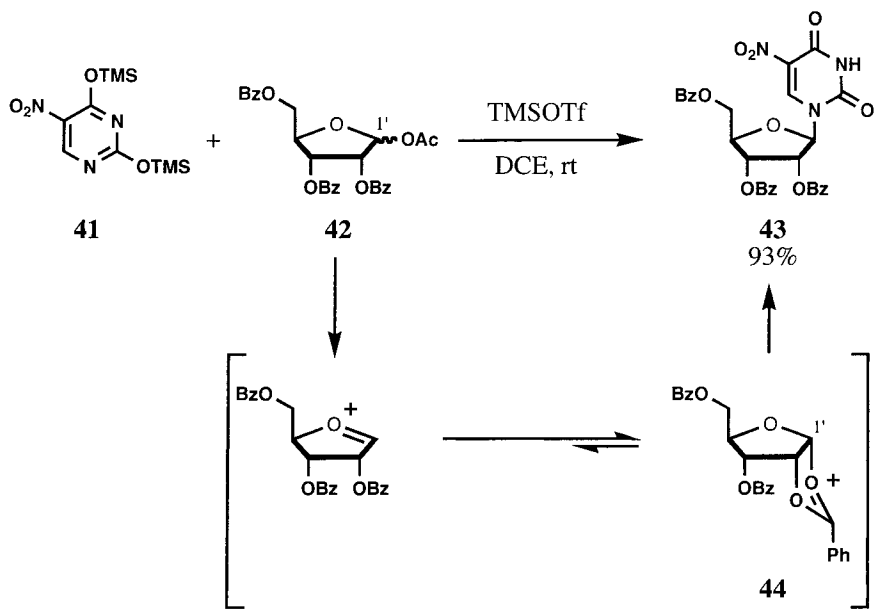
In nucleoside synthesis several glycosylation reactions had been developed to attach the base fragment to the carbohydrate moiety. Strategies revolve around either direct anomeric nucleophilic displacement of **39** or addition to oxonium intermediate **40** (Scheme 19).[25]



X = OAc, SPh, S(O)Ph, etc.
E = TMSOTf, AgOTf, $SnCl_4$, NBS, etc.

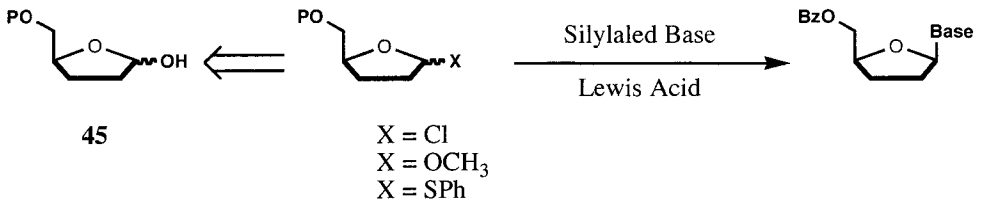
Scheme 19

A very common approach involving an oxonium intermediate is the silicon variant of the Hilbert-Johnson reaction first introduced by Vorbrüggen (Scheme 20).[26] Under these conditions, TMSOTf catalyzes the reaction between silylated base **41** and acetylated ribose **42** to yield coupled product **43**. In the presence of an α-C-2 benzoyloxy group, bridging oxonium intermediate **44** forces β-attack at the 1′-position, hence the stereoselective outcome. Thus, neighboring group participation is a key requirement for β-selectivity in intermolecular reactions.



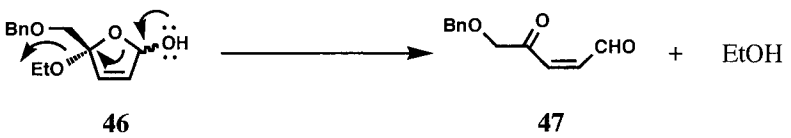
Scheme 20

The scope of the Vorbrüggen coupling has since been expanded to permit the use of halides, ethers, and sulfides as leaving groups (Scheme 21).[27] All aforementioned glycosyl donors are prepared from hemiacetal precursor **45**.



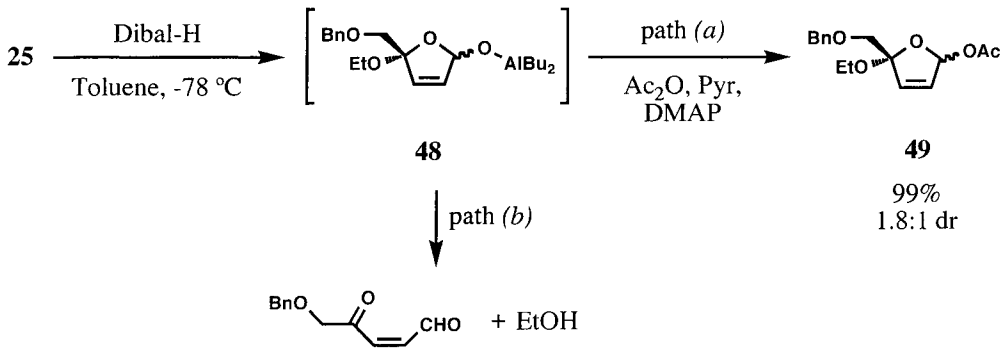
Scheme 21

It bears noting that in the system under discussion, the presence of a 4′-ethoxy group precludes the use of hemiacetal **46** since it would irreversibly lead to ring opening product **47** (Scheme 22). Thus the coupling precursor required the avoidance of a free hemiacetal structure.



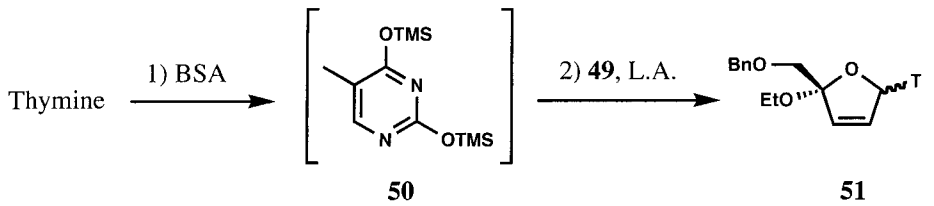
Scheme 22

By relying on the Rychnovsky protocol,[28] butenolide **25** was reduced with Dibal-H followed by trapping of the lactol aluminate **48** with acetic anhydride, to give acetate **49** as a 1:1 mixture of C-1 anomers (Scheme 23). The use of an in situ trap obviated ring opening via ejection of ethanol (Scheme 23, path *b*).



Scheme 23

Vorbrüggen coupling partner **49** was reacted with freshly-prepared silylated thymine **50** to produce **51** as a 1:1 mixture of anomeric diastereomers (Scheme 24). This lack of selectivity is consistent with the absence of a C-2 substituent providing anchimeric assistance (vide supra).

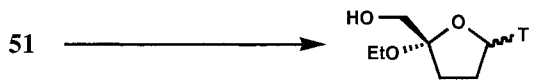


50 **51**

L.A.	Yield
TMSOTf, MeCN	65%
$SnCl_4$, DCE	63%
$SnCl_4$, MeCN	87%

Scheme 24

Deprotection of the 5′-hydroxyl concurrent with olefin reduction using Pearlman's catalyst afforded nucleoside analogue **26** in good chemical yield (Scheme 25).



26

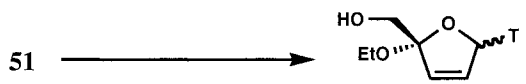
Conditions	Result
$Pd(OH)_2/C$, H_2, MeOH	88%
Pd/C, $Pd(OAc)_2$, HCO_2NH_4, MeOH	Decomposition

Scheme 25

Attempts to synthesize 2′,3′-dideoxy-didehydro analogue

It was postulated that **51** could also serve as a precursor to analogue **27** by relying on established debenzylation protocols. Unfortunately, reduction to practice proved

problematic. Lewis acidic, reductive, and oxidative conditions failed to selectively 5′-debenzylate the substrate (Scheme 26).



27

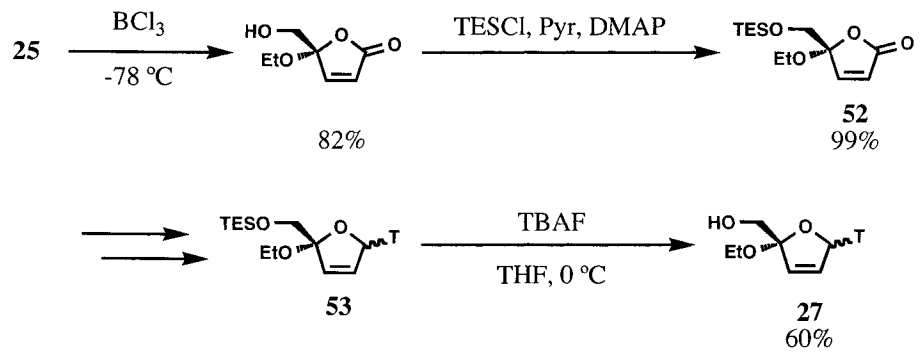
Conditions	Result
Ph_3CBF_4, $CHCl_3$	Decomposition
BCl_3, CH_2Cl_2	Thymine
Oxone, $NaHCO_3$, Acetone/H2O	Recovered **51**
DDQ, CH_2Cl_2	Recovered **51**
Na/NH_3, THF/EtOH	Decomposition
Li/NH_3	Decomposition
Ca/NH_3	Decomposition
Raney Ni, EtOH	Recovered **51**

Scheme 26

These results pointed to the necessity of removing the benzyl group at an earlier step in the synthesis (vide infra).

Geisler/Riches route to 2′,3′-dideoxy-didehydro analogue[29]

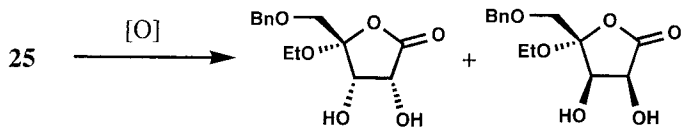
Project collaborators L. Geisler and Dr. A. Riches applied the aforementioned strategy by replacing the 5′-benzyl group in **25** with a silicon protecting group (**52**, Scheme 27). Pursuant to the established protocol, thymine-coupled product **53** was obtained as a mixture of anomers. Final deprotection afforded 2′,3′-dideoxy-didehydro analogue **27**.



Scheme 27

Geisler/Riches studies toward 2'-deoxy- and ribose analogues[29]

Prior in-house studies directed at the synthesis of neplanocin A revealed a β bias during dihydroxylation of **25** (**54**α and **54**β, Scheme 28).[30]



	54α	**54**β
Conditions	**54-**α	**54-**β
$KMnO_4$	-	50%
$NaIO_4/RuCl_3$	12%	40%
OsO_4/NMO	5%	9%

Scheme 28

Various attempts to increase the diastereoselectivity failed to breach the 1:1 α:β ratio, and ultimately syntheses of analogues **28** and **29** were not succesful.

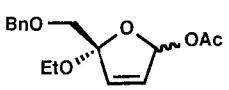
IV. Conclusion

Relying on an optically active butenolide **25** template, nucleoside analogue **26** was stereoselectively prepared. Coworkers Geisler and Riches succesfully extended the

application of the template to the completion of analogue **27**. Having synthesized two novel nucleoside analogues, this de novo approach offered the additional advantage of access to either enantiomer of **25**. This can be accomplished via the use of either enantiomer of ene carbamate **23**, or potentially the elaboration of epimerized lactone **38** (***epi*-38**). Further oxygenation studies on **25** failed to efficiently yield the desired a configuration, thus preventing the syntheses of analogues **28** and **29**.

V. Experimental

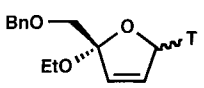
General Methods. THF was distilled from sodium-benzophenone ketyl, DMF was distilled from $MgSO_4$, and CH_2Cl_2, benzene, toluene, and Et_3N were distilled from CaH_2. Commercially available reagents were used as received except as indicated. ^1H NMR, NOE, COSY (300 MHz), ^{13}C NMR (75 MHz), and HSQC (400 ^1H MHz) spectra were recorded in $CDCl_3$ unless otherwise noted and chemical shifts are given in ppm relative to $CDCl_3$ (7.27 ppm). Column chromatography was performed with ICN 32-66 nm, 60 Å silica gel using flash column techniques. Elemental analyses were performed by M-H-W Laboratories, Phoenix, AZ. FAB high-resolution mass spectrometry (HRMS) was obtained with a Fisons VG AutoSpec mass spectrometer with a Cs ion gun, *m*-nitrobenzyl alcohol was used for the matrix, and the resolution was set to 10000. All reactions were performed in flame-dried glassware under an atmosphere of argon, unless otherwise noted. Compounds **33**, **34**, and **25** were prepared according to published procedures.[23]



49

(5*S*)-2-Acetoxy-5-(benzyloxymethyl)-5-ethoxy-2,5-dihydrofuran (49). The starting material **25** (450 mg, 1.85 mmol) was dissolved in toluene (10 mL) and cooled to -78 °C. Dibal-H (2.41 mL, 2.41 mmol, 1 M in toluene) was added via syringe, and the reaction was stirred at that temperature for 2 h. Pyridine (450 μL, 5.55 mmol), a solution of DMAP (226 mg, 1.85 mmol) in toluene (3 mL), and Ac2O (700 μL, 7.4 mmol) were sequentially added. The reaction was warmed to 0 °C, stirred for 5 h, then quenched with a solution of Rochelle's salt. After warming to room temperature the solution was extracted twice with CH_2Cl_2.

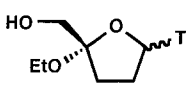
The combined organic layers were dried over $MgSO_4$, the the solvent was removed in vacuo to give an oil. Purification by flash chromatography (3:1 hexane/EtOAc) afforded an anomeric mixture of **49** as an oil (541 mg, 1.85 mmol, 99%). ^{1}H NMR δ 7.38-7.26 (m, 5H), 6.89 (s, 0.5H), 6.75 (s, 0.5H), 6.23-6.11 (m, 2H), 4.64 (s, 1H), 4.6 (s, 1H), 3.77 (d, J = 12.5 Hz, 0.5H), 3.73 (d, J = 12.3 Hz, 0.5H), 3.56 (d, J = 15.9 Hz, 0.5H), 3.53 (d, J = 16.2 Hz, 0.5H), 3.65-3.3 (m, 2H), 2.1 (s, 1.5H), 2.03 (s, 1.5H), 1.19 (t, J = 7 Hz, 3H); ^{13}C NMR δ 170.5, 170.1, 138.4, 138.2, 134.5, 133.7, 130.3, 130.2, 128.5, 128.4, 127.8, 127.6, 115.2, 114.2, 100.7, 99, 74.1, 73.8, 73.7, 73.6, 58.8, 58.4, 21.3, 21.2, 15.5, 15.4; IR (neat) 2975, 2932, 2866, 2358, 2336, 1748 cm^{-1}; FAB-LRMS calcd for $C_{14}H_{17}O_3$ (M - OAc): 233.13, found 233.13.



51

(4′*S*)-5′-*O*-Benzyl-4′-ethoxy-2′,3′-dideoxydidehydro-thymidine (51). A two-necked flask was charged with thymine (16.6 mg, 0.132 mmol) and 2.5 mL CH_3CN. *N*,*O*-bis(trimethylsilyl)acetamide (0.065 mL, 0.26 mmol) was added via syringe, and the mixture was stirred for 30 min. The solution went from a cloudy white suspension to a clear solution. Acetate **49** (35 mg, 0.12 mmol) was added dissolved in 1 mL of CH_3CN and the solution was cooled to 0 °C. $SnCl_4$ (15 μL, 0.13 mmol) was added via syringe down the sidearm of the flask to precool the solution. The solution was stirred at 0 °C for 20 min until no starting material was present by TLC (silica gel, 4:1 hexane/EtOAc). The reaction was quenched cold with saturated aqueous $NaHCO_3$, extracted with CH_2Cl_2, dried with $MgSO_4$, and concentrated. The crude residue was purified by flash column chromatography (100% EtOAc → 100% MeOH gradient elution). The fractions were collected, concentrated, dissolved in CH_2Cl_2,

and filtered to removed any silica particles. Coupled **51** (27 mg, 0.075 mmol, 63%) was obtained as a separable mixture of anomers: α-Anomer: ^{1}H NMR δ 9.74 (s, 1H), 7.4-7.25 (m, 5H), 6.93 (s, 1H), 6.38 (dd, J = 1.1 Hz, 5.6 Hz, 1H), 6.02 (dd, J = 0.8 Hz, 5.8 Hz, 1H), 4.61 (d, J = 12 Hz, 1H), 4.56 (d, J = 12 Hz, 1H), 3.83 (d, J = 10.5 Hz, 1H), 3.7-3.35 (m, 2H), 3.48 (d, J =10.5 Hz, 1H), 1.9 (s, 3H), 1.18 (t, J =7.1 Hz, 3H); ^{13}C NMR δ 164.2, 151.3, 137.7, 136.1, 133.9, 129, 128.6, 128, 127.8, 112.5, 111.4, 87.86, 73.69, 70.71, 58.86, 15.53, 12.57. β-Anomer: ^{1}H NMR δ 9.69 (s, 1H), 7.53 (s, 1H), 7.4-7.25 (m, 5H), 7.13 (s, 1H), 6.12 (s, 2H), 4.56 (s, 2H), 3.73 (s, 2H), 3.7-3.35 (m, 2H), 1.47 (s, 3H), 1.16 (t, J =7.1 Hz, 3H); ^{13}C NMR δ 164.2, 151.1, 137.4, 136.4, 135.5, 131.3, 128.7, 128.2, 127.9, 114.2, 111.2, 88.67, 73.74, 72.9, 57.85, 15.33, 11.93. IR (neat) 1695 cm^{-1}. Anal. Calcd for $C_{19}H_{22}N_2O_5$: C, 63.67; H, 6.18; N, 7.82. Found: C, 63.62; H, 6.07; N, 7.58.



26

(4′*S*)-4′-Ethoxy-2′,3′-dideoxythymidine (26). A solution of **51** (11 mg, 0.030 mmol) in MeOH (2 mL) was stirred over 20% $Pd(OH)_2/C$ (4 mg) under an H_2 atmosphere (1 atm) for 1 h. Argon was bubbled through the solution. Filtration of the reaction mixture through Celite and removal of solvent afforded **26** as a white solid and as a 1:1 mixture of diastereomers (7.0 mg, 0.047 mmol, 88%): ^{1}H NMR δ 9.1 (s, 1H), 9.05 (s, 1H), 7.43 (d, J = 1.1 Hz, 1H), 7.34 (d, J = 1.1 Hz, 1H), 6.45 (t, J = 6.6 Hz, 1H), 6.26 (d, J = 4.2 Hz, 0.5H), 6.24 (d, J = 3.8 Hz, 0.5H), 3.9-3.5 (m, 8H), 2.7-2 (m, 8H), 1.95 (s, 1.5H), 1.9 (s, 1.5H), 1.24 (t, J = 6.9 Hz, 1.5H), 1.17 (t, J = 7 Hz, 1.5H)); ^{13}C NMR (400 MHz) δ 163.8, 163.7, 150.8, 150.4, 136.0, 135.8, 111.4, 109.9, 109.8, 86.3, 86.1, 63.0, 62.6, 57.7, 57.6, 33.1, 31.6, 30.8, 30.0, 15.7, 15.6, 12.6; IR (neat) 3430, 1692 cm^{-1}; FABHRMS calcd for $C_{12}H_{18}N_2O_5$ (M + 1): 271.1294,

found 271.1289.

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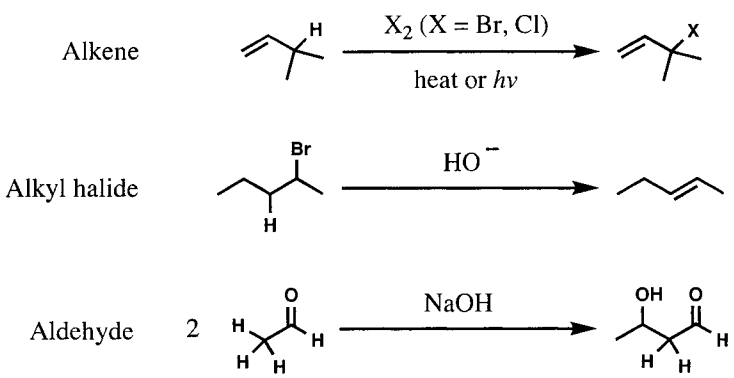
Chapter 2: Diastereoselective Synthesis of α-Substituted Propargylamines Via Dicobalt Complex Methodology

I. Introduction

Functional groups, molecular structural motifs comprising various atoms and connectivities conferring reactivity, represent a main focus of organic chemistry. However, carbons α to functionalized carbons can exhibit characteristic reactivities as well (Scheme 1).



Scheme 1

The carbon α to a carbon-carbon triple bond is referred to as the *propargylic* carbon (Figure 1).

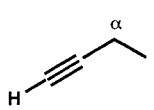
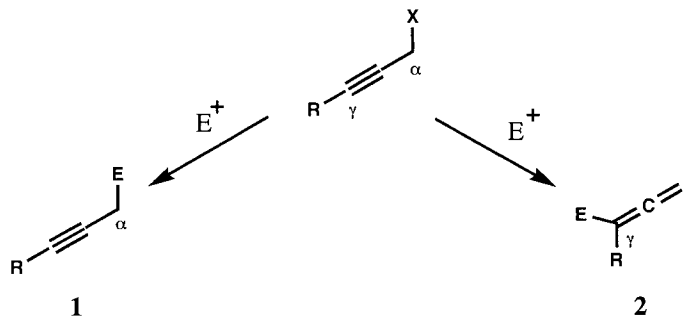


Figure 1

It can be functionalized so as to react with with electron-poor or electron-rich reagents, electrophiles and nucleophiles respectively.

Propargyl nucleophiles

Propargylic substrates usually present two sites for reaction with electrophiles (Scheme 2). Attack at the α-position maintains the propargyl motif in the product (**1**), while γ-addition yields the allenyl adduct **2**.

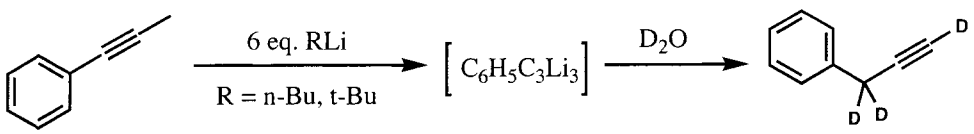


1 **2**

Scheme 2

Mixed-site reactivity

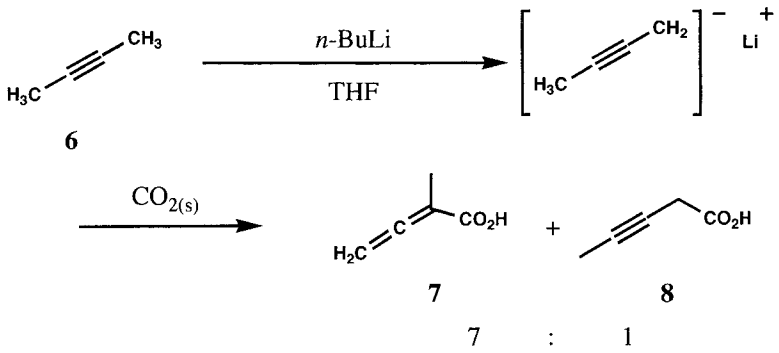
In one of the earliest examples involving internal alkynes, Mulvaney showed that excess alkyllithium reagent isomerized 1-phenyl-propyne (**3**), via polylithiated species **4,** to terminal alkyne **5** (Scheme 3).[1]



3 **4** **5**

Scheme 3

Stoichiometric treatment of 2-butyne (**6**) with butyllithium followed by solid CO_2 yielded a mixture of allenyl (**7**) and propargyl (**8**) carboxylic acids (Scheme 4).[2]



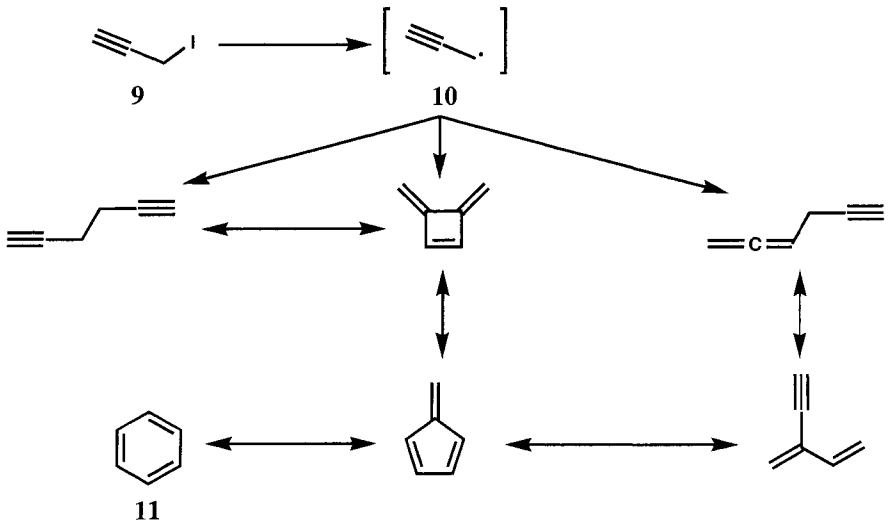
Scheme 4

Reich subsequently demonstrated that allenyl/propargyllithium substrates showed a pronounced tendency for the allenyl tautomer in solution (Scheme 5), either as monomers or dimeric adducts.[3]

Propargyl Allenyl

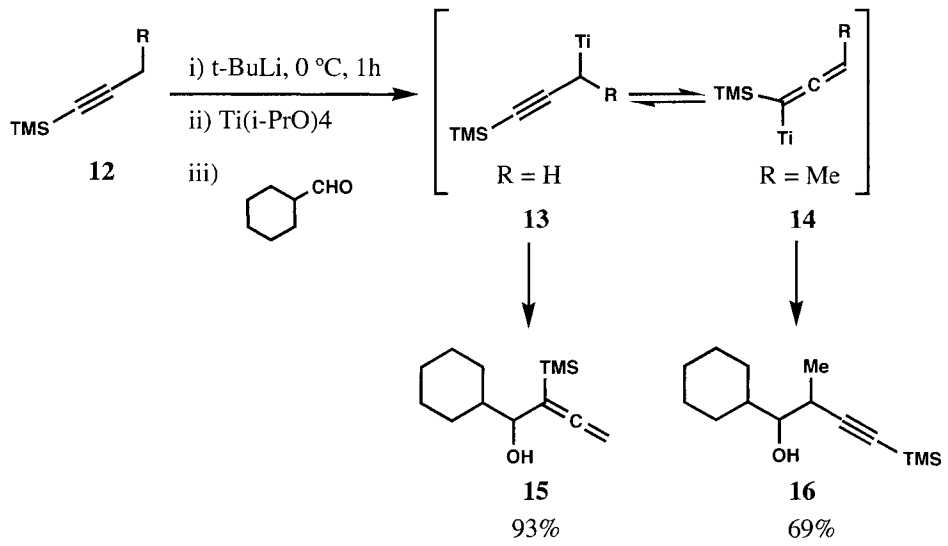
Scheme 5

The self-coupling of propargyl radicals represents an important reaction in the synthesis of benzene.[4] Activation of propargyl iodide **9** in a shock tube generated the requisite radical **10** which led to the formation of benzene **11** along with several intermediates, consistent with a quasi-indiscriminate radical-radical coupling mechanism (Scheme 6).[5]



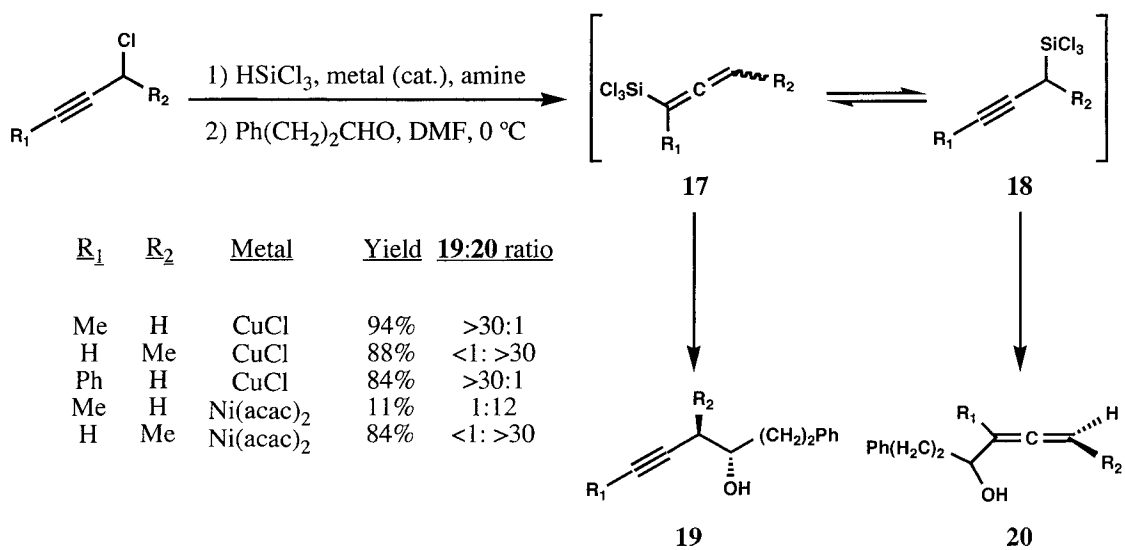
Scheme 6

Other propargyl metal species exhibit a tendency to combine with carbonyl compounds in uncontrolled fashion to provide allenic and propargylic products. This arises from a propargyl-allenyl tautomerization akin to propargyllithium species.[6] The position of the equilibrium however can be influenced by substitution of the starting material.[7] Deprotonation of **12** followed by transmetallation to titanium (**13**, **14**) provided either α-allenyl alcohol **15** or homopropargyl alcohol **16** upon addition to cyclohexanal (Scheme 7).[8]



Scheme 7

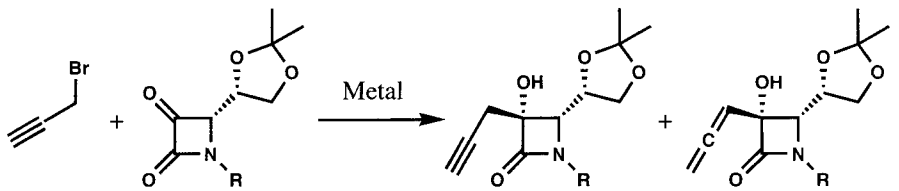
Kobayashi showed that acetylenic groups influenced the propargyl-allenyl equilibrium of trichlorosilanes **17** and **18**, ultimately determining the final product ratio (**19** and **20**, Scheme 8).[9]



Scheme 8

The product distribution can be further controlled by reaction conditions. Solvent

choice had considerable impact on substrate chemoselectivity in the addition of propargyl bromide (**21**) to azetidine-2,3-dione **22** (Scheme 9).[10]



21 **22**

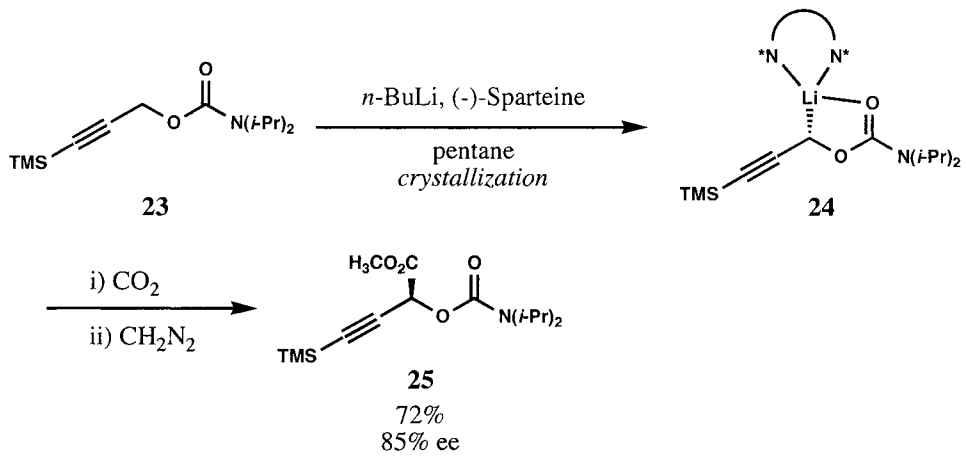
Entry	Metal	Solvent	Product ratio	Yield
1	Zn	THF/NH_4Cl	100:0	70%
2	Zn	MeOH/NH_4Cl	50:50	65%
3	In	THF/NH_4Cl	71:29	67%
4	In	THF/H_2O	42:58	50%
5	Sn	THF/NH_4Cl	25:75	65%

Scheme 9

With multiple variables influencing regioselectivity, it becomes clear that the ambident nature of propargyl anions is problematic to the synthetic chemist.

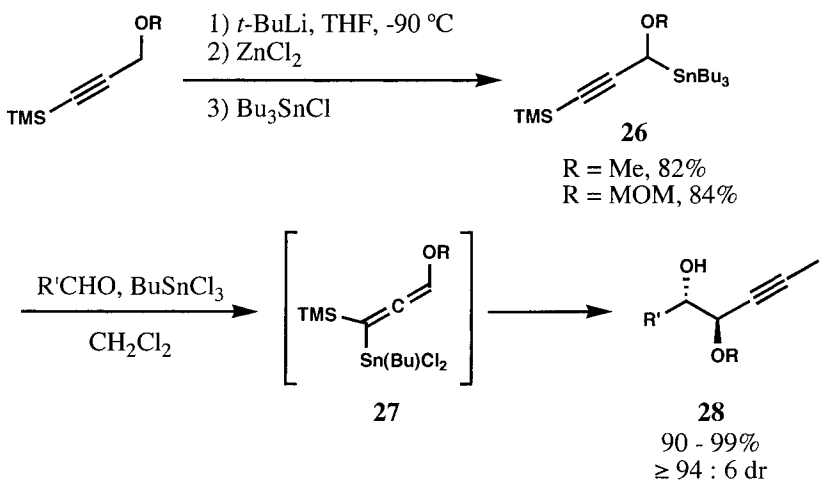
Net α-addition of electrophile

Hoppe overcame the propensity of propargyllithium equilibration by relying on internal chelation control (Scheme 10).[11] Asymmetric deprotonation of **23** with selective crystallization of one epimer (**24**), followed by electrophilic quench afforded α-substituted propargyl carbamate **25**.



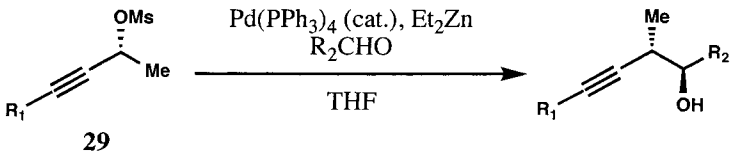
Scheme 10

Roush's propargyl tin species **26** proved amenable to isolation (Scheme 11).[12] Based on prior art,[13] it was proposed that treatment with $BuSnCl_3$ generated intermediate **27** which added to aldehydes, forming *anti*-1,2 diols **28**.



Scheme 11

Marshall adapted a Pd-Zn transmetallation protocol to synthesize mesylate **29** (Scheme 12).[14]

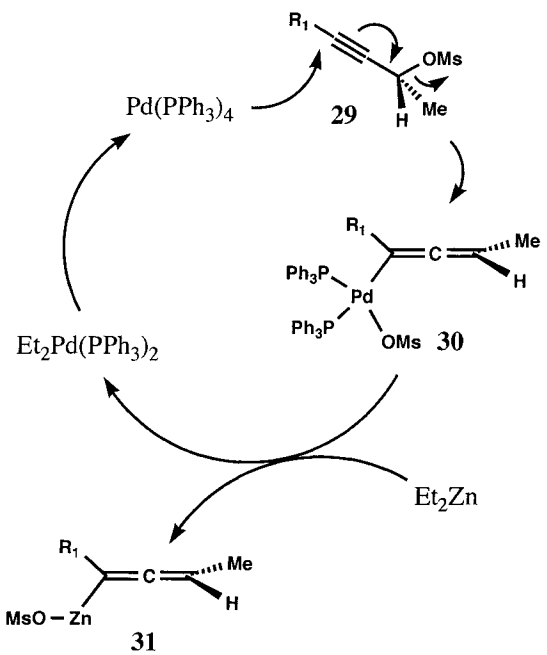


29

R_1	R_2	*anti*:*syn*	Yield	ee
H	Cy	95:5	85%	95%
CH_2OAc	Cy	95:5	51%	96%
CH_2OAc	*i*-Pr	95:5	47%	96%

Scheme 12

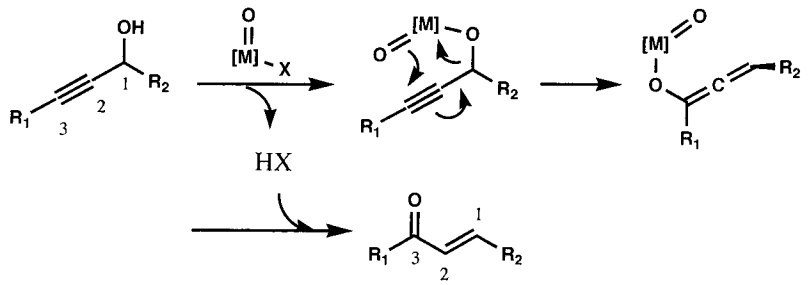
An *anti*-S_N2' oxidative addition of Pd^0 to **29** generated allenylpalladium **30**.[15] Transmetallation with Et_2Zn led into allenylzinc **31**, the nucleophilic species (Scheme 13).



Scheme 13

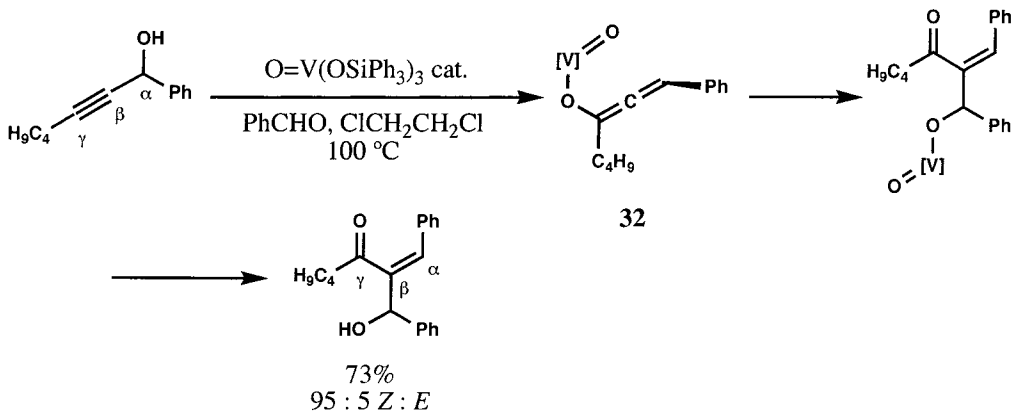
Net β-addition of electrophile

The 1,3-transposition of allylic and propargylic systems has been observed with oxo complexes of vanadium,[16] molybdenum,[17] tungsten,[18] and rhenium[19] (Scheme 14).



Scheme 14

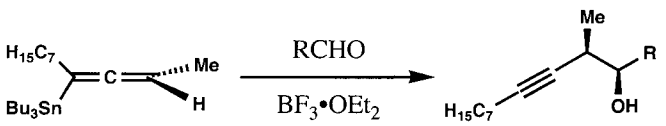
Relying on a vanadium catalyst, Trost successfully intercepted the allenolate intermediate **32** via an Aldol reaction with benzaldehyde to effect a net β electrophilic addition (Scheme 15).[20]



Scheme 15

Net γ-addition of electrophile

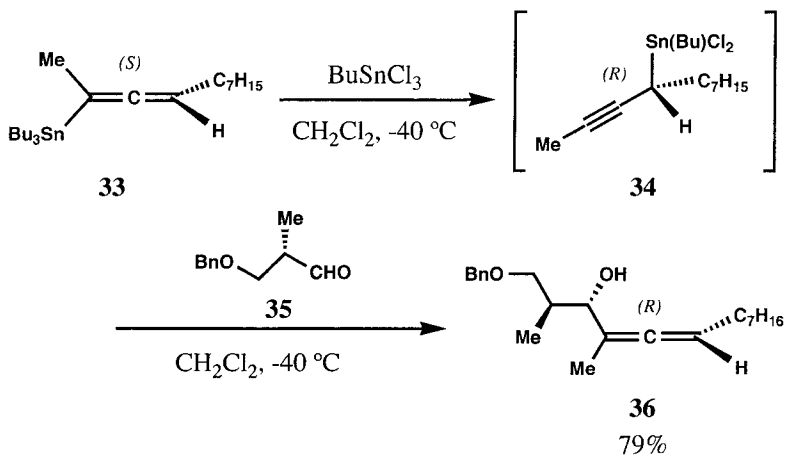
The incorporation of acetylenic functionality has traditionally relied on the addition of electrophiles to allenes, as in the reaction of allenylmetals with aldehydes to produce homopropargyl alcohols.[21] Especially noteworthy is Marshall's work with chiral allenyltin compounds (Scheme 16).[22]



R	Yield	*syn:anti*
i-Pr	80%	99:1
t-Bu	92%	99:1

Scheme 16

Treatment of allenyl stannane **33** with $BuSnCl_3$ stereospecifically produced transient propargyl stannane **34**, presumably via an *anti* S_E' transmetallation; this species has been characterized spectroscopically (Scheme 17).[21] Reaction with aldehyde **35** gave allenyl alcohol **36** as the exclusive product.

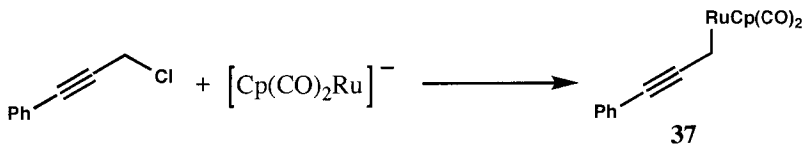


Scheme 17

Comparing the Marshall and Roush methodologies, it becomes clear that Roush's method to effect α-alkylation on a propargylstannane required inducing an in situ allenyl tautomerization (**27** → **28**, Scheme 11) prior to nucleophilic addition.

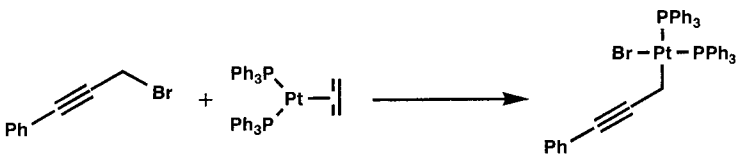
Tautomerization is rare with transition metal species,[23] although recent studies have demonstrated reversible conversion between certain η^1-propargyl and η^1-allenyl complexes of Pt and Pd.[24] Propargyl complexes of Mo, W, Mn, Fe, Ru, Co, Pd, and Pt are well known, and they can be selectively prepared using several methods (Scheme 18).[25, 26] Products **37**, **38**, and **39** are referred to as mononuclear η^1-propargyl complexes. The Greek letter *eta* (η) alludes to the metal's hapticity, the number of atoms in the ligand which are directly coordinated to the metal.[27]

Anionic metal addition:



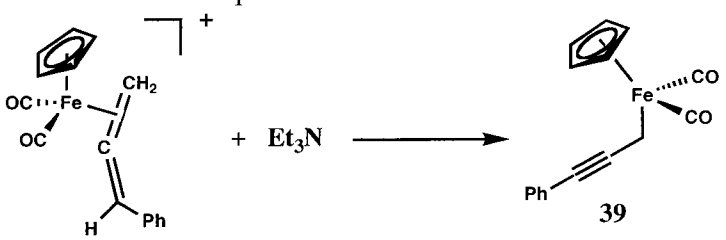
37

Metal oxidative addition:



38

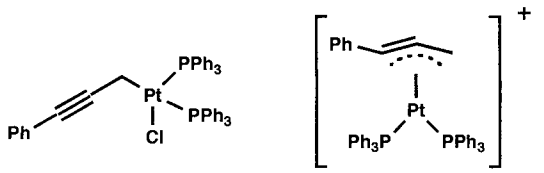
Deprotonation of metal-allene complex:



39

Scheme 18

With tautomeric isomers (e.g., **40** and **41**), it bears stressing that they are distinct species with differing reactivities (Figure 2).[28]

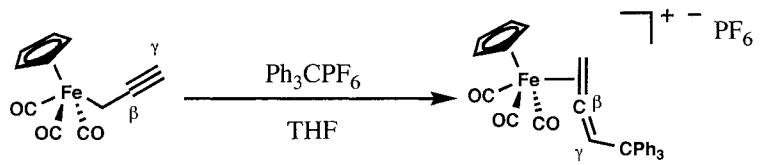


40 **41**

Hapticity: η^1 η^3

Figure 2

The synthesis of η^1-propargyl complexes, excluding their allenyl tautomers, effectively leads to γ-addition of electrophiles. Propargyl complex **42** precipitated air-stable cationic π-allene complex **43** upon treatment with trityl hexafluorophosphate (Scheme 19).[29]

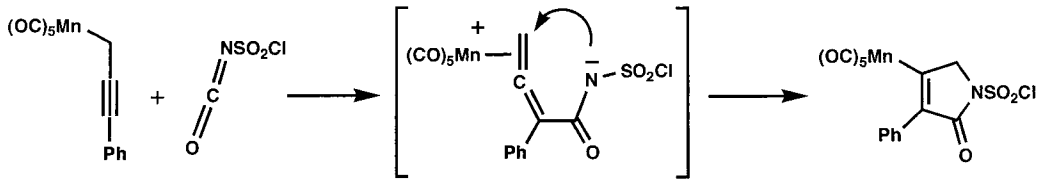


42 **43**

>80%

Scheme 19

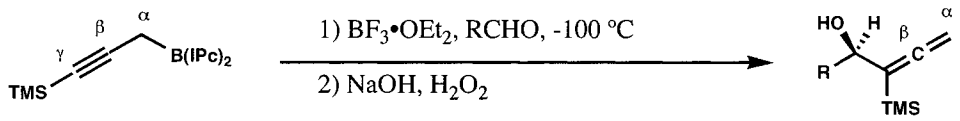
Unsaturated electrophiles undergo a [3+2] cycloaddition with η^1-propargyl complexes (metal = Mn, Fe, Ru, Mo, W, inter alia). Thus manganese complex **44** reacted with isocyanate **45** to form **46** (Scheme 20).[30]



44 45 46

Scheme 20

Analogous non-metallic propargyl substrates can be prepared, and their reactions with electrophiles are equally chemoselective. Brown's chiral propargyl borane **47** (derived from α-pinene) added to aldehydes with good selectivity, providing α-allenyl alcohol **48** (Scheme 21).[31,32]



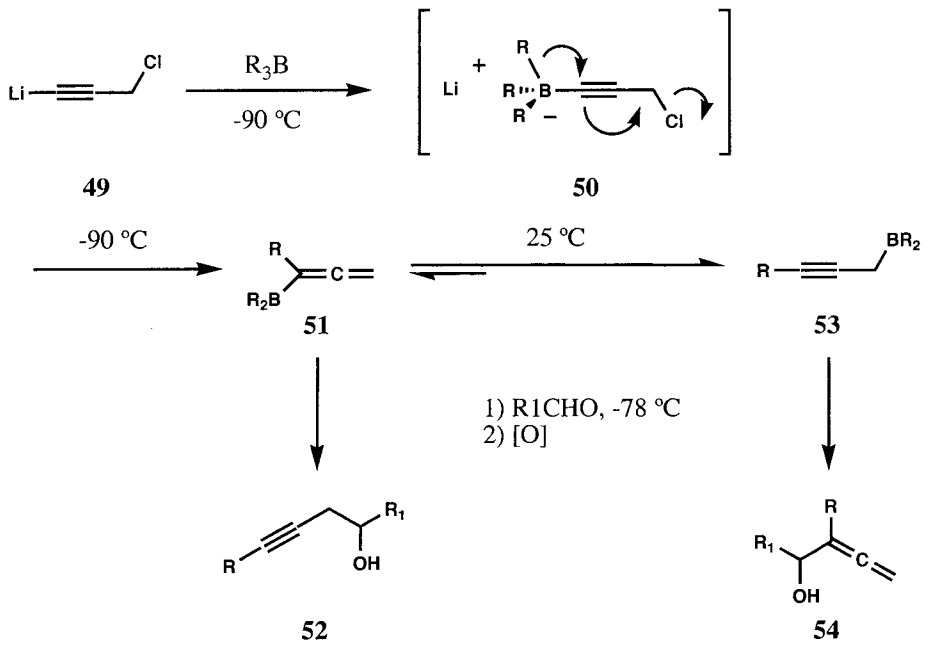
47 **48**

IPc =

R	yield	ee
Me	72%	87%
i-Pr	76%	99%
Ph	74%	89%

Scheme 21

Zweifel cleverly demonstrated the fluxional nature of propargyl borane species. The reaction of lithium chloropropargylide **49** with a trialkylborane formed short-lived borate **50** which rearranged under reaction conditions to allenyl borane **51** (Scheme 22).[33] In the presence of an aldehyde, this species rapidly reacted to afford homopropargyl alcohol **52** (kinetic control). However, if the reaction was allowed to warm to room temperature prior to addition of the aldehyde, equilibration of **30** to propargyl borane **53** occured, leading to the α-allenyl alcohol product **54** (thermodynamic control).



Scheme 22

Thus several methods are available to control propargyl tautomerization and achieve regioselective addition.

Propargyl electrophiles

Activated propargylic species present multiple sites for nucleophilic addition, analogous to reactions with electrophiles (Figure 3).

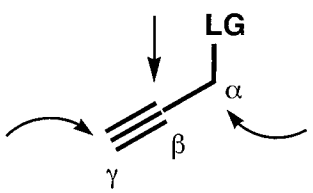
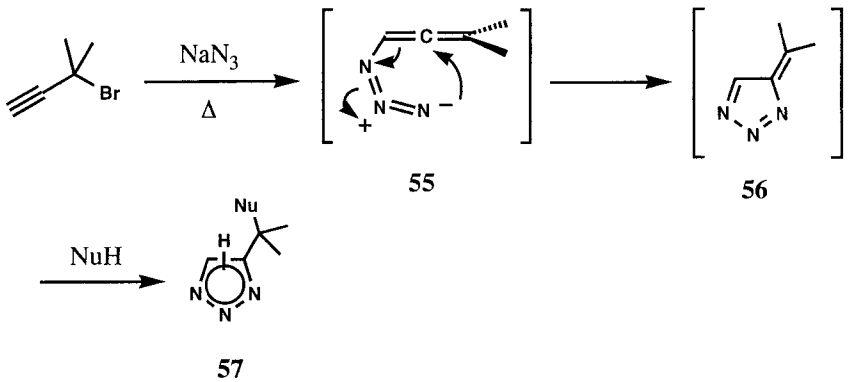


Figure 3

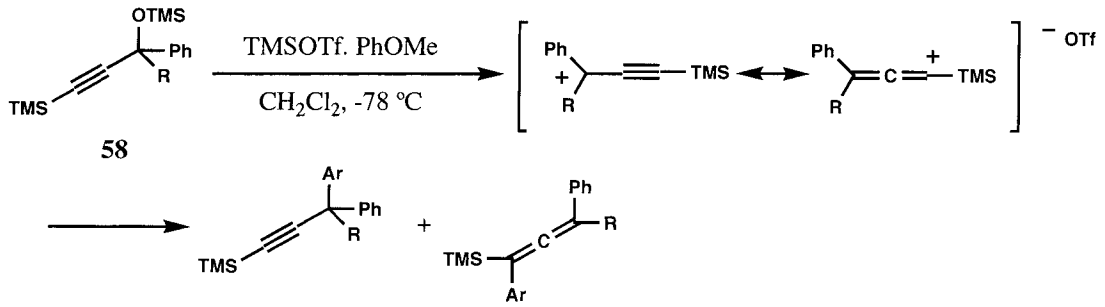
Bimodal reactivity

The Banert cascade, comprising sequential α- and γ-additions, perhaps best exploits the promiscuous nature of propargyl electrophiles (Scheme 23).[34] Nucleophilic displacement by NaN_3 produces allenyl azide **55** which undergoes intramolecular 1,3-dipolar cycloaddition to transient triazafulvene **56**. Subsequent nucleophilic trapping affords 1,2,3-triazole **57**.



Scheme 23

Substrate substitution can significantly influence product distribution. Reminiscent of the Meyer-Schuster rearrangement,[35] albeit in a non-aqueous medium, Ishikawa et. al demonstrated that propargyl substituents (R, **58**) determined reaction outcome (**59** vs. **60**, Scheme 24).[36]

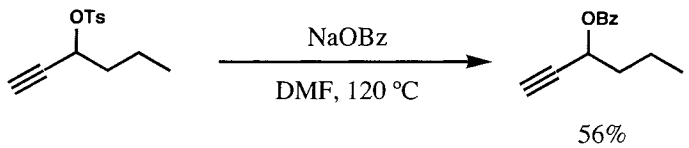


59		60
R	**59**	**60**
Ph	100%	-
Me	98%	-
H	-	88%

Scheme 24

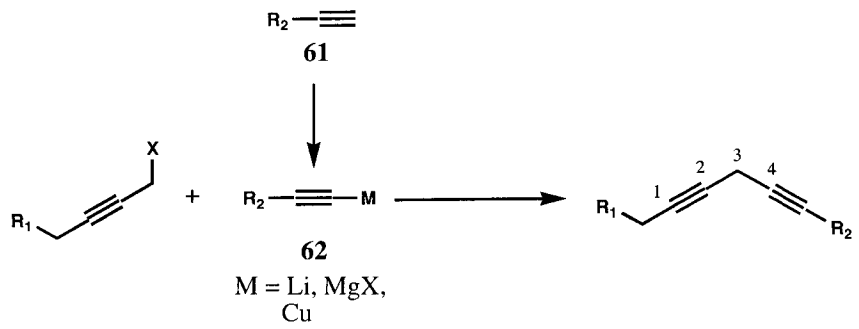
Net α-addition of nucleophile

The S_N2 displacement at a propargylic carbon is well established (Scheme 25).[37]



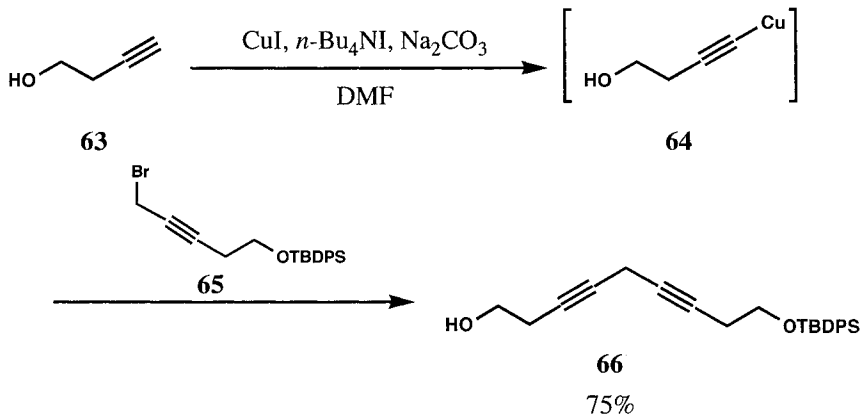
Scheme 25

Organometallic reagents have been applied to this transformation, as in the preparation of 1,4-diynes (Scheme 26).[38]



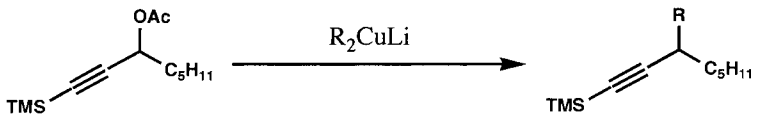
Scheme 26

Today, precursory deprotonation of the terminal alkyne **61** to **62** (Scheme 26) is no longer required.[39] The coupling of 3-butyn-1-ol (**63**), via the in situ-generated copper acetylide **64**, to propargyl bromide **65** proceeded in good yield (Scheme 27).[40] Skipped diyne **66** was further elaborated to THC-mimic analogues.



Scheme 27

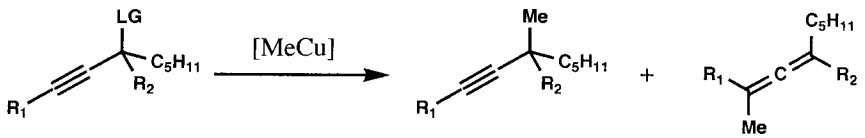
Brinkmeyer et. al extended copper methodology to higher order cuprates, thus permitting the addition of more varied groups (Scheme 28).[41] It should be noted that in all cases no allene side-product was detected.



R	Yield
Me	79%
n-Bu	86%
H_2C=CH	78%
Ph	65%

Scheme 28

Since the addition of organocuprates to propargylic scaffolds are known to produce allenes,[42] careful study of this reaction revealed that factors influencing product distribution included organocupprate stoichiometry and counterion (Mg^{2+}, Li^{+}), and acetylenic substitution (**67**/**68**, Scheme 29).[43]

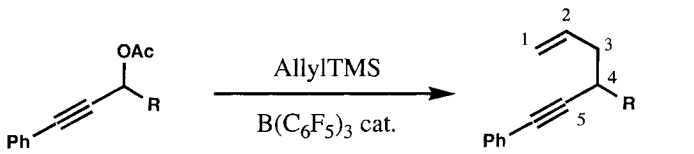


LG = OAc, OCO_2Me

			67	**68**
R_1	R_2	[MeCu] (eq.)	**67**	**68**
t-Bu	H	Me_2CuLi (2)	98%	-
Ph	H	Me_2CuLi (2)	33%	63%
n-Bu	H	Me_2CuLi (2)	10%	90%
Cy	H	MeCu•LiBr•MgBrI (6)	-	100%
Cy	H	MeCu•MgBrI (2)	75%	25%
Cy	Me	MeCu•MgBrI (2)	32%	69%

Scheme 29

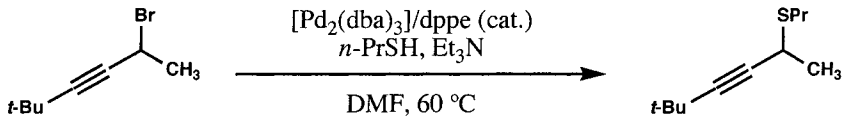
Although the literature is rife with examples of Lewis acid-mediated couplings of nucleophiles to propargyl electrophiles (e.g., Scheme 30),[44] stereoselective bond formation on propargylic scaffolds has proven elusive. [36,45,46]



R = Ph, 93%
$CC\text{-}C_5H_{11}$, 79%

Scheme 30

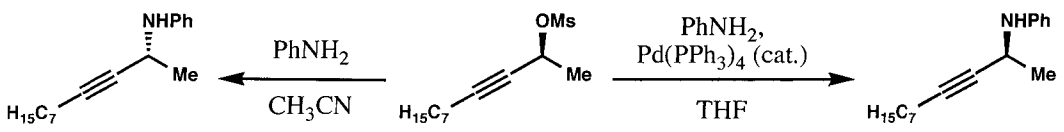
In contrast to ubiquitous allylic substitution reactions catalyzed by transition metals,[47] propargylic variants have only recently been disclosed.[48] Despite the typical poisoning effects of sulfurous compounds on catalysts,[49] Tsutsumi et. al reported the palladium-catalyzed addition of thiols to propargyl halides (Scheme 31).[48b]



95%

Scheme 31

Mechanistic insight can be gained from Marshall's work using chiral mesylate **69** (Scheme 32).[50] Reaction with aniline provided **70** with the expected inversion of chirality, while the presence of palladium catalyst afforded ***ent*-70** with net retention of stereochemistry.



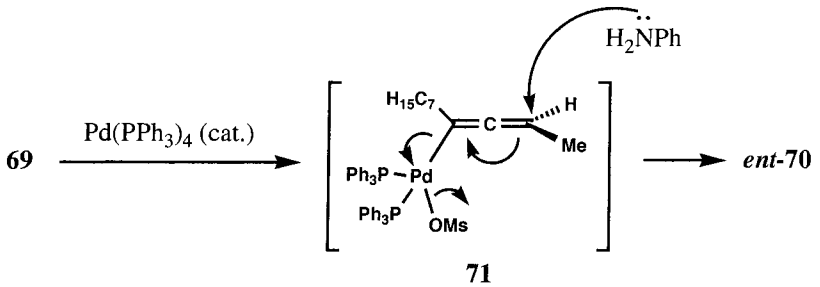
70
63%

69

***ent*-70**
78%

Scheme 32

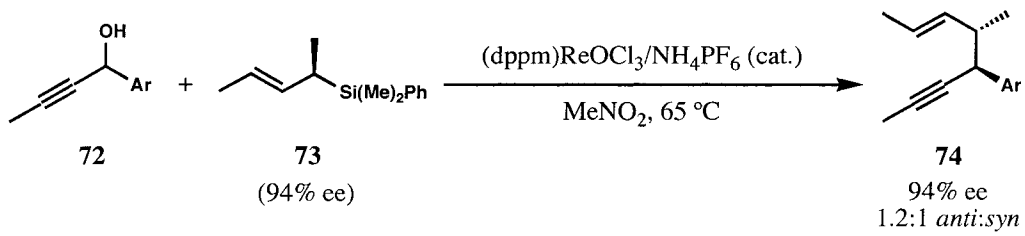
A proposed pathway for the palladium-catalyzed product invoked an *anti*-S_N2' oxidative addition of the metal to the mesylate,[15] followed by *anti*-S_N2' attack by the amine on allenyl palladium intermediate **71** (Scheme 33). Thus the net retention of stereochemistry is interpreted as the product of consecutive inversions.



Scheme 33

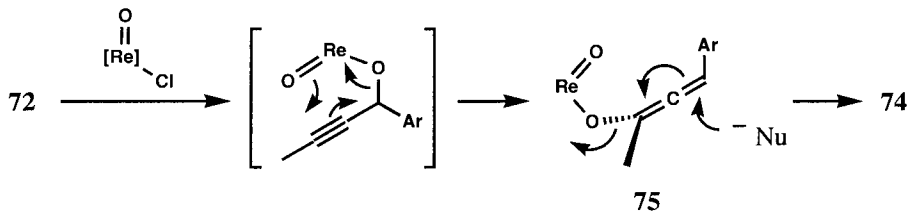
Alternatively, the amine may be discriminating between allenyl and propargyl palladium intermediates.

Toste elaborated a stable rhenium catalyst to effect aromatic[48d] and allylic alkylation. Propargyl alcohol **72** reacted with chiral crotylsilane **73** to afford **74** with complete chirality transfer but poor diastereoselectivity (Scheme 34).[48c]



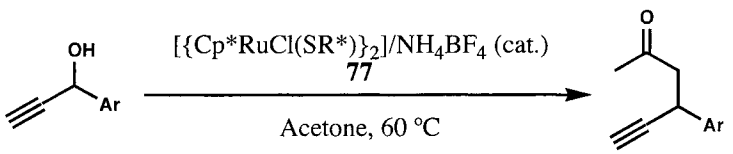
Scheme 34

On the basis of prior reports,[51] it was proposed that the catalyst drove a [3,3] sigmatropic rearrangement of **72** to allenoate intermediate **75** which underwent S_N2' addition of the nucleophile (Scheme 35).



Scheme 35

Nishibayashi effected the net enantioselective alkylation of propargyl alcohols (**76**) with acetone in the presence of a diruthenium catalyst (**77**);[52] monoruthenium complexes were unreactive (Scheme 36).[53]

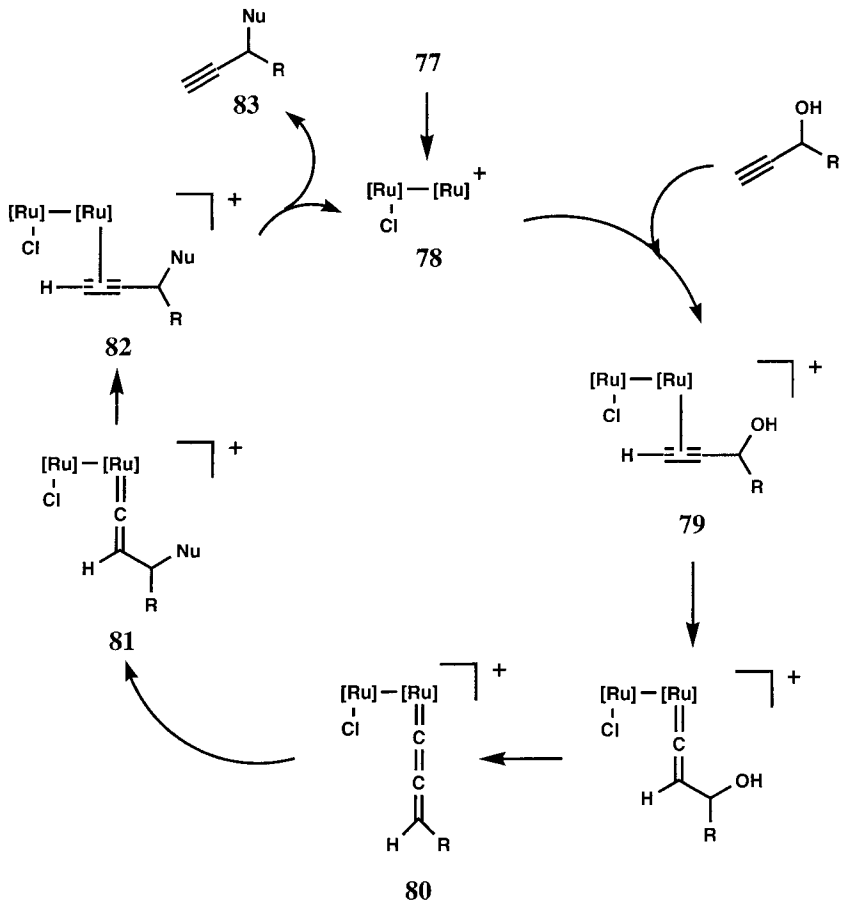


76

Ar	Yield	ee
3,5-Ph_2-Ph-	58%	82%
Ph	56%	74%

Scheme 36

This transformation was proposed to occur via an allenylidene[54] intermediate (Scheme 37).[55] Ligand loss from the catalyst generated a cationic species (**78**) which formed π-complex **79** with the substrate. 1,2-migration of the acetylenic hydrogen, followed by spontaneous water loss gave allenylidene **80** as the key reactive intermediate. As allenylidenes are electrophilic at the α– and γ-positions,[56] nucleophilic addition yielded vinylidene complex **81**. A reverse hydrogen migration lead to cationic π-complex **82;** release of the product **83** regenerated the catalytic species **79**.



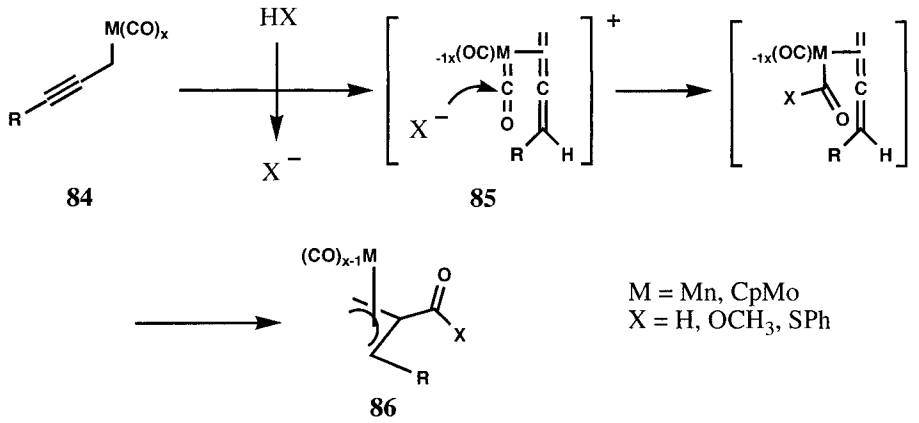
Scheme 37

Nishibayashi, Hidai, and Uemura expanded the scope of this methodology to oxygen, nitrogen, and phosphorus nucleophiles.[57]

Net β-addition of nucleophile

Since most of the transition-metal η^1-propargyl complexes are not charged, their reactions with nucleophiles are rare. Propargyl manganese and molybdenum complexes were reported to undergo reaction with a variety of protic nucleophiles to afford η^3-allyl products (Scheme 38).[58] It was postulated that initial protonation of **84** formed η^2-allene

85. Attack of the nucleophile at CO, followed by migration of the resultant acyl group lead to the C_β-substituted η^3-allyl complex **86**.

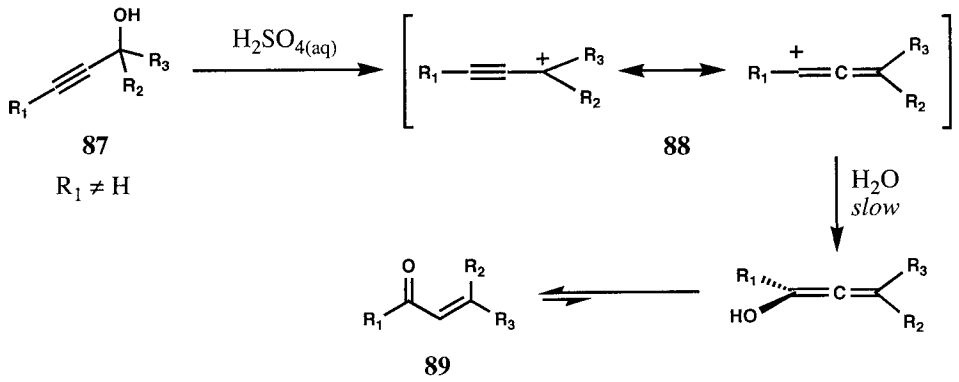


Scheme 38

More recently, Lin disclosed the corresponding transformation using an analogous tungsten complex.[59]

Net γ-addition of nucleophile

The classic acid-catalyzed rearrangement of 2° and 3° propargyl alcohols to α,β-unsaturated carbonyls, known as the Meyer-Schuster rearrangement, perhaps best exemplifies γ addition of nucleophiles (Scheme 39).[35] Upon mixing with aqueous sulfuric acid, tertiary propargyl alcohol **87** eliminates water, forming transient cationic intermediate **88**. The rate-limiting nucleophilic addition of water yields α,β-unsaturated ketone **89**.



Scheme 39

Propargyl cations

Long before their spectroscopic detection, propargyl cations had been postulated as experimental intermediates (e.g., Meyer-Schuster rearrangement).[60] Publications dating to 1921 report bright coloring of acidic solutions of tris(alkynyl) methanols (**90**, Figure 4).[61]

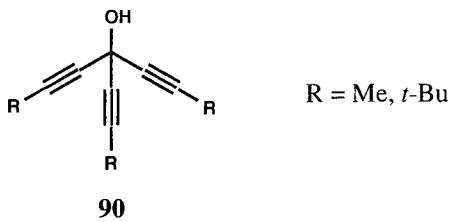


Figure 4

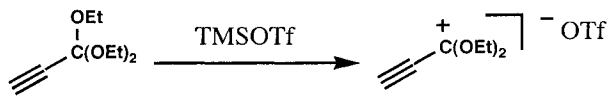
Alkynylcarbenium ions are represented by two canonical structures (**91** and **92**) whose reactivities are influenced by the nature of R_1, R_2, and R_3 (Figure 5).

91 92

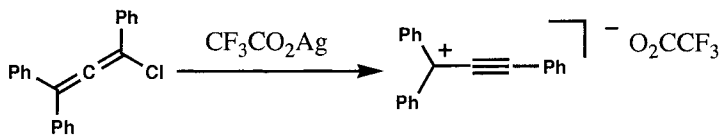
Figure 5

In principle, methods suitable for the generation of carbenium ions can also be applied to the preparation of alkynyl cations. Published procedures include: (a) detachment of a propargylic leaving group;[62] (b) abstraction of a leaving group from an allene;[63] and (c) addition of an electrophile to an unsaturated system (Scheme 40).[64] However, methods (a) and (c) are the most common approaches to alkynylcarbeniums.

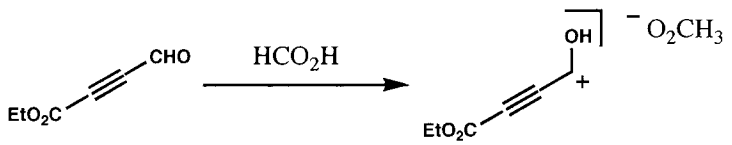
(a) Propargyl leaving group:



(b) Leaving group abstraction:



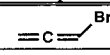
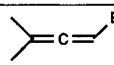
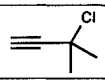
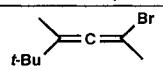
(c) Electrophilic addition:



Scheme 40

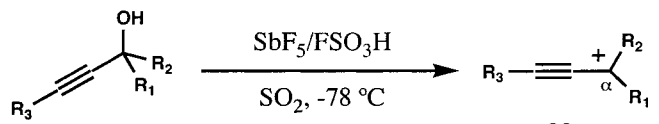
Solvolysis studies offered kinetic evidence for an S_N1 mechanism, implicating the intermediacy of cationic intermediates (Table 1).[65]

Table 1: Compound solvolysis rate.

Compound	Relative solvolysis rate [a]
	4×10^{-7}
	0.011
	0.025
	1.0
	40
	60
	65

[a] 80% EtOH, 25 °C.

More definite structural insight was provided by the first NMR observation of alkynyl cations in 1965.[66] Generally, cations were prepared from the acidic treatment of 3° alcohols (Scheme 41).[67]



93

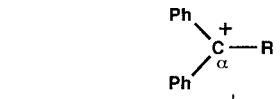
Compound	R_1	R_2	R_3	Methyl δ (ppm)
93a	Me[a]	*p*-Me[b]-Ph	Me[c]	3.05[a], 2.45[b], 2.59[c]
93b	Ph	Me	Ph	3.14
93c	Me	Me	Ph	3.39
93d	Me[a]	Me[a]	Me[b]	3.67[a], 3.13[b]

Scheme 41

Several conclusions can be drawn. The chemical shift of the α-methyl group increases with decreasing charge delocalization by the other two substituents (**93a** < **93b** < **93c** < **93d**). Furthermore, unlike the *t*-butyl cation (δ^{Me} = 4.35 ppm),[68] the propynyl fragment markedly redistributes the positive charge (**93d**, δ^{Me} = 3.67 ppm). Collection of

^{13}C NMR data provided more insight into charge delocalization compared to other groups (Table 2).[69]

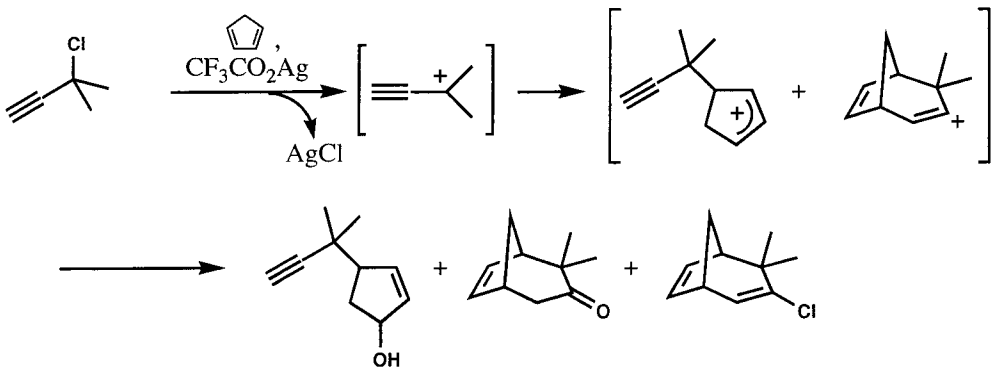
Table 2: Cation ^{13}C NMR chemical shifts.



R	C_a δ (ppm)
	195.7
	211.9
	227.0
	229.3
	235.1

The propensity of 2° propargyl alcohols to polymerize under ionizing conditions illustrates the delocalization limit of the alkynyl group.[68]

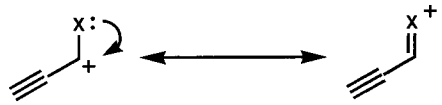
The first systematic studies on the application of alkynyl carbenium ions were carried out by Mayr, relying on alkenes and dienes as nucleophiles.[70] Low yields and multiple products, arising from cationic rearrangements, ultimately hampered applicability (Scheme 42).



Scheme 42

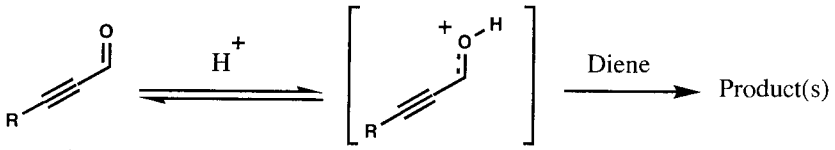
Alkynyl oxonium ions

Heteroatoms adjacent to cations are known to exert a stabilizing influence, and their chemistry is well established (X = O, [71] N,[72] Scheme 43).



Scheme 43

The addition of acid to aldehyde **94** generates alkynylhydroxycarbenium ion **95** (Scheme 44).[64] Three products were observed upon reaction with dienes, depending on the nature of R. Diels-Alder adduct **96** results from electronic activation of the alkyne dienophile. Aldehydes **97** and **98** are the product of γ- and α- addition, respectively.

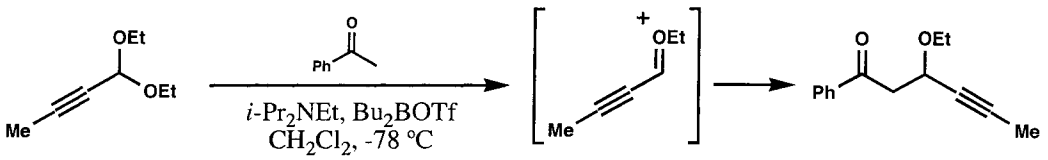


94 95

R (96)	Diene	Product(s)
CHO, CO_2Et	$n = 1, 2$	96
$CONMe_2$, CN		96 + 97
p-Cl-Ph		98

Scheme 44

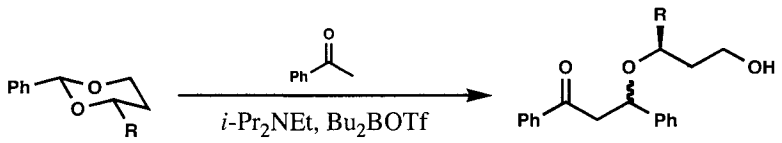
Acetylenic acetal **99** reacted regioselectively with acetophenone via alkynyl oxonium **100** (Scheme 45).[73]



99 **100** 82%

Scheme 45

That the process occurs via an S_N1 mechanism, analogous to the $TiCl_4$-mediated reaction of silyl enol ethers with acetals,[74] was evident from the reaction of acetophenone with chiral acetal **101** (Scheme 46). The formation of a diastereomeric mixture of **102** cannot be the product of an S_N2 displacement.



101 **102**

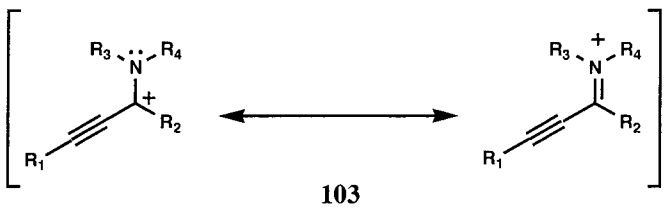
R	dr
Me	1.7:1
Ph	1.6:1

Scheme 46

It should be noted that this variant of the Mukaiyama methodology obviates the need for a silyl enol ether nucleophile.

Alkynyl iminium ions

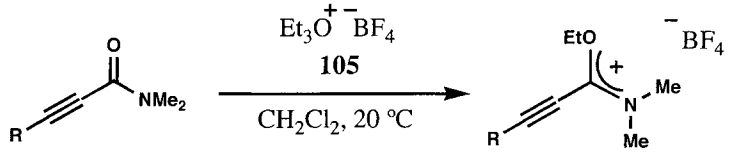
Several methods have been reported for the preparation of nitrogen-stabilized propargyl cations of the form **103** (Figure 6).



103

Figure 6

Treatment of alkynyl amide **104** with Meerwein's salt (**105**) at room temperature resulted in the formation of air-stable, recrystalizable, propynylamidium salt **106** (Scheme 47).[75]



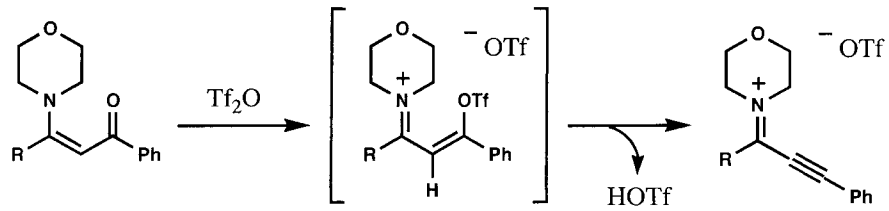
104 **106**

R	Yield

Ph	85%
t-Bu	98%
H	93%

Scheme 47

Maas eliminated triflic acid from iminium triflate **107**, generated from the enaminone, to produce alkynyliminium salt **108** (Scheme 48).[76]



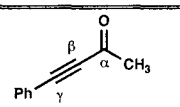
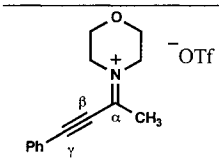
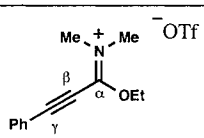
107 **108**

R	Yield
Me	80%
Ph	31%

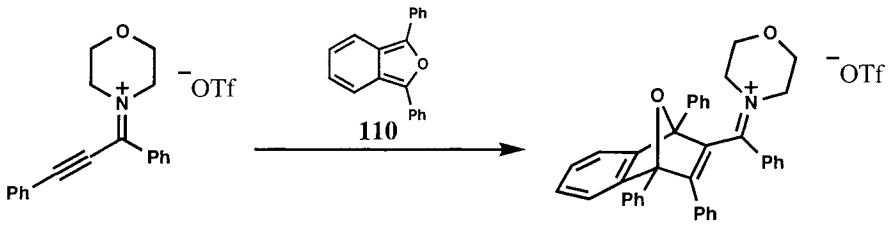
Scheme 48

Spectroscopic evidence suggested a polarization of the C-C triple bond arising from the electron-withdrawing nature of the adjacent iminium moiety (Table 3).[76]

Table 3: Alkynyl iminium ^{13}C NMR chemical shifts.

	^{13}C NMR (ppm)		
	C_α	C_β	C_γ
	183.5	88.7	89.7
	164.9	84.0	119.0
	156.1	73.5	111.8

The alkyne activation by iminiums found synthetic application in cycloadditions.[60,75] Iminium **109** reacted with 1,3-diphenylisobenzofuran **110**, affording the [4+2] adduct **111** in good yield (Scheme 49).[76] Other reported cyclizations include the [2+2] and 1,3-dipolar cycloadditions.

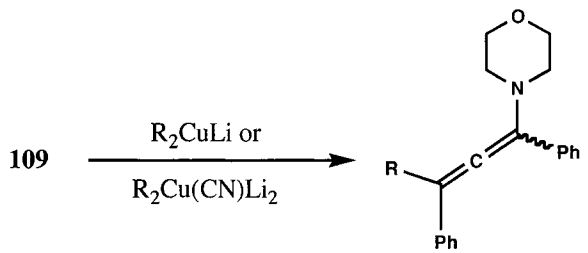


109 **111**

74%

Scheme 49

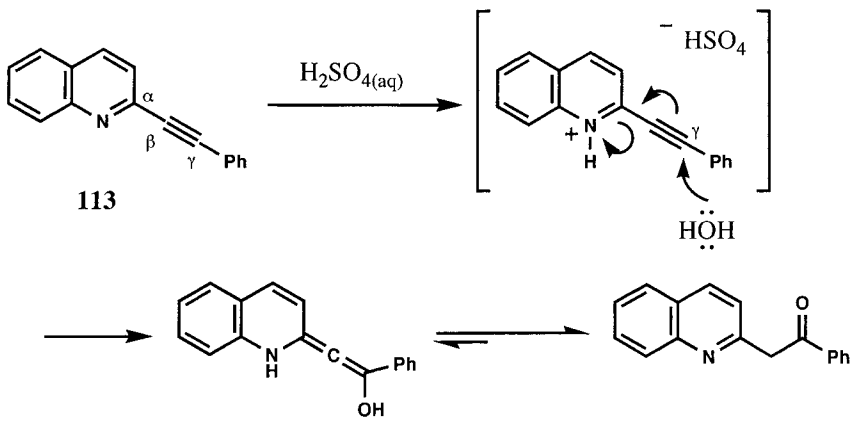
Cuprates, however, provided allenes (**112**) upon reaction with **109** (Scheme 50).[77]



112

Scheme 50

When the iminium fragment is part of an aromatic ring, the alkyne is activated for exclusive γ-addition of nucleophiles.[60] In this manner, water readily added to quinoline **113** in acidic media (Scheme 51).



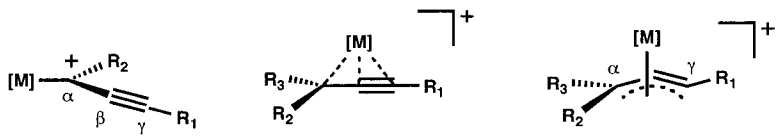
Scheme 51

This methodology has been applied to the synthesis of cyanine dyes[78] and other unsaturated heterocycles.

Metal-stabilized propargyl cations

Traditional alkynylcarbenium chemistry faces two obstacles. First, as the cation contains contiguous prochiral carbons (see Figure 5), the α-addition of nucleophiles leads to racemic product (e.g., Scheme 45). Second, promiscuous reactivity patterns hamper applicability (see Scheme 44). Fortunately, advances in organometallic chemistry have offered remedies.[79]

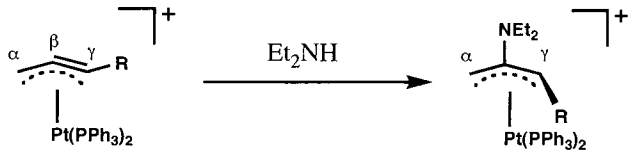
Several modes of propargyl stabilizations can be envisioned for transition metals: attachment at the α-position (**114**), direct π-complexation via η^2/η^3 coordination (**115**), or η^1/η^3 allenyl/propargyl complex **116** analogous to its allylic counterpart (Figure 7).



114 **115** **116**

Figure 7

Allenyl/propargyl complexes such as **116** will be excluded from this discussion as their reactions with nucleophiles lead to exclusive β-addition products (Scheme 52).[26,80]

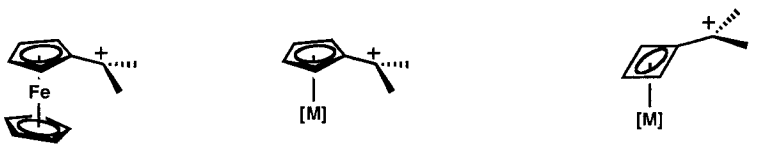


Scheme 52

When two or more metals are involved, the term *cluster* is used. As will be shown, clusters can be viewed as three-dimensional, polarizable electron clouds capable of stabilizing a proximal positive charge.

Monometallic cationic motifs

The ability of π-ligand transition metal complexes to stabilize α-carbocations is well established.[79a,b] Although ferrocenyl-substituted cations (e.g., **117**) have been extensively studied, other reported species include **118** and **119** (Figure 8).[79d,81]



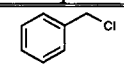
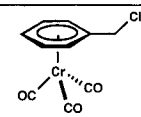
117 **118** **119**

[M] = $Cr(CO)_3$, $Cr(CO)_2NO$, $Mn(CO)_3$ [M] = $Fe(CO)_3$, CoCp

Figure 8

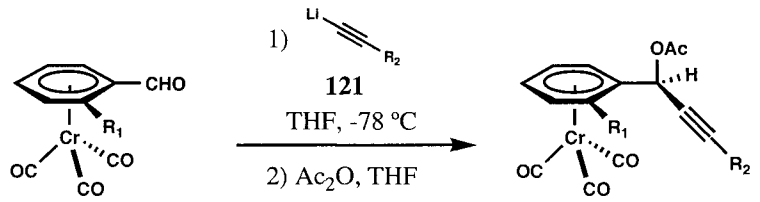
Indeed, Holmes et. al disclosed a 100,000-fold rate enhancement in the solvolysis of benzyl chloride once π-complexed to $Cr(CO)_3$ (Table 4).[82]

Table 4: Compound solvolysis rate.

Compound	Relative solvolysis rate [a]
	1
	$\sim 10^5$

[a] 80% Acetone(aq), 25 °C.

With scant reports of complex-substituted alkynyl carbonium ions,[83] Muller applied known arene chromiumcarbonyl methodology to propargylic manifolds.[84] *Ortho*-substituted η^6-(benzaldehyde)$Cr(CO)_3$ complex **120** was stereospecifically converted, via addition of lithium acetylide **121**, to propargyl acetate **122** in high yield (Scheme 53).

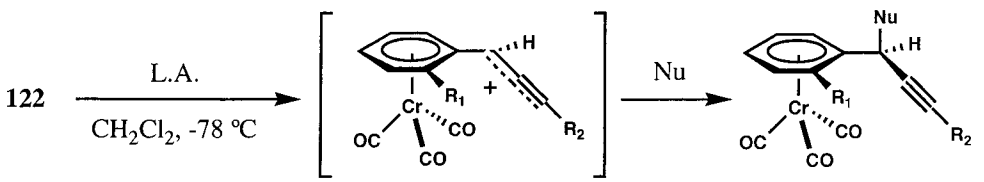


120
$R_1 = CH_3, OCH_3, Cl$
R_2 = Aryl, Alkyl

122
73 - 100%
100 : 0 dr

Scheme 53

Treatment of the starting material with a Lewis acid afforded propargyl cation **123**, whose reaction with various nucleophiles proved highly stereoselective (Scheme 54).



L.A. = TMSOTf, $SnCl_4$, BF_3•OEt_2, $TiCl_4$

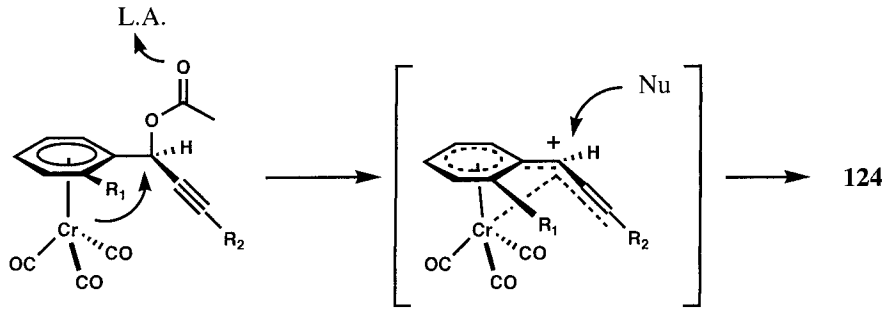
123 **124**

Nu	Yield	dr
i-PrSH	82%	>99:1
$(i\text{-Pr})_2NH$	89%	95:5
Morpholine	90%	97:3
AllylTMS	86%	91:9

Scheme 54

The stereochemical outcome is rationalized using a double-inversion mechanism (Scheme 55). The ionization of the starting material results from the *pull* of the Lewis acid on the acetate as well as the *push* of metal d electrons, thus effecting an inversion at C_α. Most crucial in this model is the configurational stability of the propargyl cation **123** imparted by intraligand π-p and metal-ligand d-p interactions, thus preventing rotation about the C_{ipso}-C_α bond. This proposed anchimeric assistance is supported by MO

calculations.[85] Subsequent *exo*-nucleophilic attack, with inversion, reestablishes stereochemical integrity in the product (**124**).



122 **123**

Scheme 55

Intermediates analogous to **123** were characterized by Muller in solution by NMR and UV/Vis spectroscopy.[85]

Synthesis of bimetallic alkynyl complexes

Bimetallic alkynylcarbonium ions are generated from the reaction of neutral dinuclear cluster complexes (**125**), which are prepared from substituted alkynes (Scheme 56). The most common homodinuclear complexes, bearing cobalt and molybdenum,[86] and more recently tungsten[87] are prepared in this fashion.

125

M_2
$Co_2(CO)_6$
$Cp_2(Mo_2(CO)_4$
$Cp_2W_2(CO)_4$
$W_2(t\text{-}BuCH_2O)_8$

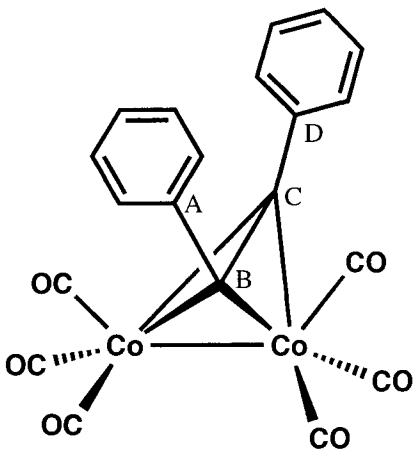
Scheme 56

In addition, transition metals spanning the periodic table have been reported to form neutral dinuclear complexes with alkynes (Figure 9).[88]

					Group						
	III	IV	V	VI	VII	VIII	IX	X	XI	XII	
						Fe	Co	Ni			
			Nb	Mo		Ru	Rh	Pd			
			Ta	W	Re	Os	Ir	Pt	Au		

Figure 9

In 1959, Sly reported the molecular structure of the dicobalt hexacarbonyl cluster of diphenylacetylene (Figure 10).[89] Worthy of note are the A-B-C and B-C-D angles, significantly distorted from linearity. The alkyne bond (B-C), formerly ~ 1.2 Å, has lengthened to 1.46 Å. The Greek letter *mu* (μ) in the complex notation indicates that the acetylenic ligand is bridging two metals, and is bound to each in an η^2 fashion.[90]



Angles:	
A-B-C	137°
B-C-D	139°

Distances:	
B-C	1.46 Å
Co-Co	2.47 Å
B-Co	1.9 Å

$[Co_2(CO)_6(\mu\text{-}\eta^2,\eta^2\text{-}RC{\equiv}CPh)]$

Figure 10

Hoffmann subsequently noted that when alkynes bridge two metal atoms, they do so in accordance with two limiting geometries: perpendicular (**126**) or parallel (**127**,

Figure 11).[91] The geometries refer to the spatial relationship between the C-C and M-M bonds. Parallel geometries are usually encountered with group VIII metals.

126 **127**

Figure 11

In perpendicular dinuclear complexes (**126**) the alkyne unit is a 4-electron donor ligand to the metal centers.[90] Bonding within the structure is a combination of ligand-to-metal σ-donation, ligand-to-metal π-donation, and metal-to-ligand π-back bonding (Figure 12).

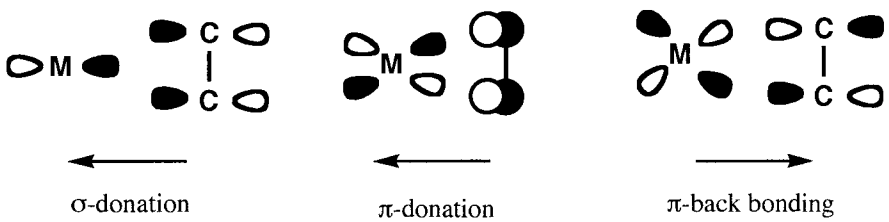
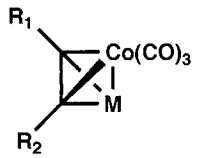


Figure 12

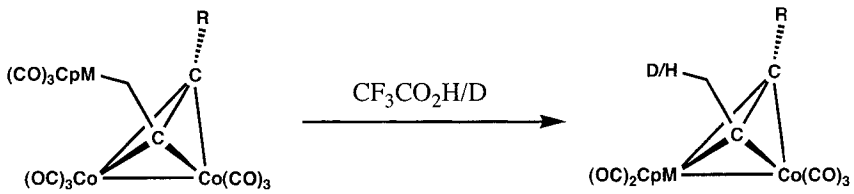
Complexes comprising heteronuclear metallic clusters also represent an important class of compounds, where M is isolobal to the $Co(CO)_3$ fragment (Figure 13).[92]



M = $MoCp(CO)_2$, $WCp(CO)_2$

Figure 13

Wojcicki reported the unusual conversion of trinuclear complexes **128** to heterobimetallic clusters **129** under acidic conditions (Scheme 57).[93]

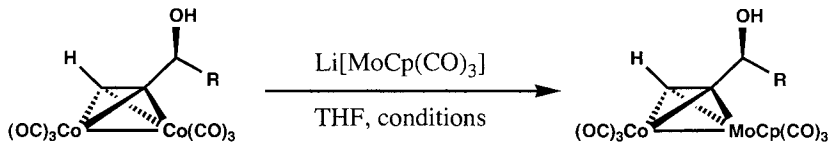


128
M = Mo, W

129

Scheme 57

More common syntheses of heterodinuclear complexes involved reaction of dicobalt clusters with preformed anionic complexes of molybdenum or tungsten.[94] Isolobal displacement on **130** afforded bimetallic clusters **131** with moderate selectivity (Scheme 58).[95]

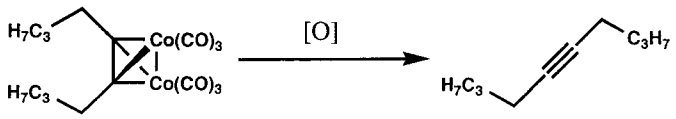


130 **131**

R	Conditions	Yield	de
Me	Δ, 1-2 h	48%	36%
i-Pr	rt, 4-6 d	56%	74%
i-Pr	Δ, 1-2 h	55%	6%
Ph	Rt, 4-6 d	48%	30%
Ph	Δ, 1-2 h	50%	71%

Scheme 58

The removal of the cluster, releasing the alkyne ligand, is undertaken under oxidative conditions (Scheme 59).[96]

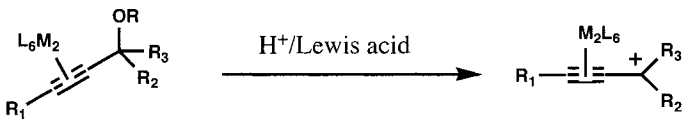


[O]	Yield
Me_3NO	99%
$Fe(NO_3)_3 \cdot H_2O$	90%
$Ce(NH_4)_2(NO_3)_6$	99%
Bu_4NF	99%

Scheme 59

Synthesis of bimetallic cationic complexes

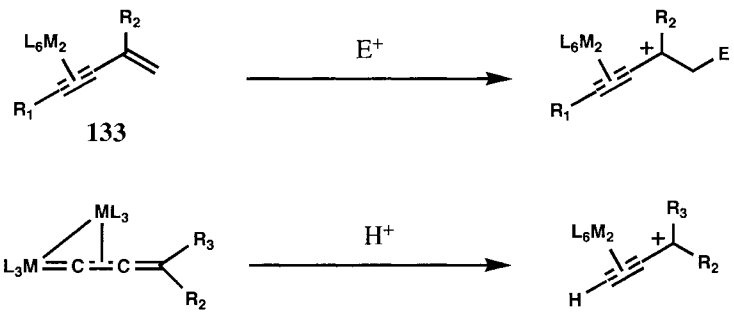
Dinuclear propargylium species have been prepared using several routes.[79d,f] The addition of a Lewis/Brönsted acid to an alcohol or ether (**132**) is the most common approach (Scheme 60).[97]



132
R = H, Alkyl

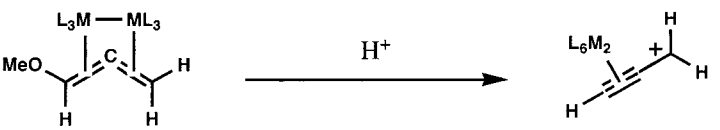
Scheme 60

Other starting materials can include enynes (**133**), allenylidenes (**134**), and allenic complexes (**135**) (Scheme 61).[97, 98, 99]



133

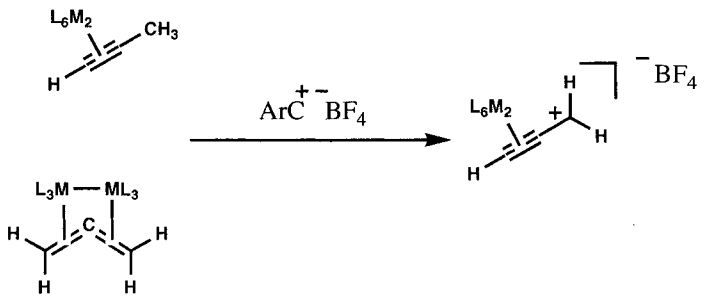
134



135

Scheme 61

Hydride abstraction from acetylenic and allenyl complexes has also been described (Scheme 62).[99]

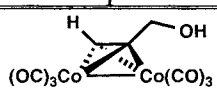
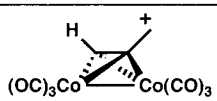
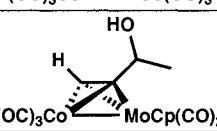
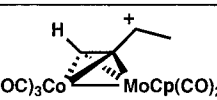
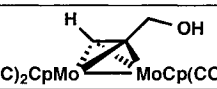
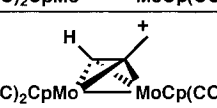


Scheme 62

Properties of bimetallic cationic complexes

The CO IR shifts of various cationic complexes and their parent alcohol are reported in Table 5.[100]

Table 5: IR data of dinuclear cationic complexes.

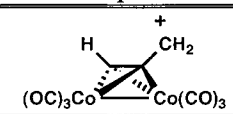
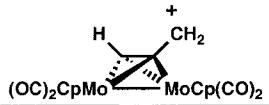
Entry	Compound	ν_{CO} (cm^{-1})
1		2025, 2050, 2090
2		2085, 2105, 2130
3		1888, 1942, 1980, 2000, 2050
4		1941, 1982, 2000, 2034, 2048, 2068, 2098
5		1829, 1903, 1986
6		1982, 1984, 1994, 2042

In all cases, ionization led to vibrational blue shifts, indicating a stronger C=O bond in the cationic species. This was interpreted as a diminution in cobalt-carbon

monoxide back bonding (see Figure 12) caused by the electron-poor nature of the cationic complexes.

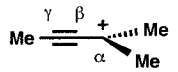
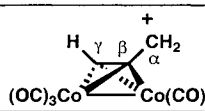
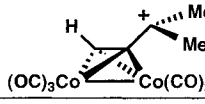
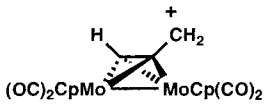
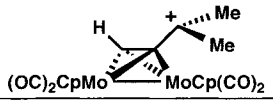
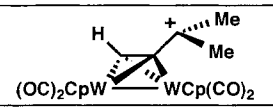
^{1}H NMR data offered additional insight into the electronic environment of α-hydrogens (Table 6).[79f] The dicobalt cluster is more deshielding than its molybdenum counterpart.

Table 6: ^{1}H NMR chemical shift of dinuclear cationic complexes.

Compound	C_α-H (ppm)
	7.67
	6.90

This trend is more apparent in ^{13}C NMR spectral data, for which resonance differences tend to be more pronounced (Table 7).[101]

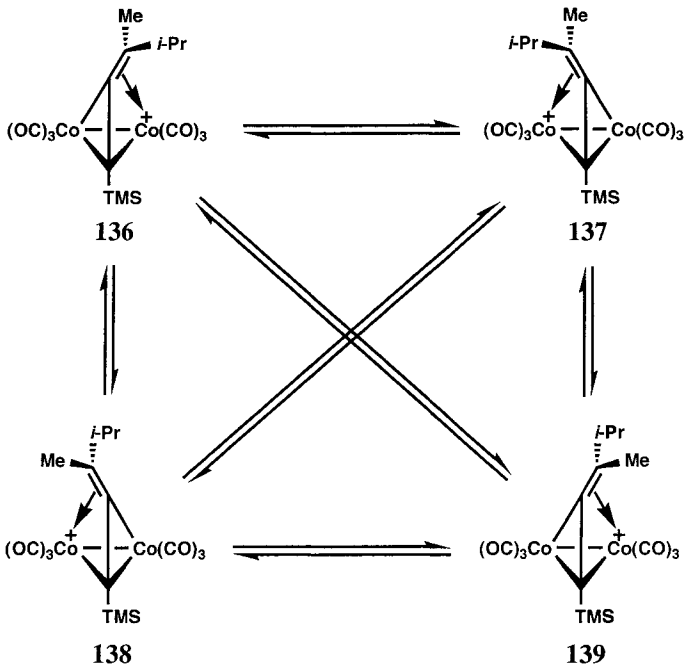
Table 7: ^{13}C NMR chemical shifts of dinuclear cationic complexes.

Entry	Compound	Solvent	C_α ($\Delta\delta$)[a] (ppm)	C_β ($\Delta\delta$)[a] (ppm)	C_γ ($\Delta\delta$)[a] (ppm)	CO ($\Delta\delta$)[a] (ppm)
1		$SO_{2(l)}$	269 (+204)	111 (+26)	218 (+140)	
2		$SO_{2(l)}$	79.5 (+14.5)	122 (+23)	80 (+9)	192 (-7)
3		$SO_{2(l)}$	146 (+77)	110 (+4)	79.5 (+7.5)	192 (-9)
4		*d*-Acetone	75.1	118.2	79.9	218 - 221
5		CD_2Cl_2	143.7	104.2	76.7	217, 227
6		CD_2Cl_2	151.9	93.2	54.2	205 - 209

[a] Chemical shift difference from the parent alcohol.

Salient features of this data include: (1) dicobalt cluster C_α resonances (entries 2, 3) are far less deshielded relative to their parent alcohol than is the free propargyl cation (entry 1); (2) increasing substitution at C_α results in a substantial increase in deshielding at C_α (entries 2 and 3, 4 and 5); (3) ionization of the parent alcohol has minimal impact on CO chemical shift (entries 2, 3).

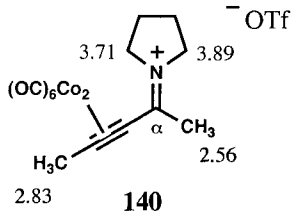
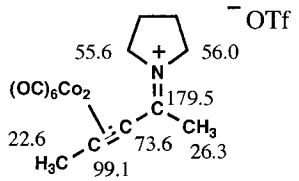
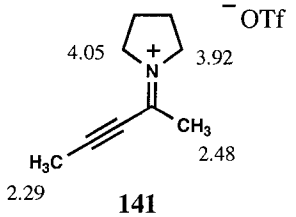
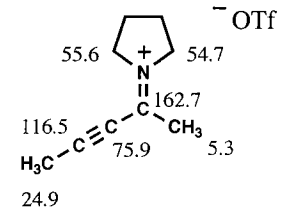
Schreiber's seminal NMR study of $[Co_2(CO)_6(\mu\text{-}\eta^2,\eta^2\text{-}Me_3Si\text{-}CC\text{-}C(i\text{-}Pr)Me]^+$ quantified two fluxional processes (Scheme 63).[102] Activation barriers for enantiomerization (**136** ⇔ **137**, **138** ⇔ **139**) and diastereomerization (**136** ⇔ **139**, **137** ⇔ **138**) were reported to be $\Delta G^{\neq}$ = 10.1 kcal/mol and $\Delta G^{\neq}$ = 12.9 kcal/mol, respectively.



Scheme 63

Extending his work on alkynyl iminiums, Maas reported the spectral properties of iminium cluster **140** and its uncomplexed parent **141** (Table 8).[103]

Table 8: NMR data of dicobalt iminium clusters.

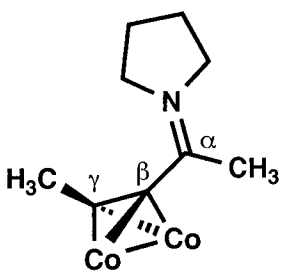
(δ, ppm) [a]	
^{1}H	^{13}C
 **140**	
 **141**	

[a] Values in CD_3CN.

The presence of a heteroatom at C_α led to further deshielding upon complexation. This observation is counter to reported shifts of unfunctionalized systems (Entries 1 and 3, Table 7). Surprisingly, the downfield shift disclosed for the pendant methyl carbon upon complexation (5.3 ppm → 26.3 ppm) did not significantly influence the resonance of hydrogens bound to it (2.48 ppm → 2.56 ppm). This iminium-stabilized complex proved amenable to X-ray analysis (Table 9).

Table 9: X-Ray structure of dicobalt iminium cluster 140.

	140	**141**
N-C_α	1.302 Å	1.265 Å
C_α-C_β	1.438 Å	1.406 Å
C_β-C_γ	1.358 Å	1.170 Å
C_α-C_β-C_γ	147.8°	176.8°
C_β-C_γ-CH_3	145.6°	180.0°
C_α-C_β-C_γ-CH_3	8.8°	

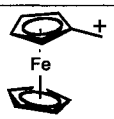
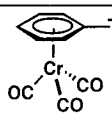
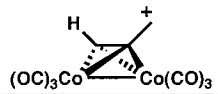
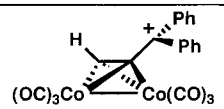
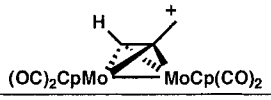


140

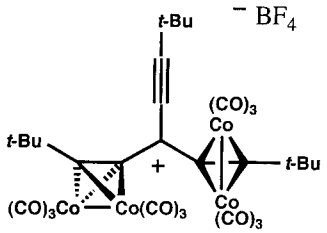
* CO ligands omitted for clarity.

The stability of cationic metallic clusters was measured by Nicholas and Gruselle (Table 10).[104] The pK_{R+} is a measure of thermodynamic stability, with increasing negative values denoting decreasing concentration of the cation at equilibrium.[105]

Table 10: Thermodynamic stability of cationic complexes.

Entry	Compound	pK_{R+}
1	Ph_3C^+	-6.6
2		-1.5
3		-11.8
4		-6.8
5		-7.4
6		3.5

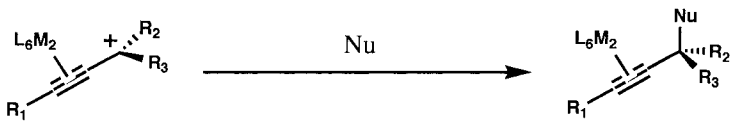
It is interesting to note that although substituted by isolobal metal fragments, dicobalt alkynyl clusters (entries 4 and 5) are ~ 10^{10} times less stable than their dimolybdenum counterpart (entry 6). This inherent disparity manifests itself in critical ways. Although X-ray structures have been obtained for $[Mo_2]$,[86, 106] $[W_2]$,[101b] as well as [Mo-Co] propargylium complexes,[107] the instability of $[Co_2]$ clusters and their sensitivity to moisture have prevented the preparation of high-quality crystals. It should be noted that Melikyan reported the X-ray structure of bis-clustured complex **142**, collected at -105 °C (Figure 14).[108] However, it is unclear to what extent this data can be correlated to cationic $[Co_2(CO)_6]$ clusters.



142

Figure 14

Conversely, thermodynamic stability permitted the use of $[Mo_2Cp_2(CO)_4(\mu\text{-}\eta^2,\eta^3\text{-}HCC\text{-}CH_2)]^+$ in water or acetonitrile, solvents that otherwise react with its dicobalt analog. Subsequently, charged nucleophiles are required to effect additions to $[Mo_2]$, $[W_2]$, and [Mo-Co] propargylic cations (Scheme 64).[86]

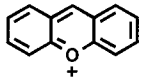
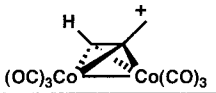
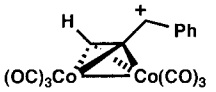
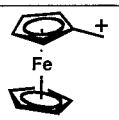
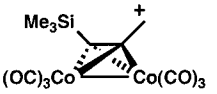
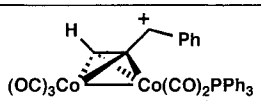


Nu = RO^-, H^-, CH_3S^-, CpLi, N_3^-

Scheme 64

The reactivity of dicobalt propargylium complexes with nucleophiles was empirically established by Mayr.[109] Measured electrophilicity parameters (E) show them to be equivalent in reactivity to α-ferrocenylmethylium ion (entry 4) and xanthylium ion (entry 1,Table 11).

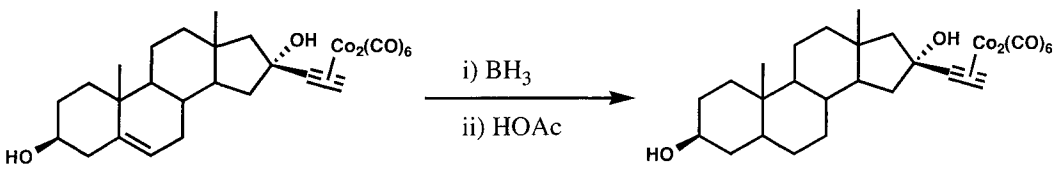
Table 11: Electrophilicity (E) of cations.

Entry	Compound	E
1		~ -1.0
2		-1.22
3		-1.34
4		-1.8
5		-2.22
6		-6.71

This data confirms their suitable reactivity with electron-rich arenes, alkenes, and alkynes, but marginally with toluene. Ultimately, it is the instability of dicobalt-complexed propargylium ions that has fueled this burgeoning field over 35 years.

Applications of $Co_2(CO)_6$-complexed propargyl cations

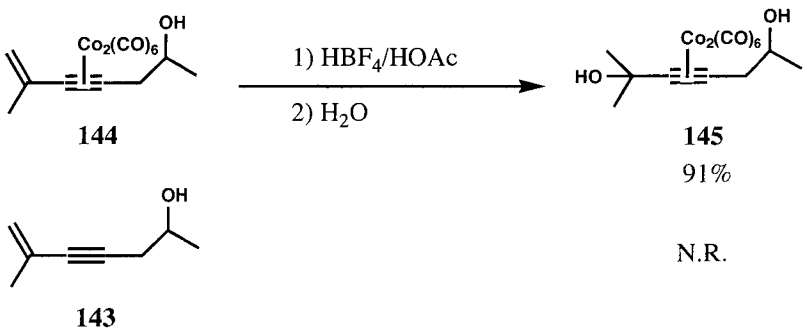
Initially, Nicholas used [$Co_2(CO)_6$] as an alkyne protecting group to permit selective transformations on a pendent olefin (e.g., Scheme 65).[110]



60%

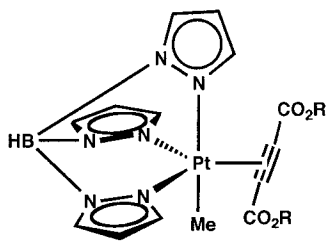
Scheme 65

When applied to vinyl acetylene (**143** → **144**), the complex underwent facile hydrolysis to **145** in high yield, while the enyne parent (**143**) proved unreactive (Scheme 66).



Scheme 66

Only one other example of an "alkyne protecting group" could be found in the literature. Platinum complex **146** reportedly overcame reaction limitations encountered with dicobalt clusters (Figure 15).[111] The stability of this complex required 60 psi of $CO_{(g)}$ to induce decomplexation.



146

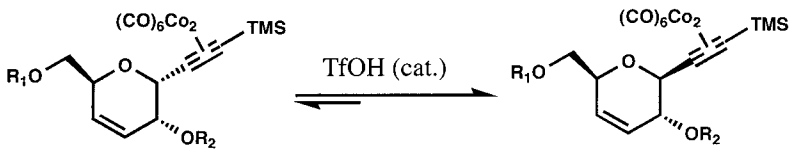
Figure 15

However, it is the dicobalt clusters' ability to stabilize an α-cation that spured developments in this field. Perhaps in recognition of their value to chemists and impact

to science, the addition of nucleophiles to these cations has become known as the *Nicholas reaction.*

Heteroatom nucleophiles

Nicholas' initial report of an oxygenated nucleophile (water) adding to a propargyl cation has been extended to the synthesis of cyclic ether-bearing ring systems found in marine natural products.[112] Relying on the reversible nature of propargylic additions, Isobe effected the isomerization of α-pyran **147** to its β-epimer **148** under acid catalysis (Scheme 67).[113] The overriding driving force was postulated to be an unfavorable 1,2-steric interaction between a large R_2 and the cluster.

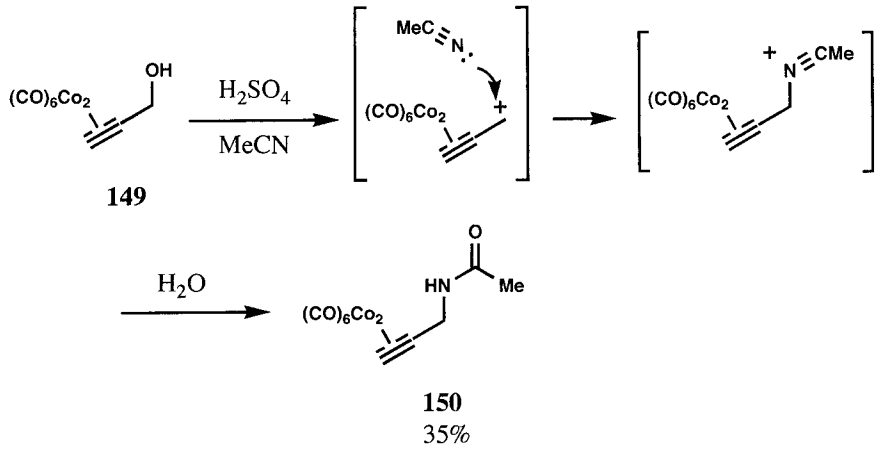


147 **148**

R_1	R_2	**147:148**	Yield
Ac	H	1:10	86%
Bz	H	1:12	95%
Ac	Ac	1:27	94%
Ac	TBDPS	1:100	84%

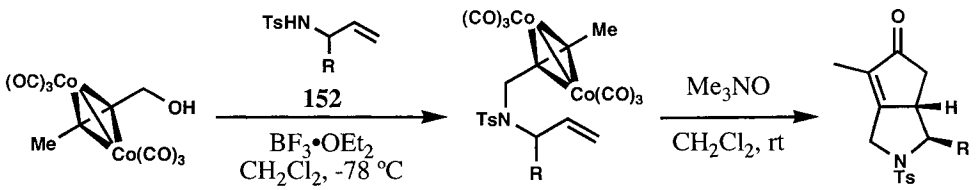
Scheme 67

It is claimed that the earliest Nicholas reaction with a nitrogen nucleophile dates to 1981, when complex **149** afforded propargyl amide **150** upon exposure to acetonitrile and acid, albeit in an unoptimized yield (Scheme 68).[114]



Scheme 68

Jeong and Yoo reported the N-propargylation of **151** with allylamides (**152**) to intermediates **153**, whose in situ reaction with Me_3NO afforded the Pauson-Khand products **154** (Scheme 69).[115]

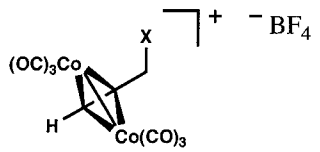


R	Yield (*syn*:*anti*)
H	90%
CH_2OBz	35% (2:1)
CH_2OMOM	50% (6:1)

Scheme 69

Still, only a few examples of the use of nitrogen nucleophiles are found in the literature.[116]

Thiols have also been reported to react with Nicholas cations.[117] Interestingly, when sulfides, phosphines, and pyridine were substituted, a novel class of propargylic cationic derivatives were isolated (Figure 16).[118]



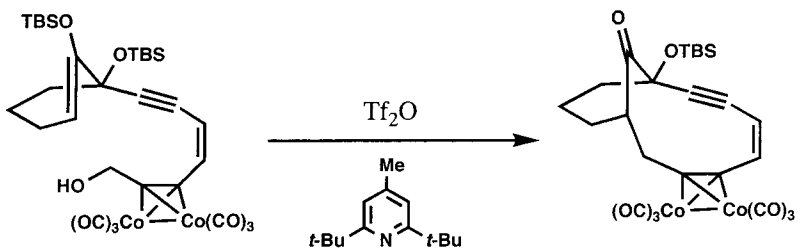
X = Me_2S, Ph_3P, Py

Figure 16

The presence of heteroatoms attenuated reactivity toward nucleophiles, which was reported to proceed via an S_N2 mechanism in the case of the sulfonium complex.

Carbon nucleophiles

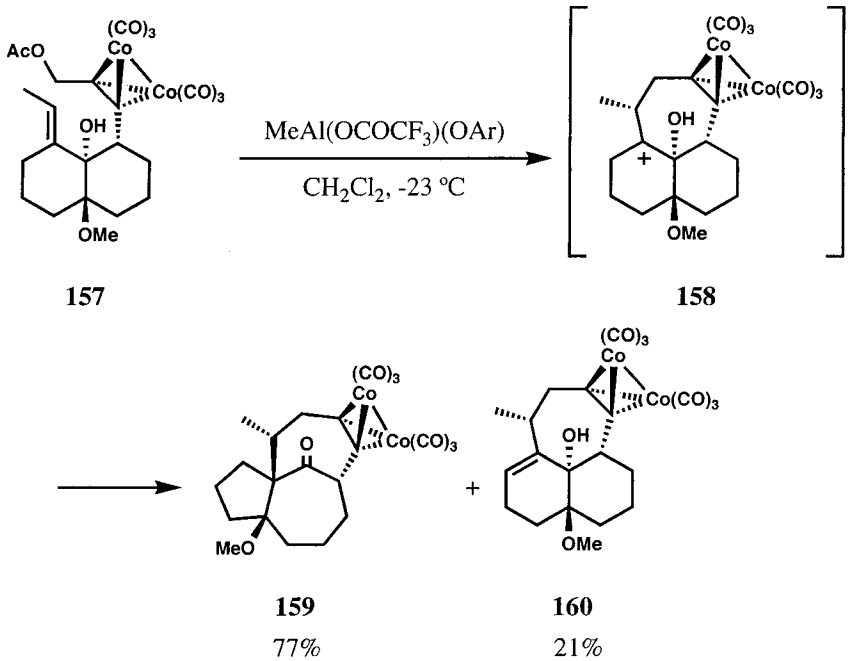
The attack of carbon nucleophiles on Nicholas cations comprises the richest subset of reactive partners. The reaction of silyl enol ethers with Nicholas cations is best exemplified by the intramolecular ring-closure of the core of enediyne antibiotics (**155** → **156**, Scheme 70).[119]



155 **156**
77%

Scheme 70

In an interesting variant, the intramolecular cyclization-rearrangement of a decalin complex was detailed.[120] Addition of a Lewis acid to **157** initiated a diastereoselective cyclization to **158**, followed by 1,2-rearrangement to ingenol precursor **159** (Scheme 71). Compound **160** was the product of a competing β-elimination.

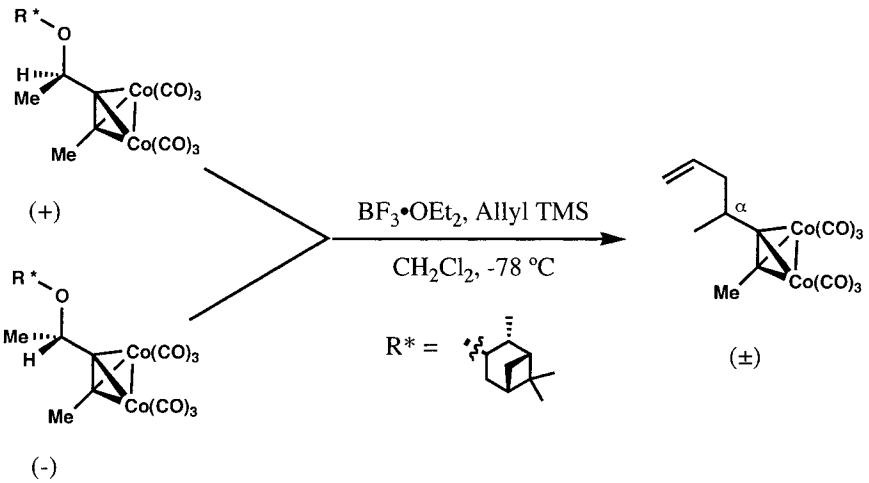


157 **158**

159 77% **160** 21%

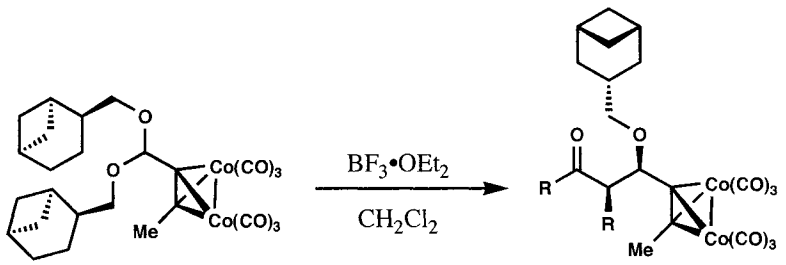
Scheme 71

With intermediates incorporating a 2° cation, rapid racemization (vide supra) restricts the ability to create α-chiral centers (Scheme 72). However, few exceptions are found in the literature.

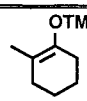
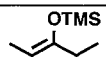


Scheme 72

If the substrate or nucleophile is chiral, the opportunity for double stereo-differentiation via kinetic resolution of a racemizing cation exists.[102,121] Montana added prochiral enol silanes to chiral acetal **161** (Scheme 73).[122] The high product diastereo-selection points to control over enantiomerization of the cation, but the lack of enantio-selectivity indicates failure to restrict diastereomerization of the intermediate prior to nucleophilic addition.

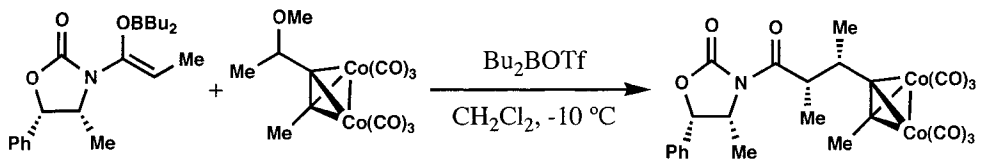


161

Enol silane	dr	ee
	94 : 6	10% (*syn*), 0% (*anti*)
	> 99 : 1	0% (*syn*)
	> 99 : 1	16% (*syn*)

Scheme 73

Reversing the setup, a mixture of chiral boron enolate **162** and racemic ether complex **163** was treated with Bu_2BOTf, resulting in an 80% yield of a 12:1 (*syn*:*anti*) mixture of product **164** (Scheme 74).

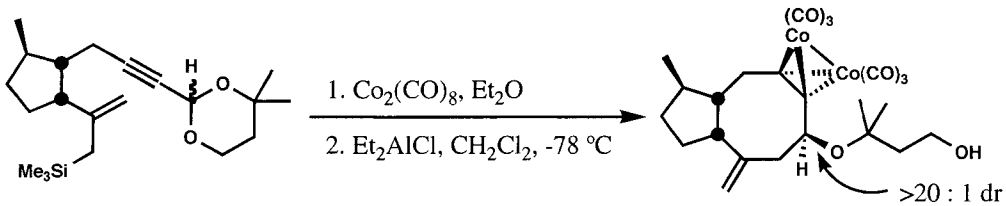


162 **163** (±) **164** 80% 12:1 dr

Scheme 74

Racemic **165** leading to **166** with high diastereoselectivity and yield (>50%) is indicative of an equilibration occurring faster than nucleophilic addition. In the synthesis of epoxydictymene, Schreiber effected the selective activation of an unsymmetrical acetal.[123] The one-pot complexation/intramolecular allylation of acetal **165** afforded one

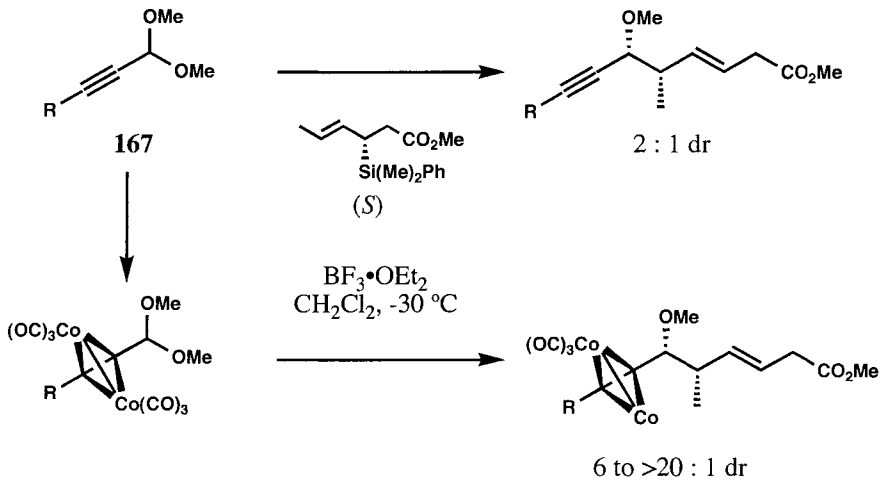
epimer of the bicyclic complex **166** (Scheme 75). This is another example of a kinetic resolution of a racemizing cation.



165 **166**
83%

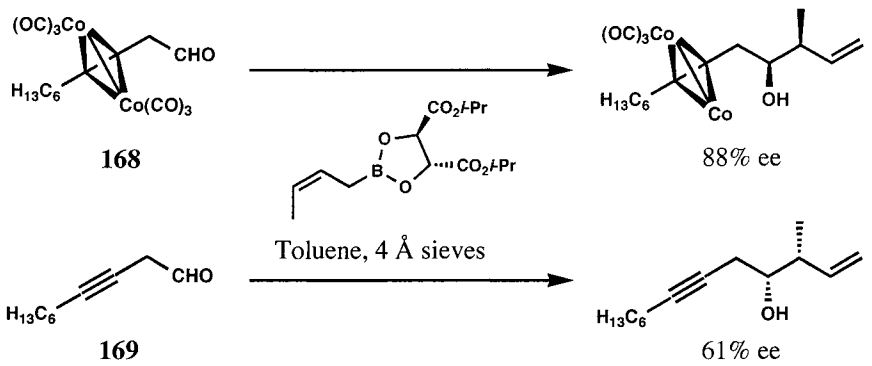
Scheme 75

Metal carbonyl complexes have been shown to enhance the enantioselectivity of allylation and crotylation reactions.[124] During the synthesis of Cystothiazole A, Panek required a *syn*-crotylation reaction to access a stereochemically defined propargyllic ether.[125] Complexation of the starting acetal **167** prior to crotylation significantly improved the diastereoselection of the reaction (Scheme 76).



Scheme 76

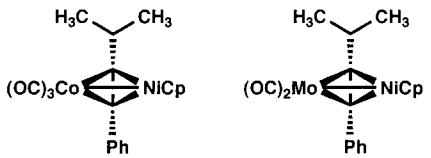
Crotylboration of the dicobalt cluster of 3-decyne (**168**) exhibited an improvement in enantioselectivity, but with a *reverse* sense of chirality compared to the uncomplexed parent (**169**, Scheme 77).[126] It was postulated that this aberrant outcome is the result of through-space interactions, although the transition state interactions responsible were not entirely clear.



Scheme 77

Chiral $Co_2(CO)_5L$-complexed propargyl cations

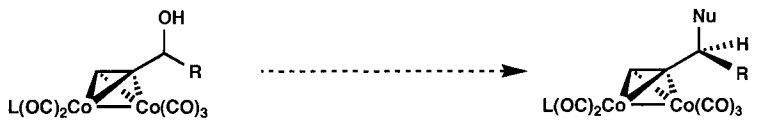
An alternate approach to effecting stereoselective propargylation is to impart chirality to the cluster.[127] Discouraging evidence had shown that some chiral clusters, including bimetallic species such as **170** and **171**, readily racemized on the NMR timescale (Figure 17).[128] In toluene-*d*, the diastereotopic methyl signals of **170** coalesced at 378 K ($\Delta G^{\neq}$ = 20.5 ± 0.5 kcal/mol).



170 **171**

Figure 17

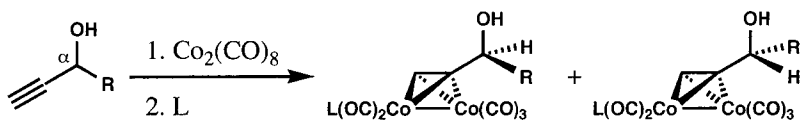
Nicholas initially sought chiral platform **172** to study diastereoselective propargylation (Scheme 78). [129]



172

Scheme 78

Complexation of readily-available chiral, but racemic, propargyl alcohols **173** followed by ligand exchange afforded scaffolds **174/175** and **176/177** with varying degrees of selectivity (Scheme 79).



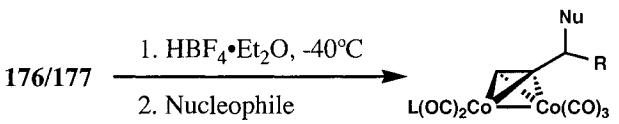
173

L = PPh_3 **174** **175**
L = $P[OCH_2(CF_3)_2]_3$ **176** **177**

L	R	dr	Yield
PPh_3	Me (a)	90:10	87%
PPh_3	Ph (b)	80:20	93%
PPh_3	*t*-Bu (c)	>95:5	84%
$P[OCH_2(CF_3)_2]_3$	Me (a)	62:38	
$P[OCH_2(CF_3)_2]_3$	Ph (b)	56:44	
$P[OCH_2(CF_3)_2]_3$	*t*-Bu (c)	>95:5	

Scheme 79

Effective chirality transfer was only achieved in the presence of large α-substitution (**174c** and **176c**). However, the diastereomeric products were readily separated by chromatography. The M-CO IR bands of **176/177** are higher (~ 40 cm^{-1}) than **174/175**, but comparable to the parent $Co_2(CO)_6$ complex. This perhaps suggests an electronic similarity between the phosphite ligand and CO. The PPh_3 derivatives (**174/175**) proved unreactive toward important carbon nucleophiles.[129a130] However, the weakly σ-donating, but strong π-accepting $[(CF_3)_2CHO]_3P$ ligand exhibited no such attenuation upon reaction with silyl enol ethers and allylsilane (Scheme 80).

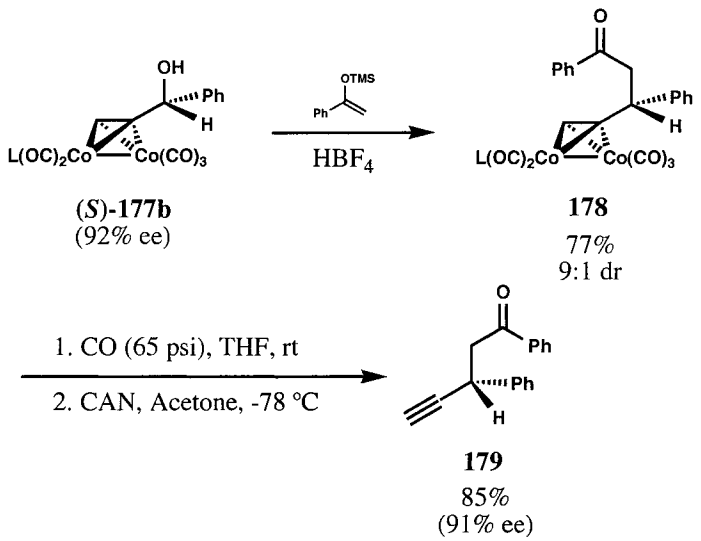


Entry	Complex	Nucleophile	dr	Yield
1	**177b**		9:1	85%
2	**176b**		1.1:1	90%
3	**177b**		10.5:1	94%

Scheme 80

Product diastereoselectivity proved independent of precursor alcohol stereochemistry, analogously to outcomes with $Co_2(CO)_6$ clusters, and consistent with a common cationic intermediate. Racemization has been demonstrated to plague propargyl substitutions of $Co_2(CO)_6$ complex (vide supra). Addition of trimethyl(1-phenylvinyloxy)silane to optically active **(*S*)-177b** provided a 9:1 mixture of diastereomeric ketones **178**, as expected (Scheme 81). Purification and decomplexation of the major isomer afforded alkynone **179**, whose enantiomeric purity was identical to

the starting material **(*S*)-177b**. Furthermore, the stereochemistry of the incipient α-bond was consistent with a cationic interemediate resistant to epimerization.



(*S*)-177b
(92% ee)

178
77%
9:1 dr

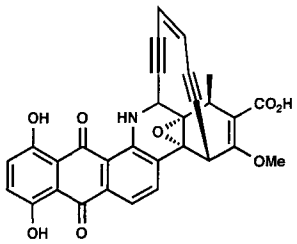
179
85%
(91% ee)

Scheme 81

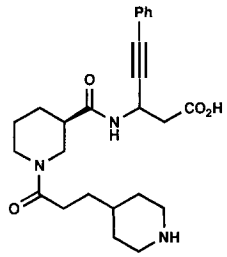
Thus absolute stereocontrol can be achieved using a properly designed cluster.

Chiral propargyl amines

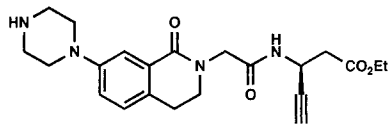
The α-substituted propargylic amine motif is found in a few important bioactive compounds (Figure 18).[131]



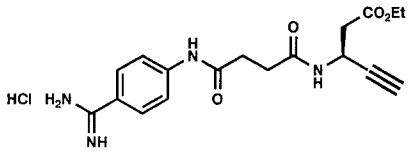
Dynemicin A
antitumor



arterial thrombosis



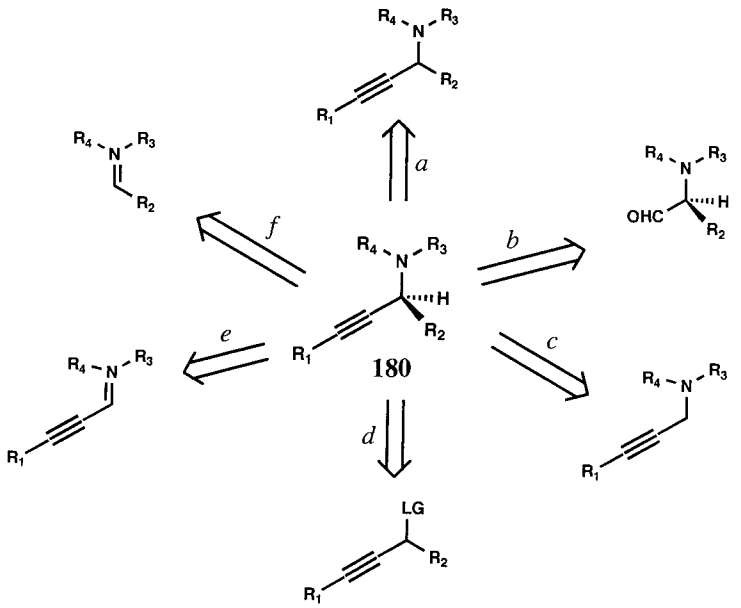
L-767,685
GPIIb-IIIa antagonist



Xemilofiban
anti-platelet agregation

Figure 18

Although considerable effort has focused on the synthesis of chiral α-propargyl alcohols,[132] less attention has been paid to their nitrogen analogues.[133] Several strategies have emerged for their selective synthesis (**180**, Scheme 82).

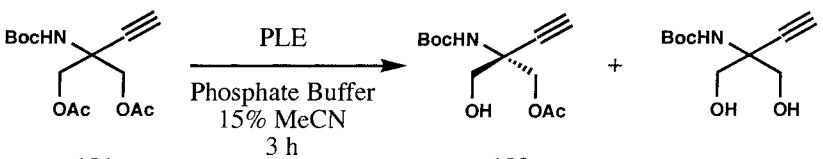


Key: (*a*) Enzymatic resolution, (*b*) functional group transform, (*c*) electrophilic addition, (*d*) propargyl displacement, (*e*, *f*) nucleophilic addition to imine and related functional group.

Scheme 82

Enzymatic resolution

During the synthesis of glycosylated amino acids, Halcomb effected the esterase-catalyzed desymmetrization of diacetate **181** to furnish required monoacetate **182** (Scheme 83).[134]

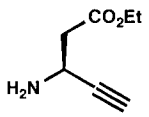


181 **182**

94% (67% conversion)
80% ee

Scheme 83

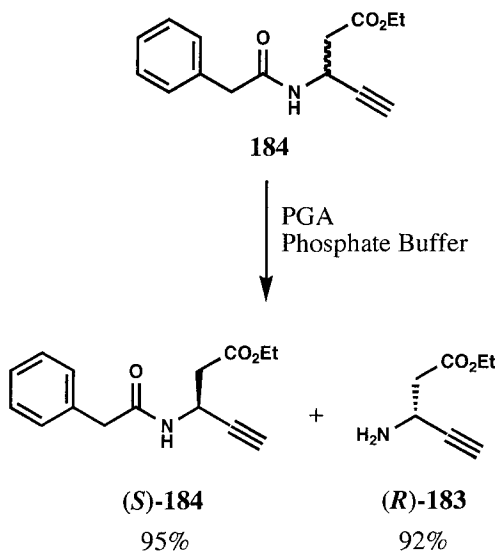
On an industrial scale, Pharmacia chemists required large quantities of β-amino acid ester **(*S*)-183** for their synthesis of Xemilofiban, an inhibitor of platelet aggregation (Figure 19).[135]



(*S*)-183

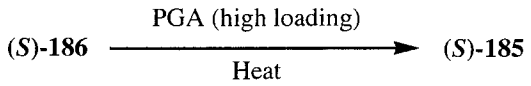
Figure 19

Using the unique enzyme Penicillin G amidohydrolase (PGA), racemic phenylacetamide **184** was deacylated to **(*S*)-184** and **(*R*)-183** in excellent yield (Scheme 84). Upon complete conversion, the mixture was extracted with ethyl acetate. Aqueous acid wash of the organic phase left **(*S*)-184** in solution.



Scheme 84

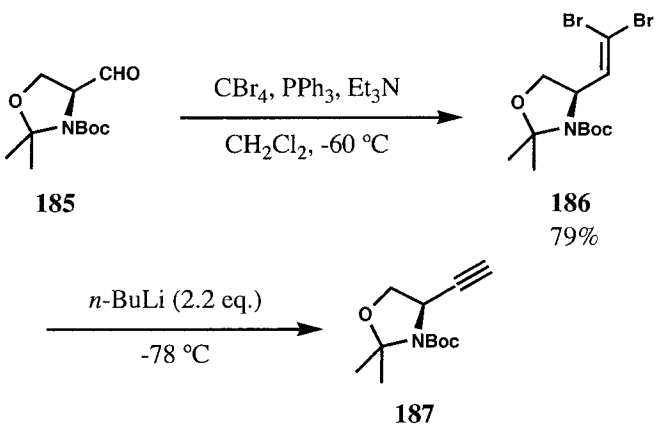
Resubjection of **(*S*)-184** to PGA, albeit under more forceful conditions, afforded the desired product (Scheme 85).



Scheme 85

Functional group transform

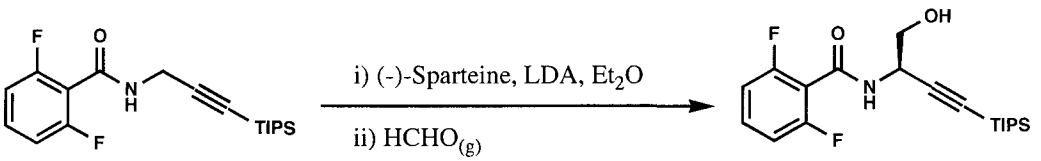
Amino acids and their derivatives offer chemists an attractive chiral pool, thus the conversion of a carbonyl group to a terminal acetylene represents an obvious pathway to chiral propargylamines.[136] The Corey-Fuchs procedure is representative (Scheme 86).[137] The Garner aldehyde (**185**) was converted to dibromide **186**, which upon reaction with excess butyllithium afforded ethynyl glycine derivative **187** in good yield.



Scheme 86

Electrophilic addition

Few examples of aminopropargylic anions, or their synthons, are found in the literature.[138] Sparteine-mediated enantioselective deprotonation/alkylation[139] of propargyl amide **188** proved poorly selective (Scheme 87).[140]

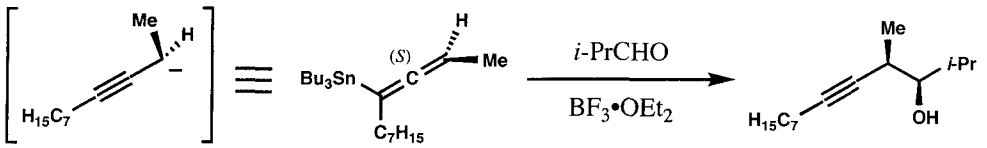


188

43% ee

Scheme 87

Greater success has been found in the use of masked propargyl anions (**189**), such as the chiral allenylstannanes (**190**) pioneered by Marshall (Scheme 88).[141]

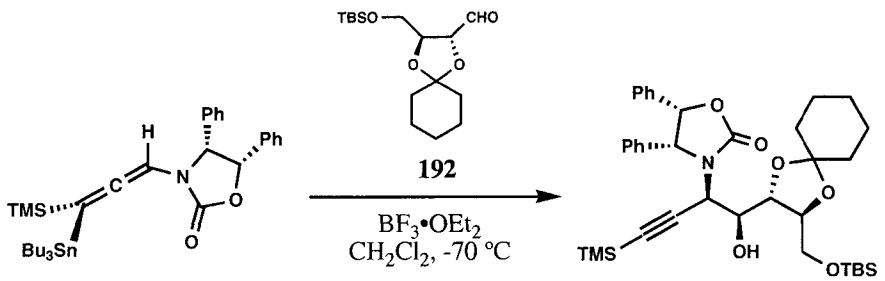


189 **190**

80%
99:1 dr

Scheme 88

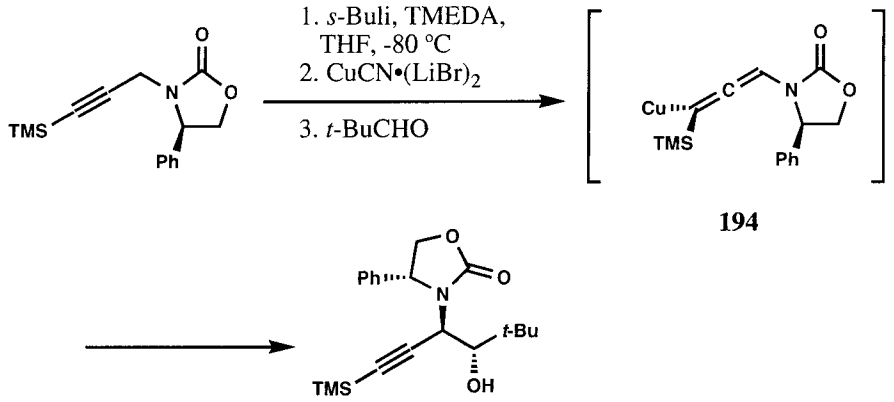
In the synthesis of 1-deoxy-D-galactohomonojirimycin, Hegedus condensed chiral allenamide **191** with aldehyde **192** to produce protected aminotetraol **193** with very high *syn* selectivity (Scheme 89).[142] This stereochemical outcome is counter to that obtained with the allenyl ether analog (see Scheme 11).



191 **193**
86%
>95:5 *syn*:*anti*

Scheme 89

The in situ generation of allenylcuprate **194** led to exclusive *anti* diastereomer **195** upon reaction with isobutyraldehyde (Scheme 90).[143]



194

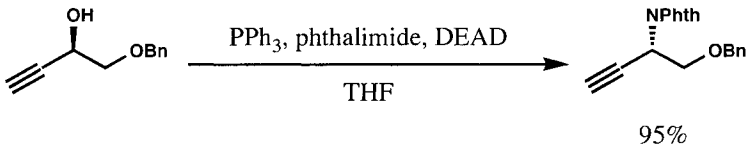
195
84%

Scheme 90

Propargyl nucleophilic substitution

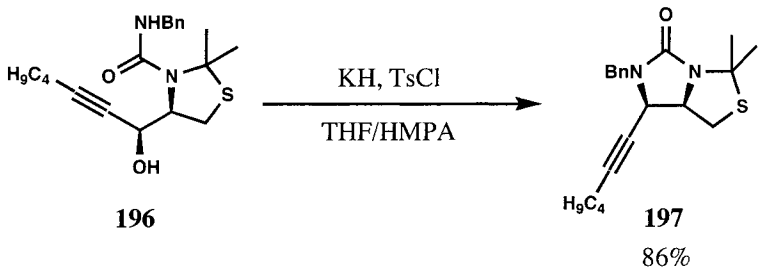
Now that chiral alkynyl alcohols are readily available,[132] the creation of a C-N bond by nucleophilic displacement of propargyl ethers has become an attractive and

simple strategy. The Mitsunobu reaction, occurring with an inversion of stereochemistry (S_N2), has become a classic route to propargyl amines (Scheme 91).[144]



Scheme 91

Marshall's previously discussed palladium-catalyzed method is worthy of mention for its net retention of stereochemistry in the product (see Scheme 32).[50] Intramolecular variants have also been reported.[145] An otherwise difficult ring closure, **196** cyclized under carefully controlled conditions to afford the *syn* urea **197**, a precursor of deoxybiotin (Scheme 92).[146]



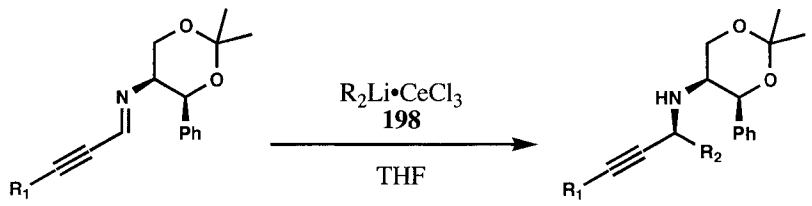
196 **197**

86%

Scheme 92

Nucleophilic addition to propargyl imines

The nucleophilic attack on propargylimines has received scant attention, with three reports in the literature. Organocerium reagent **198** added to chiral aldimine **199** with good selectivity (Scheme 93).[147]



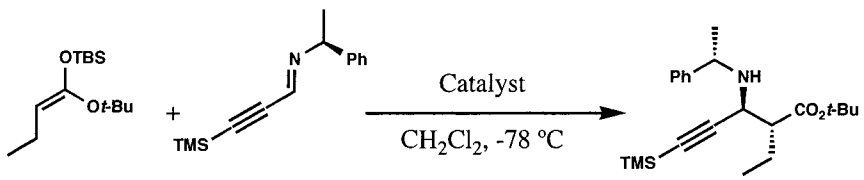
199

R_1 = Ph, *t*-Bu, TMS
R_2 = Me, Et, allyl, $TBSO(CH_2)_3$

65-91%
86-98% de

Scheme 93

Relying on a chiral boron catalyst, Yamamoto effected a double stereodifferentiated ketene acetal (**200**) condensation with imine **201** for the synthesis of *anti*-β-amino ester **202** (Scheme 94).[148]



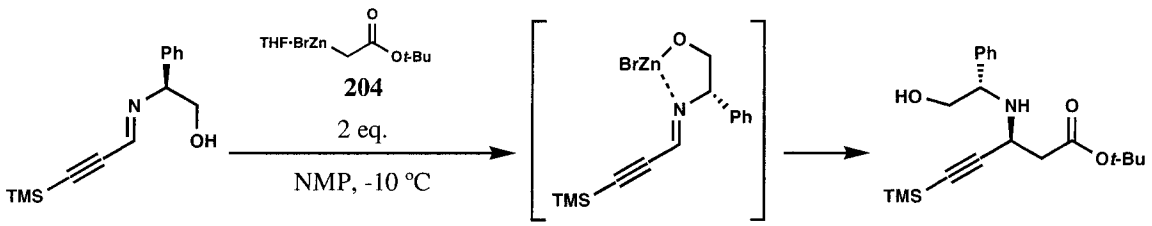
200 **201** **202**

70-80%

Catalyst	*anti* : *syn*	*anti* ratio
(*R*)-Binap-B-OPh	40:1	99:1
(*S*)-Binap-B-OPh	2:1	94:6

Scheme 94

In a more recent approach to the Xemilofiban side-chain, imine **203** required two equivalents of Reformatzky reagent **204** to form rigid chelate **205** prior to nucleophilic addition from the less-hindered face (Scheme 95).[149] Careful study of the reaction conditions indicated a correlation between solvent polarity and diastereoselectivity.

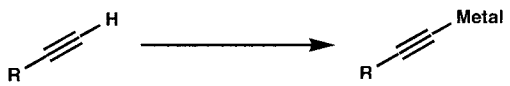


203 **205** 98% de

Scheme 95

Nucleophilic addition to imines/related functional groups

The acidity of acetylenic protons ($pK_a \approx 25$) enables the preparation of various alkynyl metal salts (Scheme 96).[150] This elemental promiscuity allows the tuning of alkyne nucleophilicity, thus optimizing reactivity and selectivity.[151]



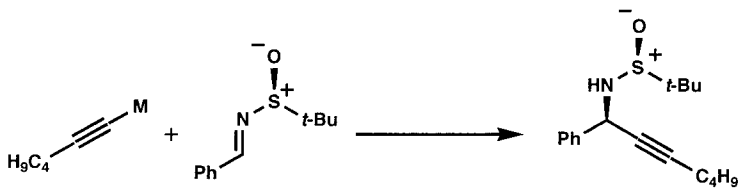
Metal = Li, MgX, Cu, Ag, Au, Zn, Hg, Al

Scheme 96

The diastereoselective addition of alkynyl metals to chiral imines remains the most reliable and efficient method for the preparation of optically active propargyl-amines.[152] Examples of alkynilides of lithium,[153] magnesium,[154], zinc,[155] and aluminum[156] are readily found in the literature.

Several base-catalyzed reactions incorporate silicon to deliver the nucleophile via a hypervalent silicate intermediate.[157] Scheidt successfully effected a diastereoselective version, with the reaction of triethoxysilylalkyne (**206a**) with *t*-butylsulfinyl imine **207** (Scheme 97).[158] Propargyl sulfinamide **208** was produced in high yield and

diastereoselectivity (entry 1). Interestingly, other alkynyl metal variants proved less selective.



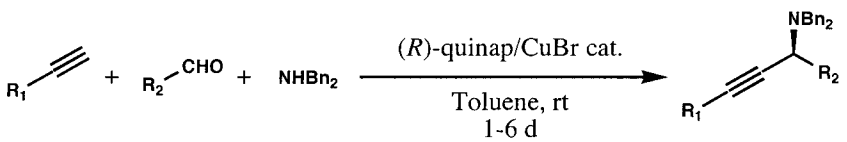
206 207 208

Entry		M	Yield	dr
1	206a	$Si(OEt)_3$	95%	20:1
2	206b	K	30%	2:1
3	206c	Li	99%	1:7
4	206d	MgEt	74%	1:3

Scheme 97

One-pot 3-component coupling

The recent trend of atom and chemical economy[159] has driven several groups to a direct propargylamine synthesis from the reaction of a terminal acetylene, aldehyde, and amine.[160] Knochel reported the enantioselective variant (Scheme 98).[161]



R_1	R_2	Yield	ee
Ph	*i*-Bu	98%	86%
TMS	*i*-Pr	87%	92%
TMS	*c*-Hex	99%	92%
TMS	1-Ethylpropyl	72%	96%

Scheme 98

The need for up to six days to achieve high selectivity is worth noting. Li reported the analogous reaction, catalyzed by a copper triflate/tridentate

bis(oxazolinyl)pyridines complex, with aromatic aldehydes and amines.[162] His method required up to four days.

II. Rationale

The synthesis of chiral α-propargylamines continues to present a challenge to chemists. Of the methodologies discussed, the addition of nucleophiles to alkynylimines remains the least developed route. Enders' organocerium procedure supports the widest nucleophile latitude. Its' reliance on highly basic and nucleophilic alkyllithium and Grignard reagents however, limits the choice of pendent functionality. The Yamamoto and Pfizer reports react enolates with propargylimines, but their aim was target-driven and no efforts were expended toward methodology developlment.

The Hegedus group developed chiral allenylamides for coupling with carbonyl electrophiles.[142] These substrates are, in effect, synthons for chiral propargyl amine anions (Figure 20).

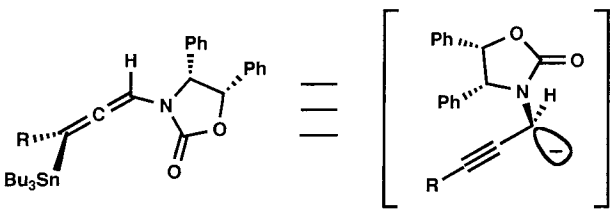
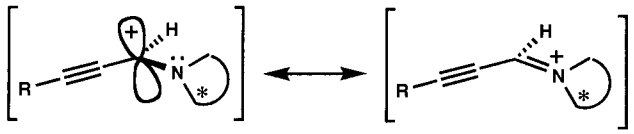


Figure 20

The focus of this work is their electrophilic Umpolung motif, which can be represented by the tautomeric structures in Scheme 99.

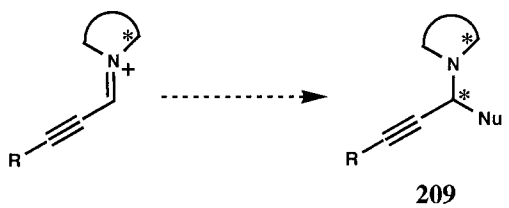


Scheme 99

These structures combine potential reactivity elements of propargyl electrophiles/cations, iminium ions, and Nicholas cations. The aims of this project are therefore to gain insight into the reactivity of this scaffold and compare it to known Nicholas cation motifs. This is to be accomplished by:

1. Preparing various propargylic *N,O*-acetals and their dicobalt hexacarbonyl complexes.
2. Establishing the parameters of their allylation.
3. Expanding their reactive scope using other nucleophiles.

Ultimately, this will lead to the assembly of chiral α-propargylamines (**209**) via stereoselective nucleophilic additions (Scheme 100).



209

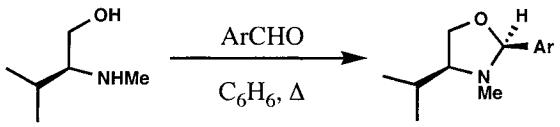
Scheme 100

III. Results & Discussion

Allylation

Oxazolidine template

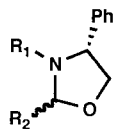
Several carbon-carbon bond-forming reactions proceed via an iminium intermediate, including the venerable Mannich,[163] Pictet-Spengler,[164] Passerini and Ugi reactions.[165] *N,O*-acetals, especially oxazolidines, have proven effective precursors for in situ iminium formation. The widespread availability of chiral 1,2-amino alcohols, derived from α-amino acids, enables easy access to chiral 2-substituted oxazolidines (Scheme 101).[166]



Ar	Yield
Ph	83%
p-Cl-Ph	81%
p-MeO-Ph	82%

Scheme 101

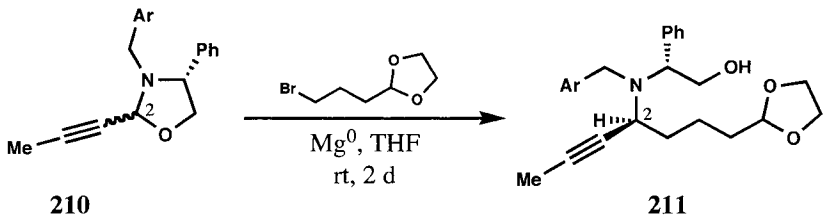
The nature of the amino alcohol and aldehyde can lead to an epimeric mixture of products (Figure 21).[156b,170]



R_1	R_2	dr
Bn	Ph	88:12
Bn	Me	90:10
Me	Ph	97:3
Me	Me	98:2

Figure 21

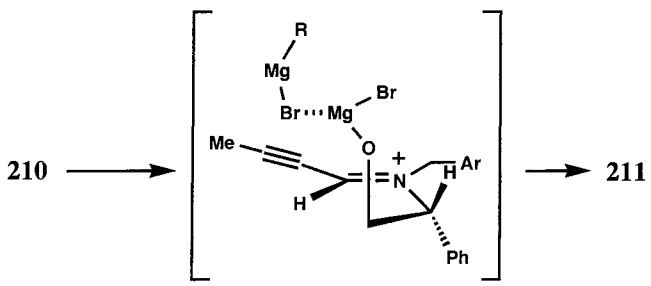
Upon exposure to Lewis acidic Grignard reagents, chiral 1,3-oxazolidine **210** afforded α-propargylamine **211** (Scheme 102).[167,168]



210 **211**

Scheme 102

Although this transformation required two days for completion, it should be noted that a mixture of epimers was converted to one product in high yield. Mechanistically, iminium intermediate **212** is invoked for the intramolecular delivery of the nucleophile from the face opposite the oxazolidine phenyl group (Scheme 103).



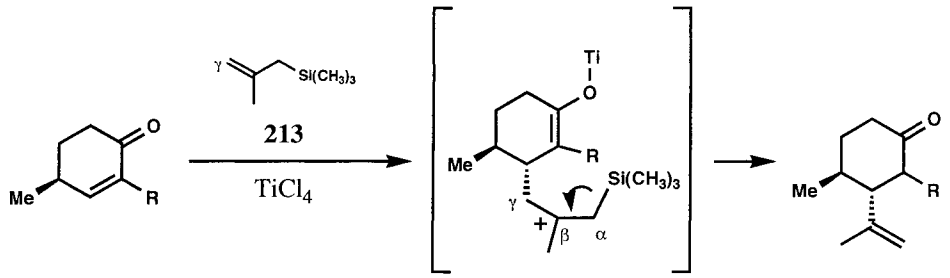
212

Scheme 103

Other classes of compatible nucleophiles include dialkyl zincs,[169] alkyllithiums,[170] silyl enol ethers,[171] and organotitanates.[172]

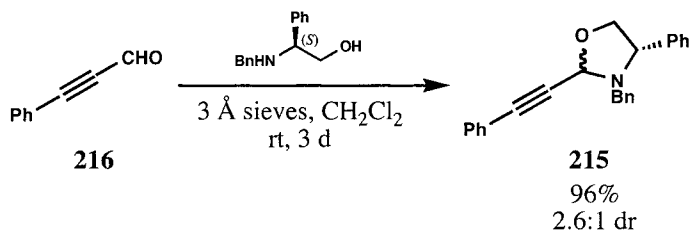
Allylsilanes (e.g., **213**), mild nucleophilic reagents for the introduction of unsaturated 3-carbon (or greater) fragments, are significant contributors to organic

synthesis (Scheme 104).[173] The ability of silicon to stabilize a β-cation (**214**) enables selective γ-reactivity.[174]



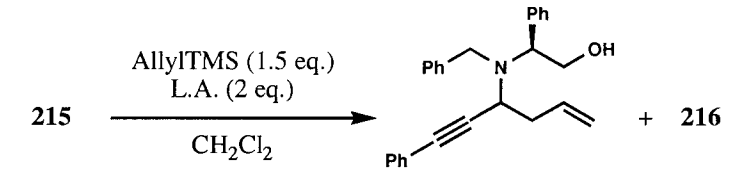
Scheme 104

Results. Based on these precedents, (±)-(4*S*)-3-benzyl-4-phenyl-2-(phenylethynyl)oxazolidine **215** was prepared from 3-phenylpropiolaldehyde (**216**)[175] in high yield as a 2.6:1 mixture of diastereomers (Scheme 105).[176]



Scheme 105

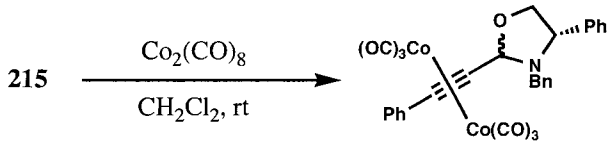
Initial allylation studies of **215** failed to provide the desired propargylamine (**217**) (Scheme 106). Only unreacted and hydrolyzed starting material (**216**) were isolated.



L.A.	Conditions	Recovered **215** dr	**217**	**216**
BF_3•OEt_2	-78 °C, 4 h	2.8:1	-	5%
BF_3•OEt_2	-40 °C, 4 h	2.9:1	-	15%
TMSOTf	-78 °C, 4 h	2.1:1	-	-

Scheme 106

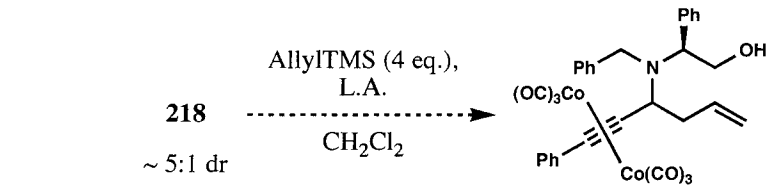
Pursuant to reports of enhanced reactivity and selectivity imparted by the dicobalt cluster (vide supra), complex **218** was prepared in good yield (Scheme 107). For brevity, the dicobalt cluster will be drawn as shown.



218
86%
4.6:1 dr

Scheme 107

Attempts at allylation proved futile as starting material was recovered under all conditions attempted (Scheme 108). Worthy of note is the partial racemization of starting material observed (entries 1, 4, 5, and 8).



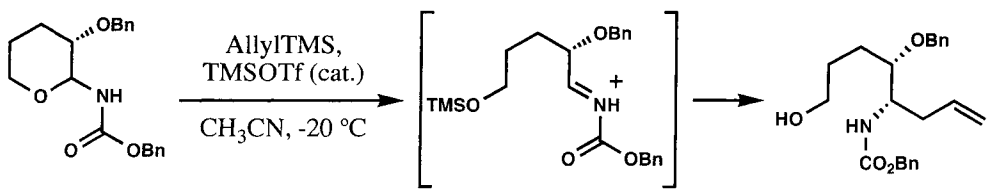
Entry	L.A. (eq.)	Temp.	Recovered **218** (dr)
1	TMSOTf (1.1)	-78 °C	+ (2:1) [a]
2	BF_3•OEt_2 (1.1)	-78 °C	+
3	Ti(O*i*-Pr)$_4$ (1.1)	-78 °C	+
4	$TiCl_4$ (1.1)	-78 °C	+ (3.5:1)
5	TMSOTf (4)	0 °C, rt	+ (3.1:1)
6	BF_3•OEt_2 (4)	0 °C, rt	+
7	Ti(O*i*-Pr)$_4$ (4)	0 °C, rt	+
8	$TiCl_4$ (4)	0 °C, rt	+ (2.8:1)

[a] Including dicobalt hexacarbonyl complex of aldehyde **216**.

Scheme 108

N-Acyl oxazolidine template

Attachment of a carbonyl group to the iminium nitrogen (**219**), a fundamental modification of the Mannich protocol, enhances its electrophilicity and synthetic scope (Scheme 109).[177, 178] Chiral amine **220** was subsequently elaborated to antimalarial agent (+)-isofebrifugene.

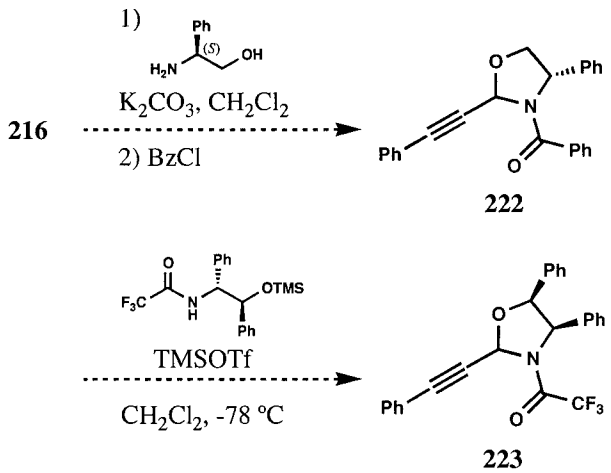


220

221
81%
86:14 *syn*:*anti*

Scheme 109

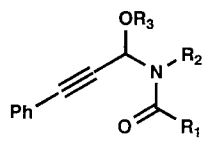
Results. Attempts to prepare *N*-acyl analogues **221** and **222** were unsuccessful, leading to the decomposition of starting material (Scheme 110).[179]



Scheme 110

Oxazolidinone N,O-acetal template

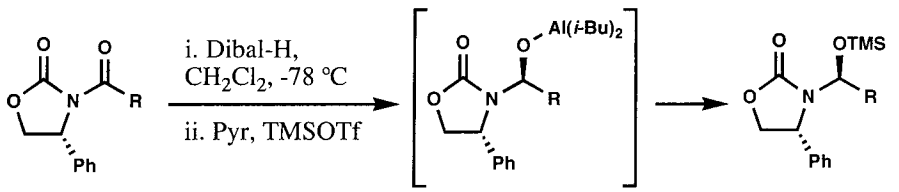
Having demonstrated the ability to generate a cluster-stabilized iminium ion in solution (albeit a weakly electrophilic one) two design challenges remained: 1) construction of an *N,O*-acetal scaffold that suppresses/prevents starting material equilibration; and 2) addition of a carbonyl group to produce an *N*-acyliminium intermediate. Model acetal **223** is illustrative (Figure 22). Additionally, this motif offers handles for incorporating chiral elements (R_1 and R_2).



224

Figure 22

Pursuant to studies on transformations of amides, Suh reported the highly diastereoselective reduction of acyl oxazolidinone **224** to aminal aluminum oxide **225**, with in situ TMS-trapping to form *N,O*-acetal TMS ether **226** (Scheme 111).[180]

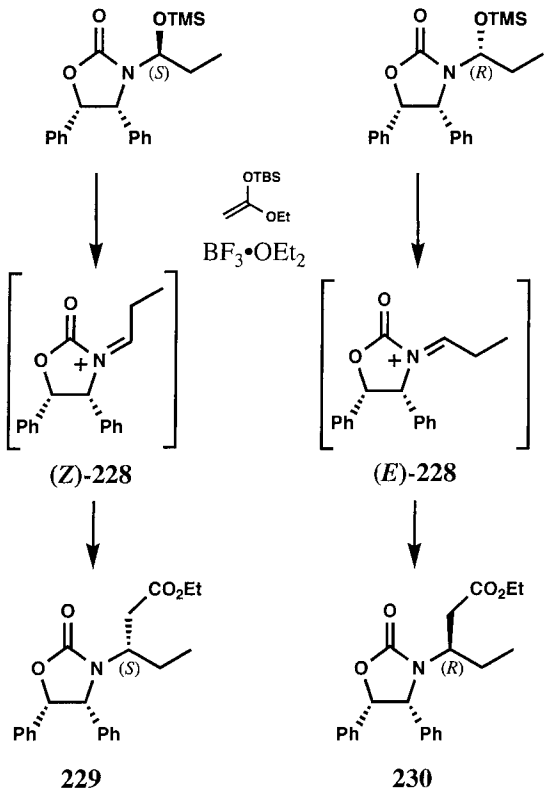


225 **226** **227**

R	Yield	dr
Me	92%	>98:2
Et	93%	>98:2
CH_2Ph	89%	>98:2

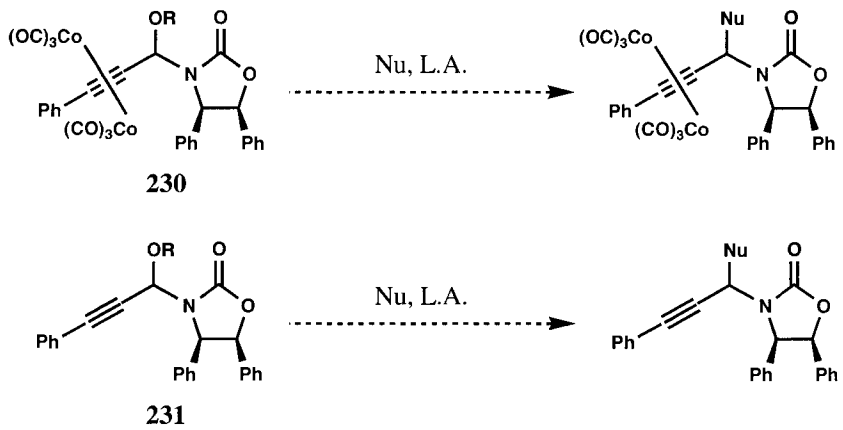
Scheme 111

Chirality transfer to the acyl iminium **(*Z*)/(*E*)-227** prior to nucleophilic attack was critical to the outcome of the reaction (**228/229**, Scheme 112).



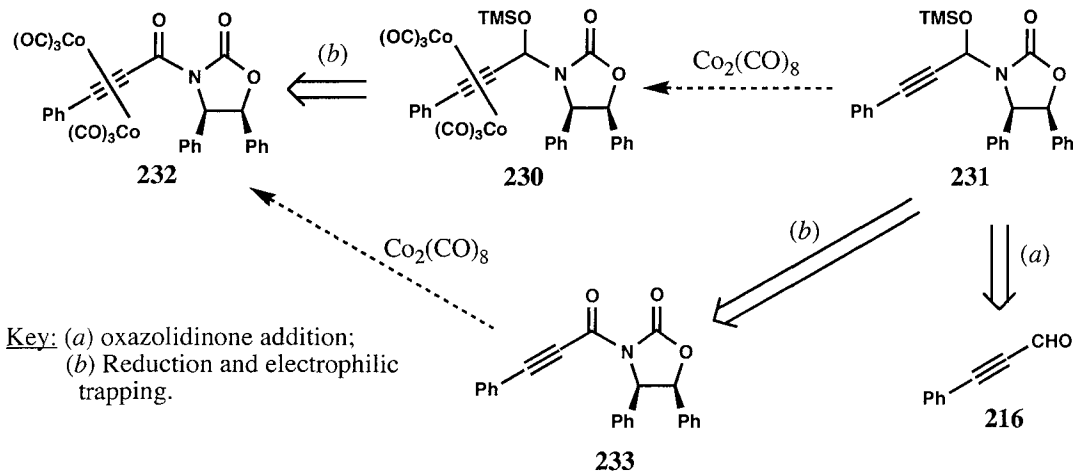
Scheme 112

Synthesis. Based on the demonstrated reactivity of the oxazolidinone acetal, scaffolds **230** and **231** were sought for the development of the α-propargylamine methodology (Scheme 113).



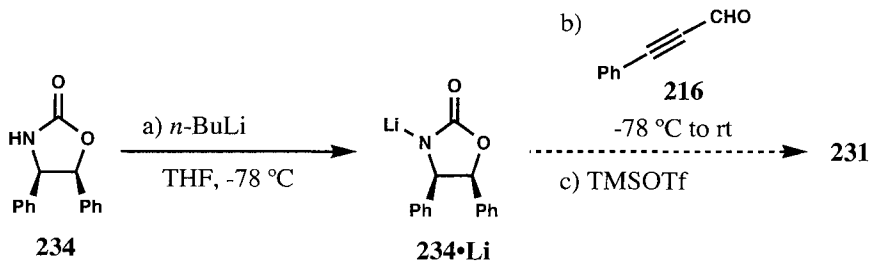
Scheme 113

Two routes were explored for their synthesis: (a) oxazolidinone addition to aldehyde **216**; and (b) Dibal-H reduction and electrophilic trapping of amide **232**/**233** (Scheme 114).



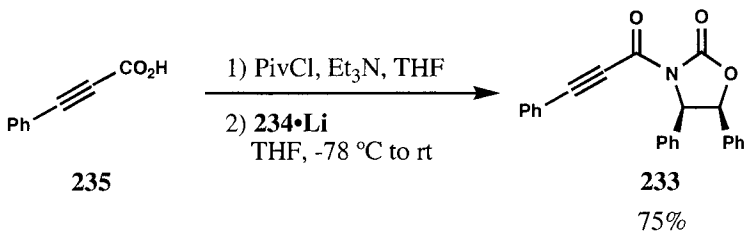
Scheme 114

To attempt the synthesis of the *N*,*O*-acetal in one pot, path (a), oxazolidinone **234** was deprotonated prior to its addition to aldehyde **216**, followed by a TMSOTf quench (Scheme 115). Only starting material was recovered from the reaction.



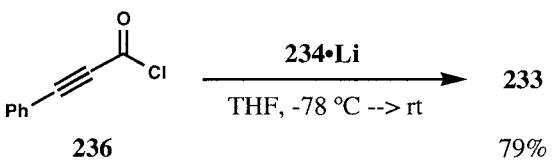
Scheme 115

Strategy (b) required phenylpropioloyl oxazolidinone (**233**), which was prepared by two methods. Pivaloyl chloride activation of 3-phenylpropiolic acid **235** followed by addition of **234•Li** afforded the desired product (Scheme 116).[181]



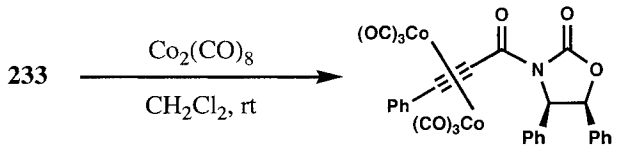
Scheme 116

Alternately, the addition of **234•Li** to phenylpropioloyl chloride (**236**)[182] circumvented the problematic pivalic acid co-product (Scheme 117).[183]



Scheme 117

Dicobalt cluster **232** was prepared by treating alkynyl oxazolidinone **233** with dicobalt octacarbonyl at room temperature (Scheme 118).

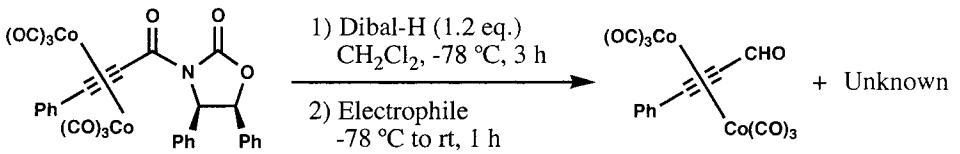


232

87%

Scheme 118

Attempts to reduce **232** to desired **230** only led to a mixture of recovered starting material, aldehyde **237**, and unknown compound **238** (Scheme 119).

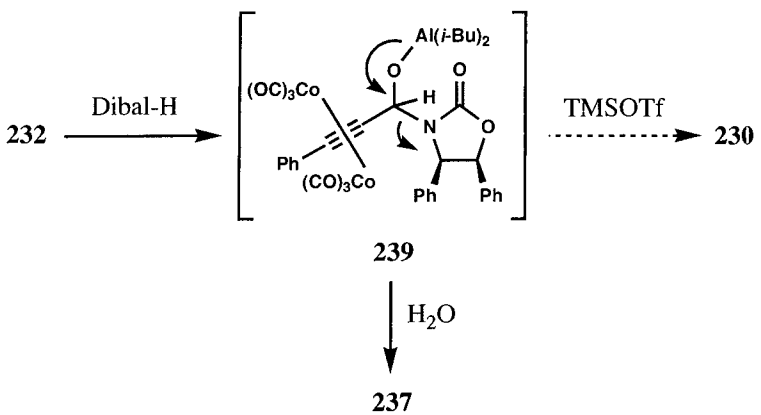


232 **237** **238**

Electrophile	Recovered **232**	**237**	**238**
Pyr (3 eq.), TMSOTf (2 eq.)	+	+	+
Pyr (4 eq.), DMAP (1 eq.), Ac_2O (5 eq.)	+		+

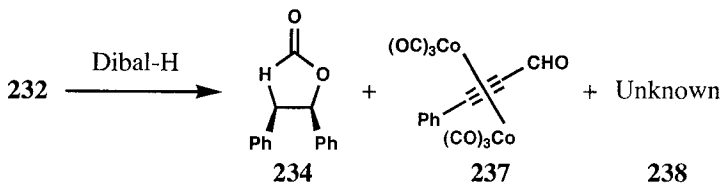
Scheme 119

The detection of **237** is consistent with failure to trap the incipient aminal aluminum oxide intermediate (**239**, Scheme 120).



Scheme 120

Several variables were examined in the simple reduction of **232** to **237** to elucidate the scope of this mixed reactivity, and identify the structure of unknown **238** (Scheme 121). These experiments demonstrated: 1) Lewis basic solvents inhibited Dibal-H reactivity (entry 4); 2) differing quenches had minimal impact on product distribution; 3) extended reaction time and warming to 0 °C were required for complete conversion to unknown **238** (entry 7); and 4) increased equivalents of Dibal-H consumed all the starting material but still led to multiple products (entries 9 and 10).

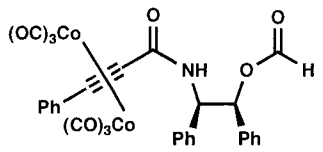


234 **237** **238**

Entry	Dibal eq.	Solvent	Temp., time (h)	Rxn quench	Recovered **232**	**234**	**237**	**238**
1	1.1	CH_2Cl_2	-78 °C, 3	$NaHCO_3$(aq)	+		+	+
2	1.1	CH_2Cl_2	0 °C, 1	$NaHCO_3$(aq)	+		+	+
3	1.1	CH_2Cl_2	-78 °C, 2	Na_2SO_4•$(H_2O)_{10}$(s)	+	+	+	+
4	1.1	THF	-78 °C, 2	Na_2SO_4•$(H_2O)_{10}$(s)	+			
5	1.2	CH_2Cl_2	-78 °C, 3	1 N HCl	+		+	+
6	1.2	CH_2Cl_2	-78 °C, 3	Na_2SO_4•$(H_2O)_{10}$(s)	+	+	+	+
7	1.2	CH_2Cl_2	-78 °C to 0 °C, 5	Rochelle salt (aq)				+
8	1.2	CH_2Cl_2	0 °C, 3	1 N HCl	+		+	+
9	2.2	CH_2Cl_2	-78 °C, 3	Na_2SO_4•$(H_2O)_{10}$(s)		+	+	+
10	5.0	CH_2Cl_2	-78 °C, 3	Na_2SO_4•$(H_2O)_{10}$(s)		+	+	+

Scheme 121

HRMS and NMR analysis (^{1}H, HMQC) of unknown **238** confirmed it to be the unexpected product of oxazolidinone reduction (Figure 23).

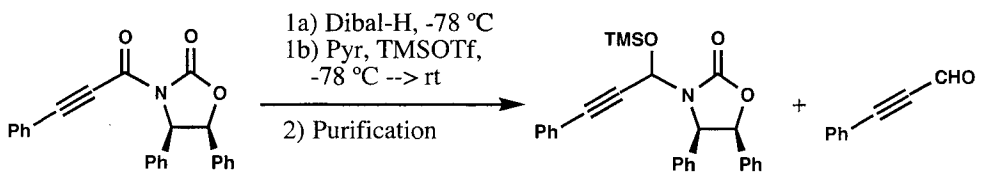


238

Figure 23

These results suggest the cluster's bulk sterically interefered with the delivery of the hydride (i.e. recovered starting material) and the approach of the electrophile to aluminum oxide intermediate **239** (**239** → **237**, Scheme 120).

Forced to replan the synthesis of **230**, alkynyl oxazolidinone **233** was subjected to the reduction/trapping conditions (Scheme 122). Although NMR analysis of the crude product revealed the presence of only desired product, various purification protocols led to the isolation of mixtures of **231** and its hydrolysis product **216**. Clean product could only be isolated on Davisil™ silica gel, albeit in moderate yield.

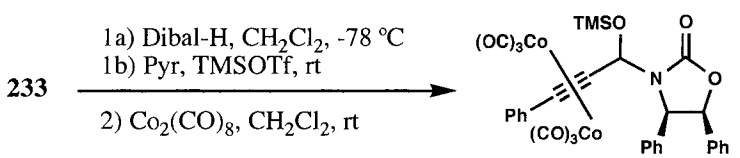


233 231 216

Chromatography	**231** (dr)	**216**
SiO_2	37% (2.2:1)	4%
SiO_2 + 1% Et_3N	-	55%
Davisil™	56%	-
Al_2O_3 Neutral	25% (2.7:1)	9%
Al_2O_3 Brockmann I	-	-
Al_2O_3 Brockmann III	38%	18%

Scheme 122

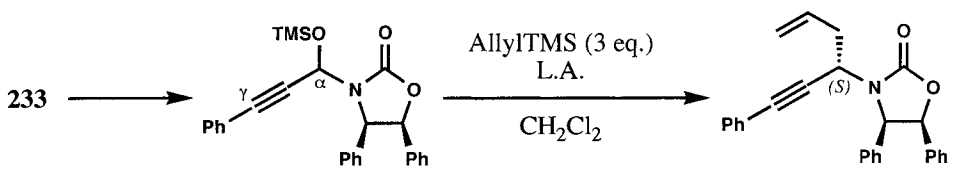
Complex **230** was prepared by sequential steps in moderate yield to avoid the purification of **231** (Scheme 123). The dicobalt cluster imparted stability to the acetal, allowing purification on SiO_2.



230
76%
2:1 dr

Scheme 123

Results. As acetal **231** purification efforts were ongoing, allylation was initially undertaken on the crude material (Scheme 124). The treatment of **231** with allyl trimethylsilane followed by a Lewis acid afforded, after workup, propargylamine **240**. The reaction proceeded with low diastereoselectivity.



231 *crude*
~1:1 dr

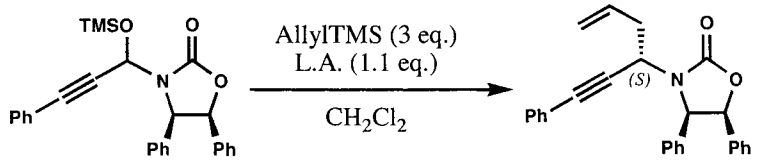
240

L.A. (eq.)	Temp.	(*S*):(*R*) [a]	Yield (from **233**)
BF_3•OEt_2 (0.3)	0 °C	2.6:1	60%
BF_3•OEt_2 (0.3)	-78 °C	- [b]	
$TiCl_4$ (2)	0 °C	1.2:1	76%
$TiCl_4$ (2)	-78 °C	**1:1.9**	84%
TMSOTf (2)	-78 °C	2.2:1	75%
TMSOTf (2)	0 °C	1.8:1	70%
TMSOTf (0.3)	-78 °C	1.8:1	63%
TMSOTf (0.3)	0 °C	2.3:1	75%

[a] Crude product mixture.
[b] After 5 h, recovered **215** and **233**.

Scheme 124

By starting with purifed **231** the outcome was unchanged (Scheme 125).



231

1.3:1 dr

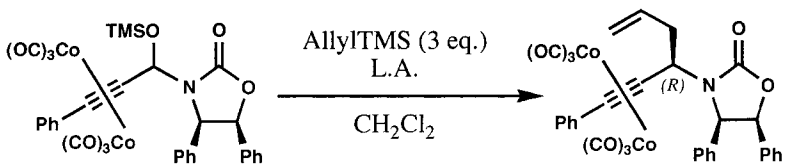
240

L.A.	Temp.	(*S*):(*R*) [a]	Yield
TMSOTf	-78 °C	2.4:1	84%
$TiCl_4$	-78 °C	**1:1.7**	76%
BF_3•OEt_2	0 °C	1.4:1	84%

[a] Crude product mixture.

Scheme 125

A pendant dicobalt cluster failed to improve diastereoselectivity (Scheme 126). The presence of the cluster influenced bond formation in two ways: higher temperatures were required for reaction, and the product (complex **241**) proved unstable on silica gel.



230

1.6:1 dr

241

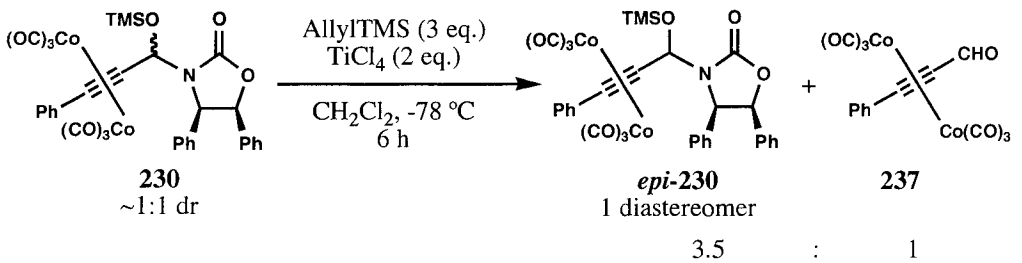
L.A. (eq.)	Temp.	Time	(*S*):(*R*) [a]	Δ*de* [b]
BF_3•OEt_2 (2)	0 °C	40 min	1:1.9	8%
TMSOTf (2)	0 °C	40 min	1:1.7	3%
TMSOTf (0.3)	0 °C	2 h	1:2.4	18%
TMSOTf (2)	rt	2 h	1:1.9	8%
$TiCl_4$ (2)	0 °C	2.5 h	Decomp.	-
$TiCl_4$ (2)	rt	30 min	Decomp.	-

[a] Crude product mixture.

[b] Difference between **241** de and **230** de.

Scheme 126

When $TiCl_4$ was added to a mixture of **230** and allylTMS at -78 °C and allowed to stir for 6 h, the NMR spectrum of the quenched reaction indicated a 3.5:1 mixture of *one* starting material diastereomer and hydrolyzed acetal (**237**, Scheme 127).



230
~1:1 dr

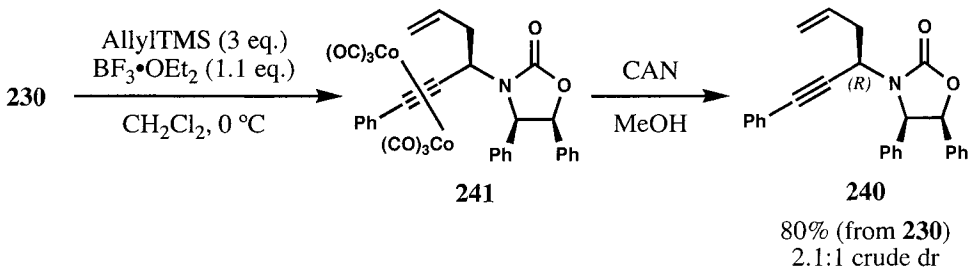
***epi*-230**
1 diastereomer

237

3.5 : 1

Scheme 127

Sequential allylation and cluster oxidation, bypassing the intermediate's purification, afforded **240** in high yield (Scheme 128).

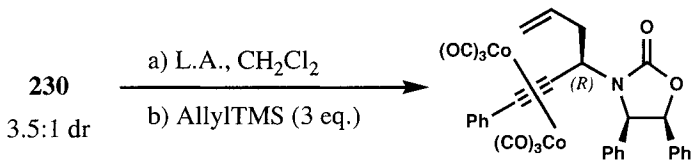


241

240
80% (from **230**)
2.1:1 crude dr

Scheme 128

Mindful of Schreiber's description of the fluxional nature of Nicholas cations (see Scheme 63),[102] **230** was allowed to stir with a Lewis acid *prior* to the addition of allyltrimethylsilane (Scheme 129).



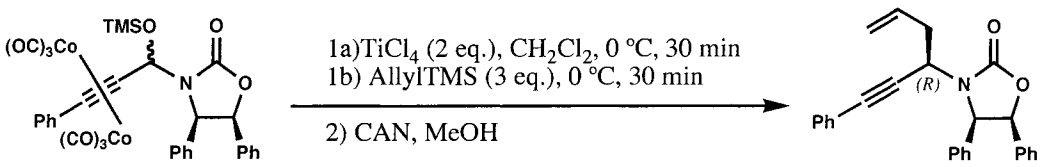
241

Entry	L.A. [a] (eq.)	Temp.	Time [b]	(*S*):(*R*) [c]
1	BF_3•OEt_2 (1.1)	0 °C	0.5 h	1:1.9
2	TMSOTf (2)	0 °C	0.5 h	1:2.7 [d]
3	$TiCl_4$ (1.1)	0 °C	0.5 h	1:8.3
4	$TiCl_4$ (1.1)	0 °C	1 h	1:10.5
5	$TiCl_4$ (2)	0 °C	0.5 h	**1:11.9**
6	$TiCl_4$ (1.1)	rt	0.5 h	decomp.
8	$TiCl_4$ (2)	0 °C	3 h	1:10.5

[a] $TiCl_4$: 1 M solution in CH_2Cl_2.
[b] Premixing time.
[c] Crude product mixture.
[d] **230** is 1.4:1 dr.

Scheme 129

Having demonstrated the positive impact of premixing the Lewis acid, optically active **230** was subjected to two equivalents of $TiCl_4$ for 30 min at 0 °C followed by three equivalents of allyl trimethylsilane. Following the quench and cluster oxidation, **(-)-240** was isolated in high yield and diastereomeric purity (Scheme 130). The absolute stereochemistry of the product was established by single crystal X-ray diffraction analysis (see Appendix A).

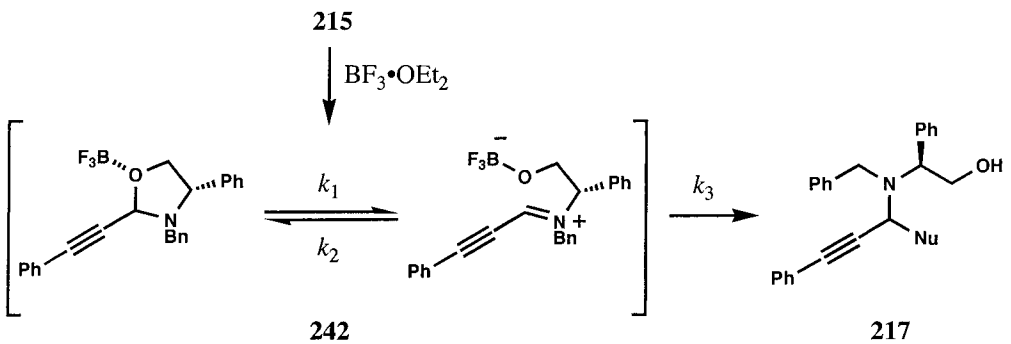


(-)-240
73% (from **230**)
94:6 crude dr

Scheme 130

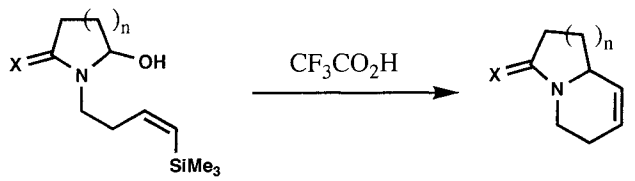
Discussion

Oxazolidine template. The failure to allylate propargyl oxazolidine **215** provides insight into these scaffolds. Despite the aqueous quench, the sparsity of hydrolysis product is indicative of the low reactivity of this platform toward external nucleophiles. The recovery of starting material however, does not preclude a pre-equilibrium (**242**) for which unimolecular ring closure is competitive with bimolecular water addition ($k_2 >> k_3$, Scheme 131).



Scheme 131

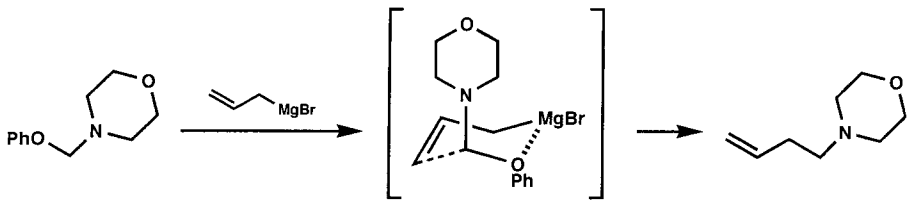
The weak electrophilicity of iminium ions is illustrated in Overman's syntheses of elaeokaine A and B (Scheme 132).[184]



X	Yield
O	> 90%
H, H	NR

Scheme 132

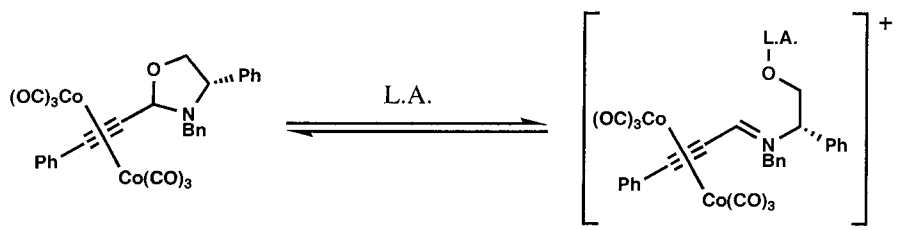
A survey of the literature found the need for organometallic species capable of coordination (**243**) to effect intramolecular delivery of the nucleophile, in agreement with aforementioned results (Scheme 133).[185]



243 75%

Scheme 133

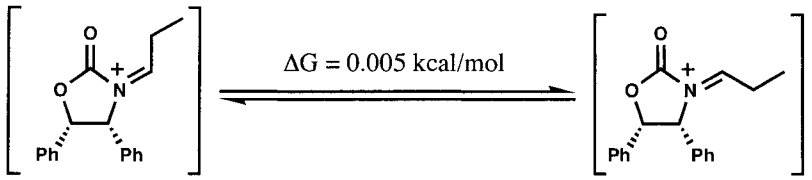
The hypothesis of an equilibrating iminium intermediate (**244**, Scheme 134) is supported by the observation that strong Lewis acids partially epimerized Co-complexed oxazolidine **218** (entries 4, 5, and 8, Scheme 108).



218 **244**

Scheme 134

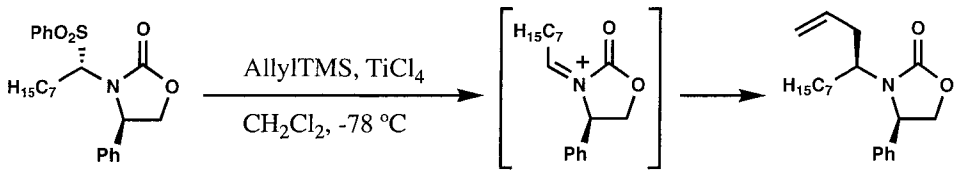
Oxazolidinone template. In his alkylation studies (see Scheme 112), Suh had *a priori* assumed product dr to be determined by an acyliminium equilibrium. However, semiempirical calculations revealed an energy difference between the (*E*) and (*Z*) iminium isomers that could not adequately account for the high product selectivity (Scheme 135).[180]



(*Z*) (*E*)

Scheme 135

Concluding that iminium isomerization was not occurring, it was reasoned that acetal stereochemistry was determining iminium geometry and penultimate propargyl chirality (see Scheme 112). The stereospecificity of the transformation is consistent with a net inversion (*S_N2-like*) mechanism. The Suh model was not applicable to Petrini's phenylsulfonyloxazolidinone **245** (Scheme 136).[186] The diastereomeric constitution of the starting material had no effect on allylation selectivity, suggesting a common iminium intermediate, **(*Z*)-246**.



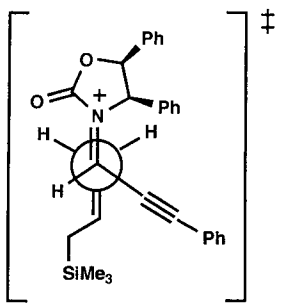
245 **(Z)-246**

90:10/100:0 dr 75:25 dr

Scheme 136

Since an ~ 1:1 mixture of *N,O*-acetal **231** diastereomers was allylated with some level of selectivity (see Scheme 124), a purely inversive alkylation mechanism cannot be operant.

The stereochemical outcome of the TMSOTf-catalyzed alkylation of **231** can be rationalized using the Yamamoto transition state model **247** for the allylation of chiral imines (Figure 24).[187]

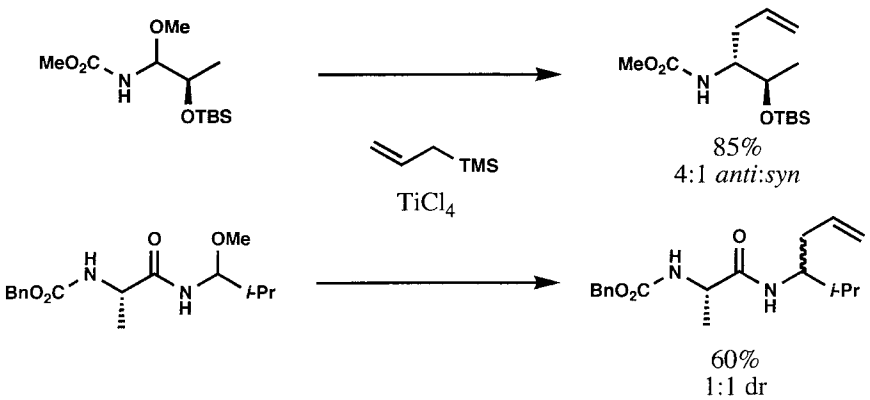


247

Figure 24

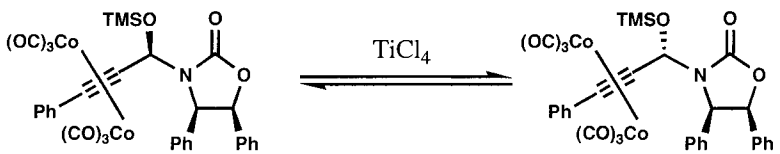
It should be noted that no allenyl product (from γ-addition) was detected in these reactions.

The poor selectivity exhibited is not surprising, as motifs lacking structural rigidity reacted similarly (Scheme 137).[188]



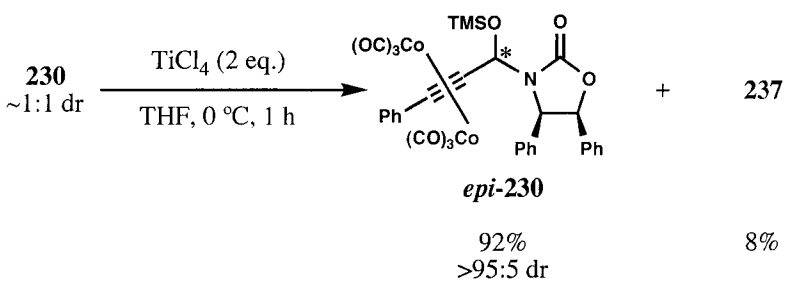
Scheme 137

Clustered oxazolidinone template. The unexpected result of Scheme 127 warrants comment. A 1:1 mixture of starting material acetal (**230**), following exposure to $TiCl_4$ and an aqueous quench, was converted to a 3.5:1 mixture of recovered acetal and aldehyde **237** (hydrolysis product). The recovery of **230** as *one* diastereomer is noteworthy. Two mechanisms can account for this outcome. The presence of aldehyde **237** could arise from a hydrolysis of a resolved starting material, or a dynamic kinetic resolution of a mixture of **230**. Whichever pathway is operant, the result indicates a starting material capable of reversible equilibration (Scheme 138).



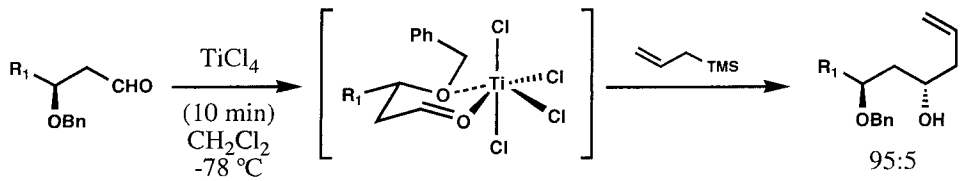
Scheme 138

The former hypothesis, resolution of the starting material, is supported by the increased selectivity reported with premixing of the catalyst prior to allyl silane addition (see Scheme 129 vs. Scheme 126). Exposure of a 1:1 mixture of **230** diastereomers to $TiCl_4$ in THF for 1 h led to the isolation of ***epi*-230**, the thermodynamic epimer (Scheme 139).



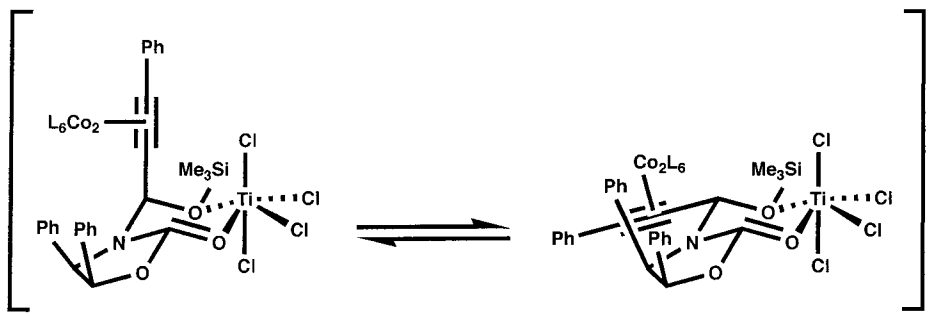
Scheme 139

Reetz spectroscopically observed a Cram-type chelate of α-alkoxy aldehydes (5-membered ring),[189] and a 6-membered chelate has been proposed in the reaction of β-alkoxy aldehydes (Scheme 140).[190]



Scheme 140

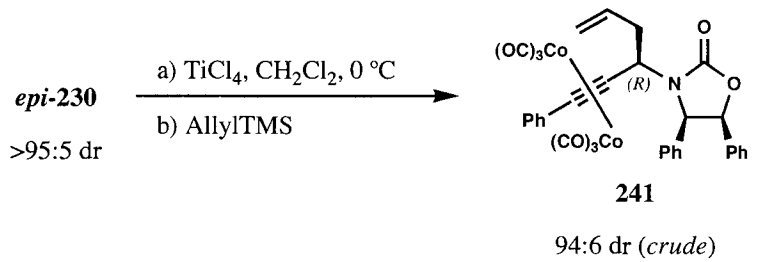
A similar chelate **248** may be responsible for the equilibration of **230** (Scheme 141).



248

Scheme 141

Subjection of isolated ***epi*-230** to the allylation protocol afforded **241** as a 94:6 mixture of diastereomers (Scheme 142). This selectivity is comparable to the one obtained when epimerization and allylation were conducted as a one-pot sequence (see Scheme 130). This result implies that ***epi*-232** is the probable intermediate generated in situ prior to addition of allylsilane.

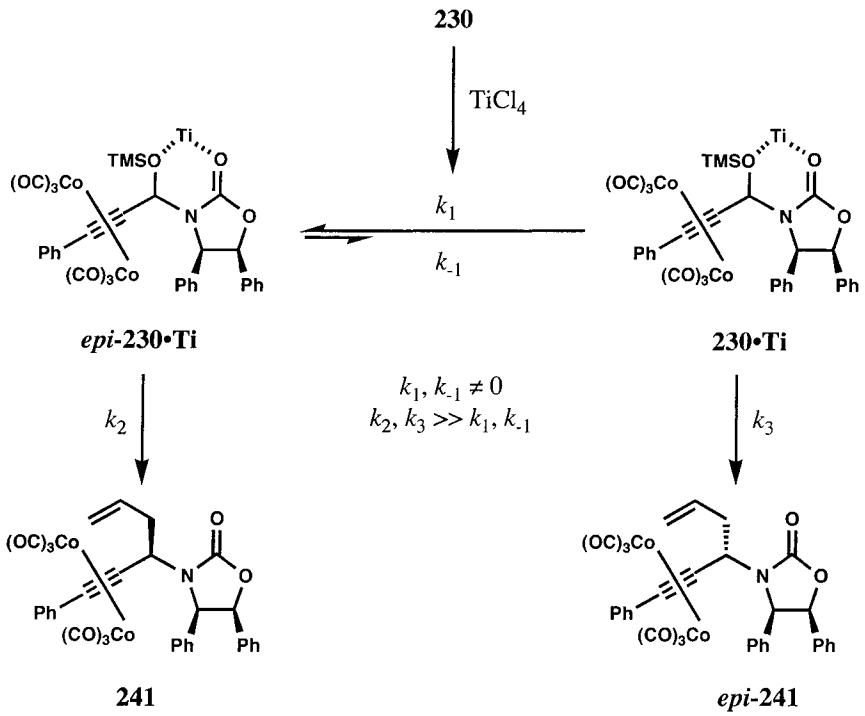


Scheme 142

In summary, the salient reaction features of complex **230** are:

- Allylation in the presence of Lewis acids led to product selectivity differing from starting material dr.
- Addition of $TiCl_4$ to the starting material allowed complete equilibration to the thermodynamic epimer (***epi*-230**). Subsequent allylation provided **241** with high selectivity.
- In situ equilibration of the substrate followed by allyl silane addition yielded the same product, with comparable selectivity.
- A mixture of starting material diastereomers converged to one diastereomeric product.

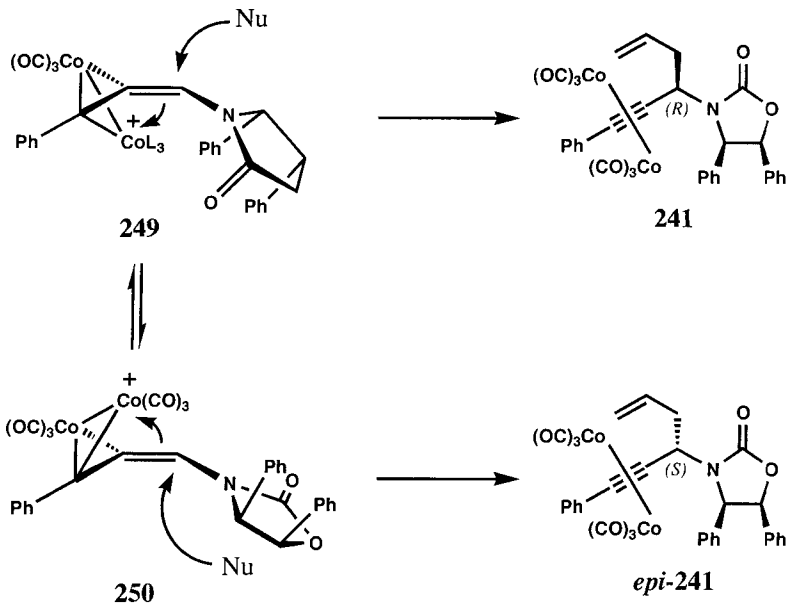
These results are consistent with a diastereomeric enrichment process (Scheme 143).[191] In this pathway, the thermodynamic ratio of intermediates ***epi*-230•Ti** and **230•Ti** determines the final product ratio (**241**:***epi*-241**). Therefore, resolution of the starting material prior to the addition of allylsilane ensures a highly stereoselective product formation.



Scheme 143

The allylation of **230** may occur via three limiting mechanistic pathways: 1) nucleophilic addition to a cluster-delocalized cation; 2) allylation of an *N*-acyliminium ion; or 3) S_N2 displacement.

Cationic cluster intermediate: This model relies on an equilibration of diastereomers (**249** and **250**), with **241** arising from a nucleophilic approach *anti* to the cationic cobalt atom (Scheme 144).

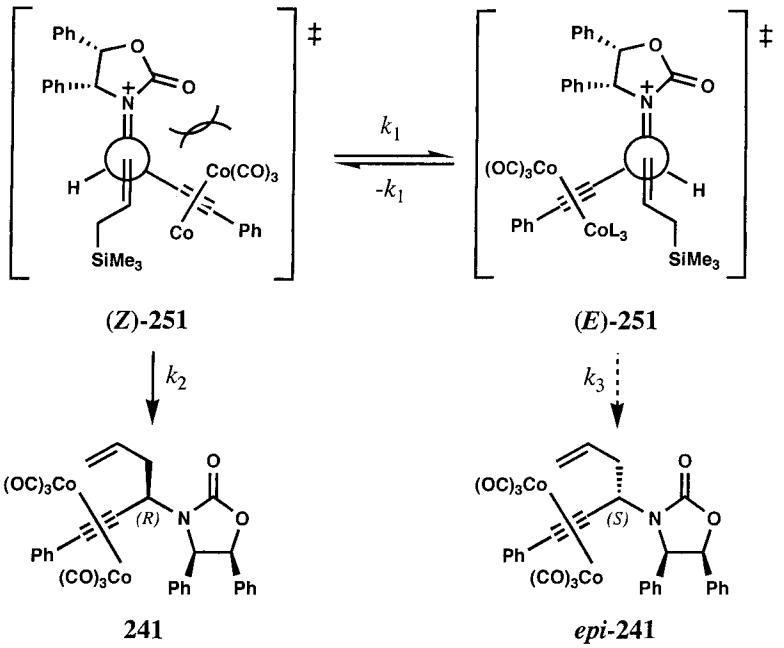


Scheme 144

The addition of Lewis acids to a mixture of **230** and allylsilane led to **241** with low diastereoselectivity (see Δde, Scheme 126). This would indicate a low energy barrier for **249** ↔ **250** interconversion. However, the reaction of diastereomerically pure ***epi*-230** proceeded with conservation of stereochemical integrity (see Scheme 142). This result is not supportive of equilibrating cationic cluster intermediates with a low inversion barrier.

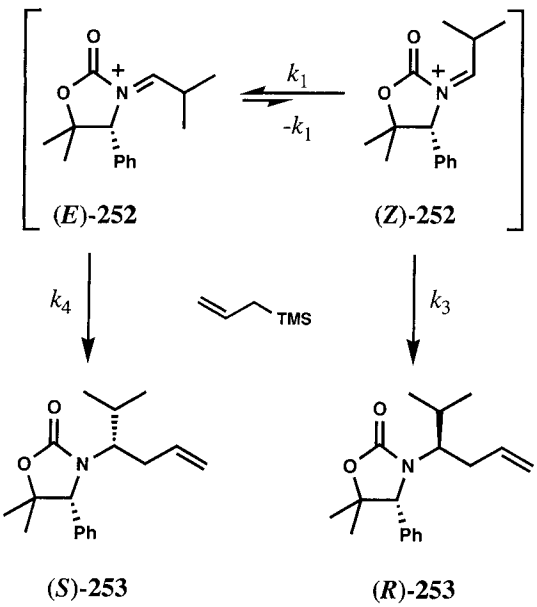
Chiral *N*-acyliminium intermediate: In this model the dicobalt cluster is treated as a large substituent. Suh's alkylation studies suggest two conclusions: oxazolidinone iminium ions do not isomerize, and iminium geometry is determined by the precursor *N,OTMS*-acetal (vide supra). If both of these assumptions were operative in the allylation of **230**, Δde would be null (Scheme 126). Since some chiral induction was observed, Suh's conclusions cannot be strictly applied to the allylation of acetal **230**.

Proposed iminium ion transition states describing this reaction are **(*E*)/(*Z*)-251**, with a nucleophile approach *anti* to the oxazolidinone phenyl rings (Scheme 145).



Scheme 145

The isolated product (**241**) would arise from a transition state exhibiting considerable 1,3-allylic strain. The analogous result was obtained by Petrini in a model system with **(*Z*)-252**, being 1.4 kcal/mol higher in energy than its (*E*) isomer by PM3 calculations, led to product **(*R*)-253** (Scheme 146).[186]



Scheme 146

His explanation invoked a dynamic kinetic resolution, with less stable **(*Z*)-252** reacting faster ($k_3 >> k_4$). If an *i*-Pr group led to an (*E*)/(*Z*) energy difference of 1.4 kcal/mol, one would expect a large cobalt cluster to result in comparable or superior diastereodif-ferentiation ($k_2 >> k_3$, see Scheme 145). This conclusion is not borne out by the data (see Scheme 126).

S_N2 displacement: This mechanism, characterized by an inversion at the reactive carbon, is stereospecific.[192] Therefore, the selective conversion of ***epi*-230** to **241** (see Scheme 130) is consistent with a possible S_N2 displacement by allylsilane. However, since the stereochemistry at the reactive carbon of ***epi*-230** has not been determined, alkylation via other pathways cannot be ruled out.

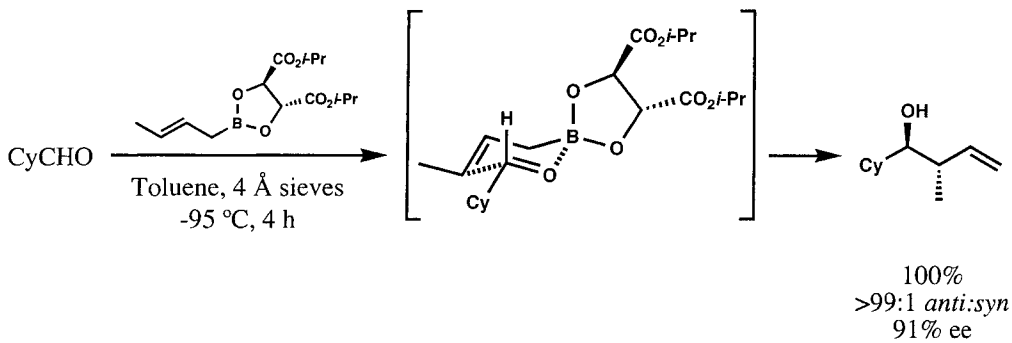
Ultimately, factors responsible for the selective allylation of ***epi*-232** are not fully understood at this time. As this substrate motif lies at the confluence of iminium and

Nicholas chemistries, it has yet to be determined which transition state modality is operative. It should be added that in the absence of a nucleophile, uncomplexed acetal **231** decomposes within minutes upon exposure to $TiCl_4$ at -78 °C.

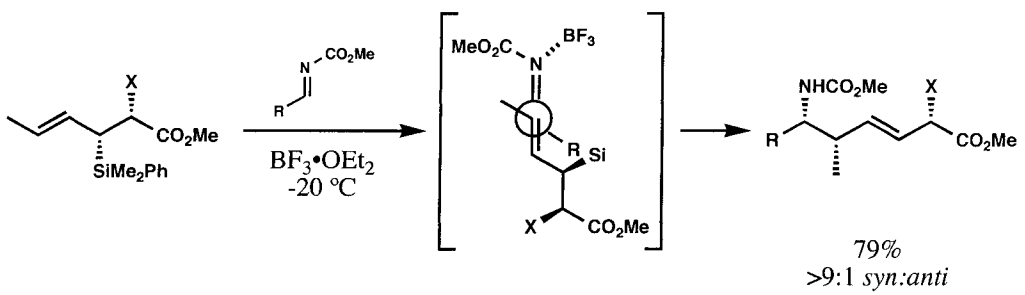
Crotylation

The asymmetric crotylation reaction has played a significant role in organic chemistry, especially in the synthesis of polyketide natural products.[193] Crotyl boranes[194] and boronate esters,[195] developed by Brown and Roush respectively, are extensively used. They react via a closed transition state and do not require an external Lewis acid (type I, Scheme 147). Conversely, chiral crotylsilanes proceed via an open transition state and require a Lewis acid (type II).[196]

Type I:

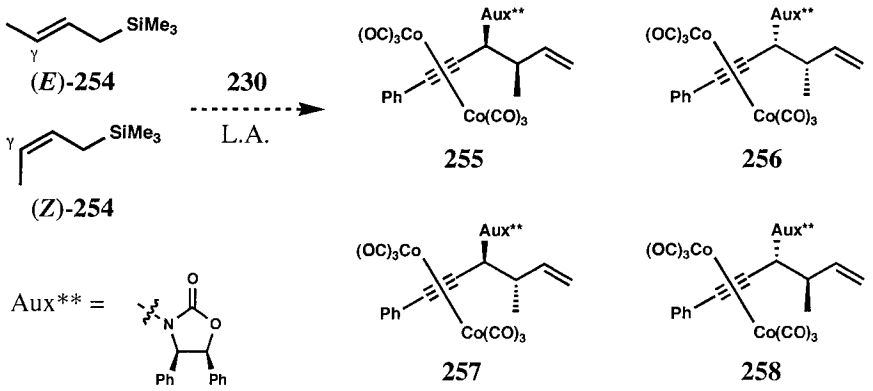


Type II:



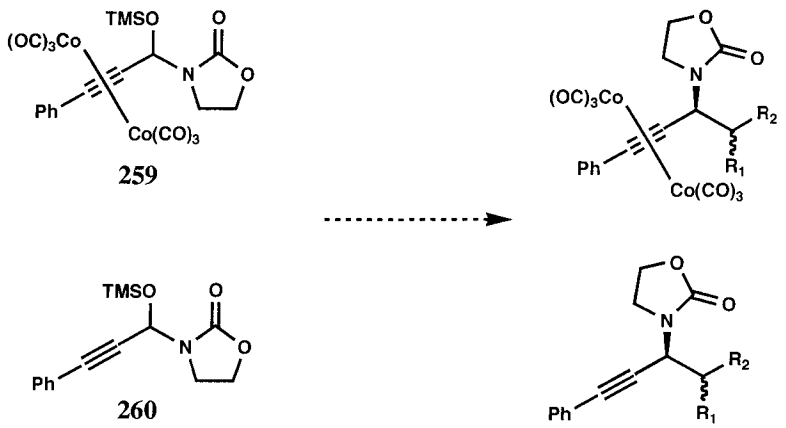
Scheme 147

The reaction of acetal complex **230** with crotyl silanes **(*E*)/(Z)-254**,[197] bearing a prochiral γ-carbon, can lead to two pairs of *syn* and *anti* diastereomers (**255, 256, 257**, and **258**, Scheme 148).



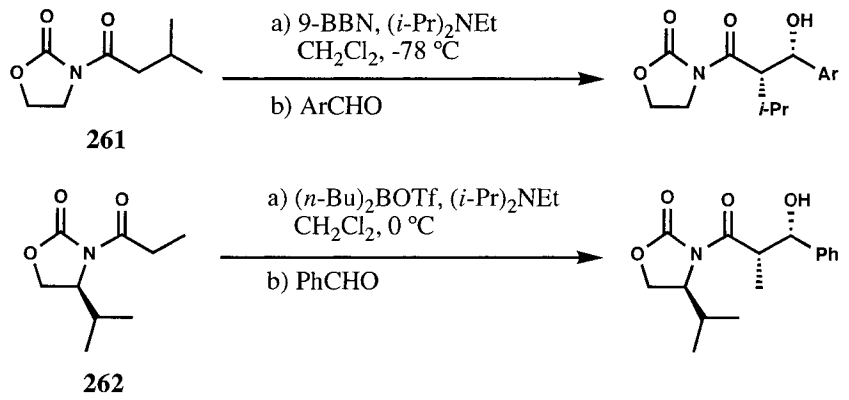
Scheme 148

It was postulated that screening reactions with alkynyl oxazolidinones **259/260** would afford uncluttered NMR spectra for measuring simple selectivity (*syn:anti* ratio) (Scheme 149). Nucleophiles exhibiting adequate *syn:anti* differentiation would then be subjected to chiral **230/231**.



Scheme 149

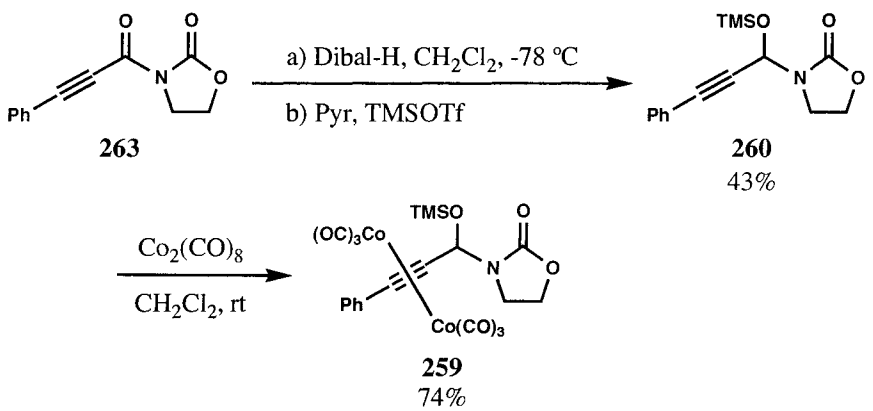
This hypothesis stems from the stereochemical correlation observed in the aldol reaction of acyl oxazolidinones **261** and **262** (Scheme 150).[198]



Scheme 150

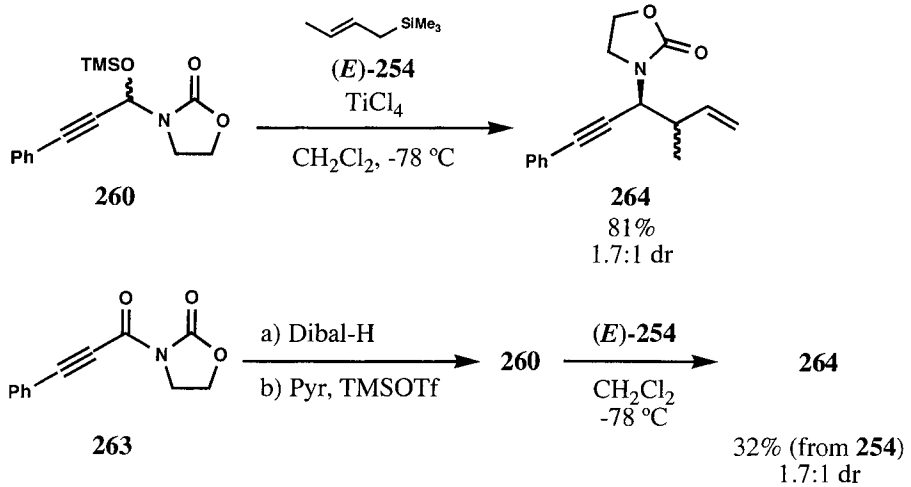
Achiral N,O-acetal template

The known 3-(3-phenylpropioloyl)oxazolidin-2-one **263**[199] was converted to *N,O*-acetal **260** using the established procedure (Scheme 151). Akin to **231**, the product was sensitive to SiO_2 chromatography. Subsequent treatment with $Co_2(CO)_8$ led to complex **259** in moderate yield.



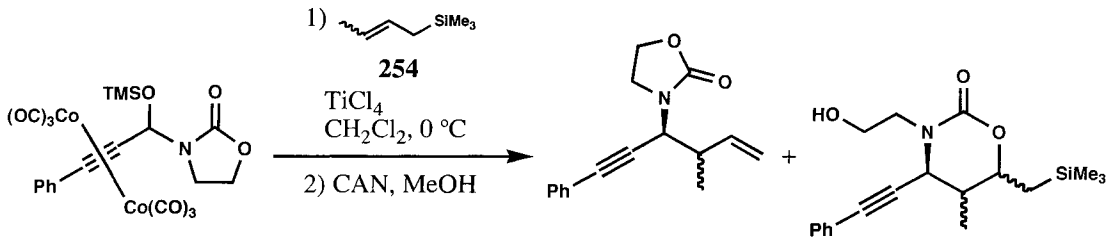
Scheme 151

The reaction of **(*E*)-254** with **260** afforded propargyl carbamate **264** in good yield but poor selectivity (Scheme 152).



Scheme 152

Application to cobalt-clustered **259** led to **264** with an increase in diastereo-selectivity (Scheme 153). Both (*E*) and (*Z*) crotyl isomers displayed the same sense of stereoinduction. Interestingly, crotylsilane **(*E*)-254** produced a small amount (~ 10%) of oxazinone **265** (entry 1).



259 **264** **265**

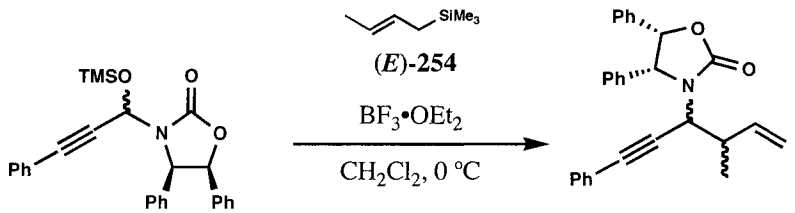
Entry	$TiCl_4$ eq.	**254**, eq.	Crude dr	**264** (dr)	**265**
1	2	(E), 3.3	85:15	69% (90:10)	10%
2	1.1	(Z), 1.3	~ 50:50 + **237** [a]		
3	2	(Z), 3.2	70:30		
4	2	(Z), 2.9	70:30	68% (73:27)	-

[a] Reaction temperature -10 °C.

Scheme 153

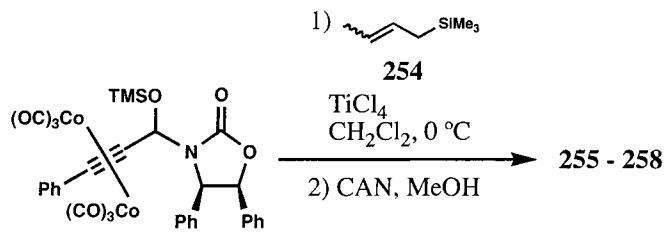
Chiral N,O-acetal template

Crotylation of the chiral series **230/231** proved less successful. The reaction of propargyl acetal **231** afforded all four diastereomers. (Scheme 154).



Scheme 154

With clustered acetal **230**, (*E*)-crotylsilane provided an equimolar mixture of two diastereomers, albeit in poor yield. The reaction of its isomeric counterpart led to a complex mixture (Scheme 155). Though no desired product was discernable in the NMR spectrum of the **(*Z*)-254** reaction, no aldehyde (hydrolysis product of the starting material) was detected.

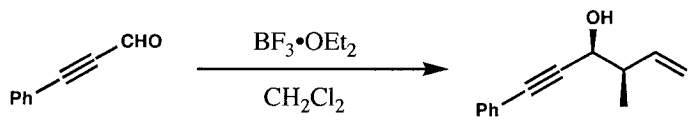


$TiCl_4$ eq.	**254**, eq.	Yield	**255-258** (dr)
2	(*E*), 3.5	44%	0:1:0:1
2	(*Z*), 3.3	-	messy

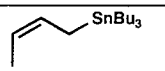
Scheme 155

Discussion

Achiral template. Brook and McGlinchey reported the addition of crotylstannanes **(*E*)/(*Z*)-266** to 3-phenylpropynal **216** (Scheme 156).[130] The high syn selectivities were postulated to arise from antiperiplanar transition states.[200]

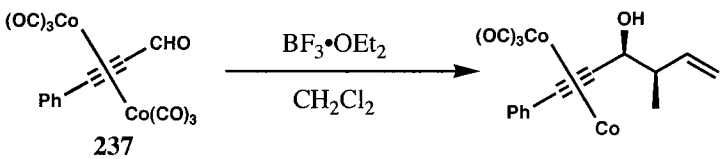


216

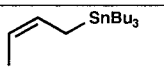
	Yield	*syn*:*anti*
 **(*E*)-266**	82%	100:0
 **(*Z*)-266**	85%	100:0

Scheme 156

Interestingly, crotyl transfer to dicobalt-complexed aldehyde **237** proved less selective (Scheme 157).



237

	Yield	*syn*:*anti*
 **(*E*)-266**	97%	86:14
 **(*Z*)-266**	95%	75:25

Scheme 157

They interpreted this erosion in selectivity to racemization of the cationic cluster via antarafacial migration (see Scheme 63). It should be stressed that no empirical evidence of this process was offered for these heteroatom-substituted cationic complexes.

The crotylation of the alkynyl acetal **260** (see Scheme 152) proceeded in good yield but poor diastereo-selectivity. Reactions of the dicobalt clustered **259** (see Scheme 153) proved marginally better. These outcomes may be construed as consistent with the results of Brook and McGlinchey.

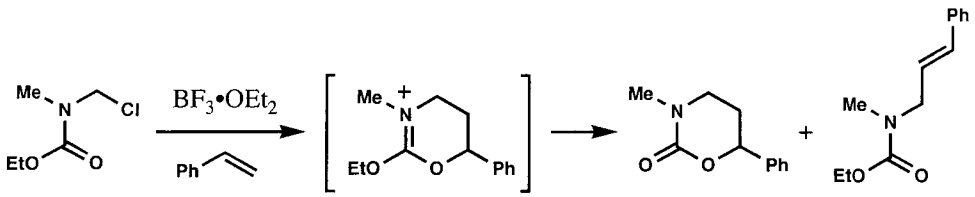
Since *N*-acyliminium ions are more reactive than aldehydes and dicobalt clusters activate propargylic carbons, one would predict their combination to lead to higher conversion. However, steric factors cannot be overlooked when considering the approach of a branched nucleophile, hence the low observed yields.

Aliphatic *N*-acyliminium ions can be described by two rotamers (Scheme 158).[178] *Ab initio* calcucations indicate the *s-cis* form is favored by ~ 3 kcal/mol.

s-(cis) *s-(trans)*

Scheme 158

In the presence of nucleophiles, *s-(trans)* immonium compounds react as traditional π-acceptors. Those that can adopt the *s-(cis)* conformation however, present an additional pathway as 4π-electron components. (Scheme 159).[201] In the presence of styrene, carbamate **267** reacted via intermediate **268**, affording a mixture of oxazinone **269** and allyl carbamate **270**.

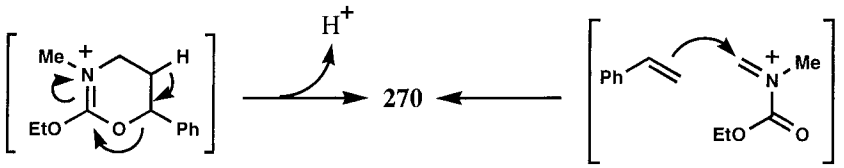


267 **268** **269** **270**

75%
13:87

Scheme 159

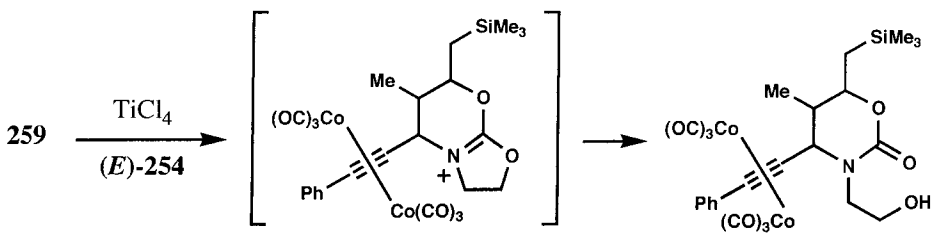
Mechanistically, it is unclear whether the acyclic product (**270**) arises from cyclic intermediate **268**, or is generated from nucleophilic attack on an ***s-(trans)*-271** iminium ion (Scheme 160).



268 ***s-(trans)*-271**

Scheme 160

Therefore, the formation of oxazinone **266** can be attributed to such a reverse-demand Diels-Alder pathway (Scheme 161).

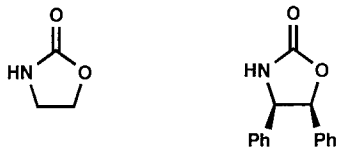


266

Scheme 161

The isolation of the oxazinone as one diastereomer is worthy of note. Since the crotylation reaction has been established to proceed with poor selectivity, it is unlikely that **266** arose from a stepwise ionic mechanism. Furthermore, inverse demand Diels-Alder reactions of *N*-acyliminium ions proceed via a stereospecific pericyclic mechanism.[201]

The postulate that oxazolidinone **272** could serve as a surrogate for diphenyl-oxazolidinone **234** is not supported by the data (Figure 25).



272 **234**

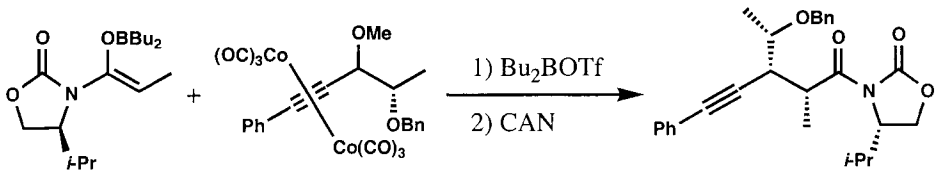
Figure 25

The crotylation of achiral acetal **260** proceeded with 64:36 selectivity (see Scheme 152), yet its chiral counterpart, acetal **231**, afforded the propargyl carbamate as an 39:39:6:16 mixture of diastereomers(see Scheme 154). The selectivity exhibited by clustered acetal **230** upon reaction with (*E*)-crotylsilane, yielding a 1:1 mixture of half of the possible diastereomers, is not consistent with results of its achiral variant (**259**, see Scheme 153).

In the final analysis, the chiral and achiral *N,O*-acetals do not adequately differentiate diastereomeric reaction pathways for crotylation to warrant further study.

Silyl enol ether nucleophiles

Silyl enol ethers, including ketene silyl acetals, are stable precursors/synthons of enolate anions. The ease of their availability and preparation has led to their application to a variety of transformations: aldol condensation, Michael addition, [4+2] cycloadditions, alkylations, etc.[202] Their reactions with acetals have been widely studied.[203] The addition of imidates (e.g., **273**, Scheme 162) and silyl enol ethers to Nicholas cations usually leads to *syn* products.[204]

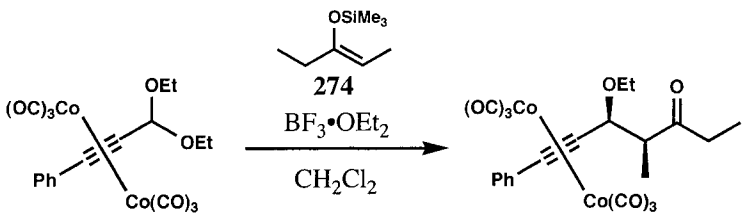


273

93%
>98:2 *syn:anti*

Scheme 162

In reactions involving dicobalt propargyl acetals, Nicholas and Montana reported similar *syn* diastereoselectivity (Scheme 163).[205] With acyclic enol ethers (e.g., **274**) low temperatures improved selectivity.

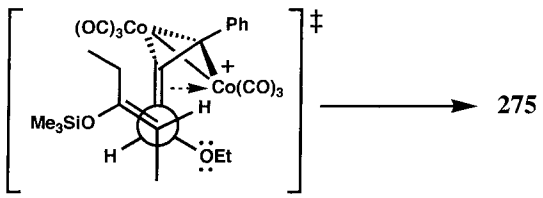


275

Temp.	Yield	*syn:anti*
0 °C	100%	11.2:1
-78 °C	93%	>15:1

Scheme 163

Based on the work of Schreiber and examination of molecular models, the stereochemical outcome in **275** is postulated to proceed via a synclinal transition state (**276**, Scheme 164).



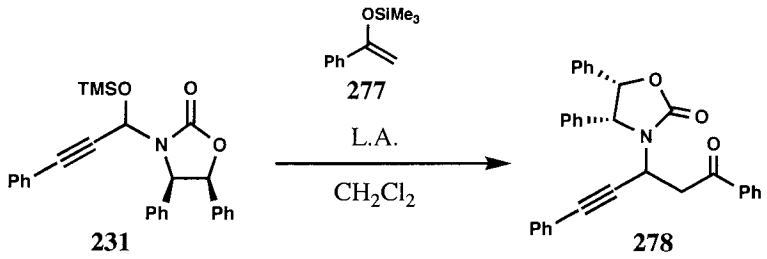
276

Scheme 164

It should be noted that in proposing the Schreiber model, the cluster fully bears the positive charge with no regard to the lone pairs of electrons on the pendant oxygen.

Acetophenone trimethylsilyl enol ether

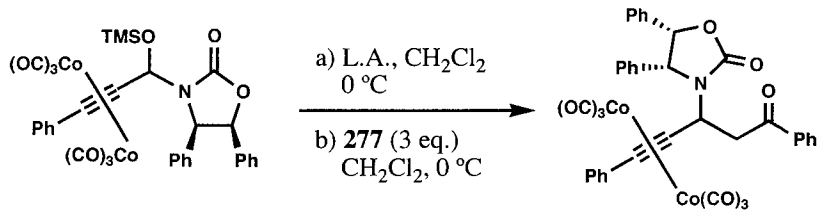
Silyl enol ether **277**,[206] upon addition to acetal **231**, produced **278** in good yield but poor selectivity (Scheme 165). In most cases, the diastereomeric integrity of the starting material did not survive the reaction conditions.



L.A. (eq.)	**277** eq.	Temp.	**278** dr	Recovered **231** dr	Yield (dr)
BF_3•OEt_2 (1.1)	1.1	0 °C	1.8:1	-	
BF_3•OEt_2 (1.1)	3	0 °C	2.6:1	-	85% (2.5:1)
BF_3•OEt_2 (1.1)	3	-78 °C	4.4:1	> 95:5	
BF_3•OEt_2 (1.1)	1.1	rt	1.8:1	-	82% (1.8:1)
$TiCl_4$ (1.1)	3	-78 °C	-	> 95:5	
TMSOTf (1.1)	1.1	0 °C	**1:1.4**	-	57% (1:1.4)
TMSOTf (1.1)	3	0 °C	**1:1.2**	-	79% (1:1.3)
TMSOTf (1.1)	3	-78 °C	1:1	-	

Scheme 165

With premixing of the catalyst, alkylation of **230** proved disappointing, with one notable exception (Scheme 166). Following the pre-equilibration of the substrate, the reaction was traditionally cooled to -78 °C prior to the addition of the silyl enol ether and subsequent warming back to 0 °C. If that cooling step is omitted, the diastereomeric enrichment of **279** was significantly improved (entry 7).



230
73:27 dr

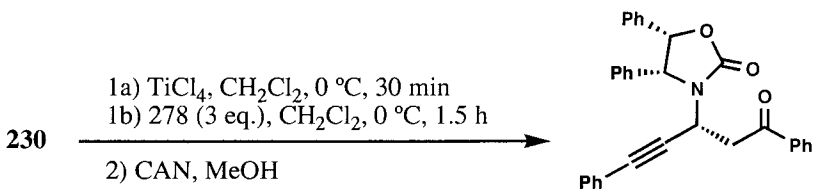
279

Entry	L.A. (eq.)	**277** time [a]	**279** dr	Recovered **230** dr
1	$Ti(O\textit{i}\text{-}Pr)_4$ (2)	3 h	-	73:27
2	$TiCl_4$ (0.3)	3 h	-	> 95:5
3	$TiCl_4$ (1)	0.3 h	58:42	-
4	$TiCl_4$ (1)	3.5 h	73:27	-
5	$TiCl_4$ (2)	0.25 h	62:38	-
6	$TiCl_4$ (2)	2 h	64:36	-
7	$TiCl_4$ (2)	1.5 h [b]	**94:6**	-
8	$TiCl_4$ (2)	0.25 h [c]	55:45	-

[a] Enol ether **277** added at -78 °C.
[b] Silyl enol ether is added at 0 °C.
[c] After addition of enol ether reaction stirred at -78 °C.

Scheme 166

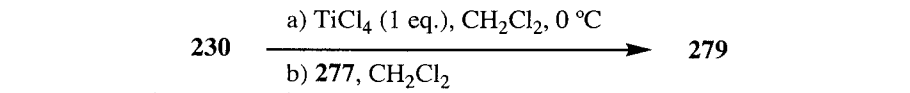
With this modified procedure at hand, γ-unsaturated ketone **278** was prepared from **230** in moderate yield (Scheme 167). Final product stereochemistry is presumed, based on the allylation reaction outcome (vide supra).



278
58%
92:8 dr

Scheme 167

Solvent effects on this transformation were studied (Scheme 168). Lewis basic solvents interfered with the alkylation, but not the resolution of the starting material.

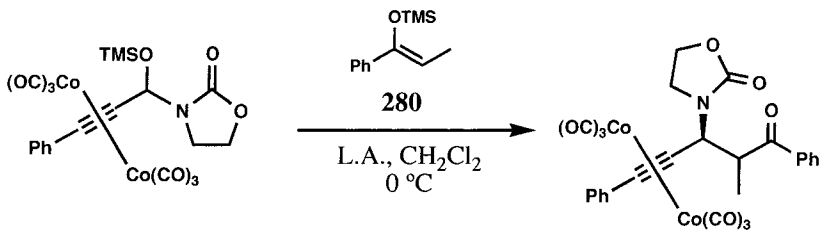


Solvent	**277** eq.	**277** temp.	**230**:**279**	**279** dr	**230** dr
THF	1	-78 °C → rt	5:1	> 95:5	> 95:5
THF	1	rt	-	-	> 95:5
Et_2O	3	0 °C → rt	-	-	> 95:5

Scheme 168

Propiophenone trimethylsilyl enol ether

The reaction of BF_3•OEt_2 with a mixture of enol ether **280**[207] and **259** was highly stereoselective (Scheme 169). Although $TiCl_4$ led to hydrolysis product (**237**), premixing of the catalyst and substrate did afford **281** selectively (entry 2).



259 **281**

Entry	**280** eq.	L.A. (eq.)	Crude dr
1	2	$TiCl_4$ (2)	RCHO (**237**)
2	2	$TiCl_4$ (2) [a]	93:7
3	1.3	BF_3•OEt_2 (2)	93:7

[a] Catalyst premixed with **259** for 30 min at 0 °C prior to addition of **280**.

Scheme 169

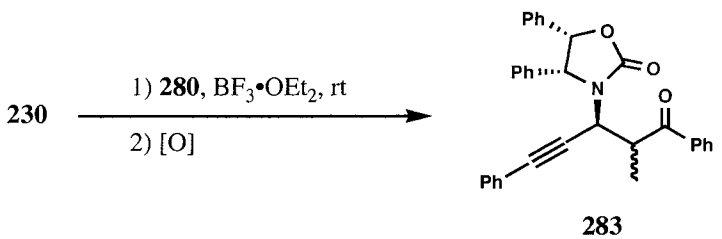
Bearing in mind that the aldol reaction with chiral complex **230** can produce up to four stereoisomers, only *one* diastereomer was detected in the crude NMR (Scheme 170). BF_3•OEt_2 and $TiCl_4$ afforded **282** with comparable chiral induction. The product was not stable to silica or alumina chromatography.

230 282

Conditions	Crude dr	Yield (dr)
280 (1.4 eq.), BF_3•OEt_2 (3 eq.), rt	> 95:5	39% (> 95:5), Neutral Al_2O_3
a) $TiCl_4$ (1 eq.), 0 °C, 30 min b) **280** (1.3 eq.), 0 °C	> 95:5	33% (> 95:5), SiO_2

Scheme 170

The sequential aldol/cluster oxidation reaction proved problematic (Scheme 171). Several conditions led to epimerization of final product **283**. The subjection of **283** to $NaOMe/CD_3OD$ in an NMR tube led to partial decomposition but no change in the diastereomeric ratio, indicating equilibrium had been already achieved.



283

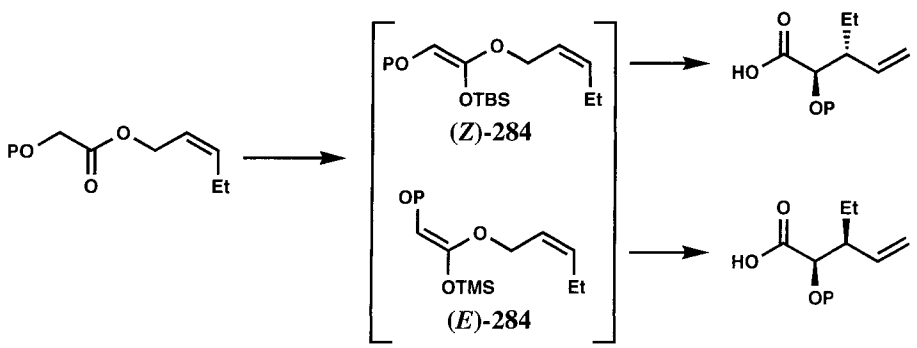
[O] conditions
CAN, MeOH
CAN, (*t*-Bu)$_2$Py, MeOH
NMO, CH_2Cl_2

Scheme 171

Silyl ketene acetal

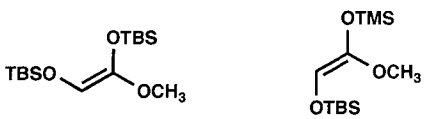
Control of enolate geometry is critical in organic reactions.[208] The Ireland-Claisen rearrangement of enolates **284** has been reported (Scheme 172).[209] The ability to

selectively generate either (*E*)/(*Z*) isomer was crucial to the high diastereocontrol of the reaction.



Scheme 172

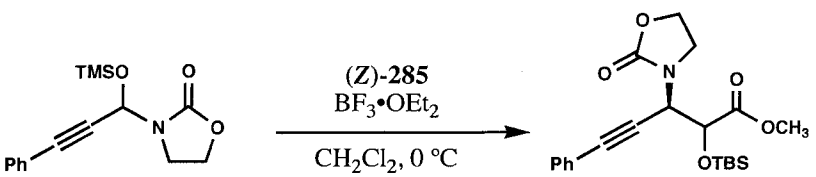
Relying on the Yamamoto protocol, **(*E*)/(*Z*)-285** were prepared (Figure 26).[209]



(*Z*)-285 **(*E*)-285**

Figure 26

The initial reaction of **(*Z*)-285** with **260** was high yielding, producing **286** as a separable mixture of diastereomers (Scheme 173).

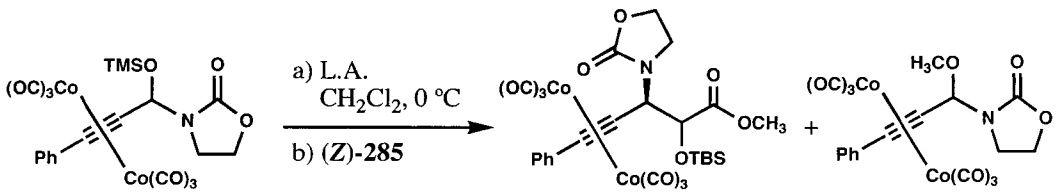


260 **286**

92%
1.2:1 dr

Scheme 173

The addition of **(*Z*)-285** to dicobalt complex **259** led to **287** with improved selectivity (Scheme 174).



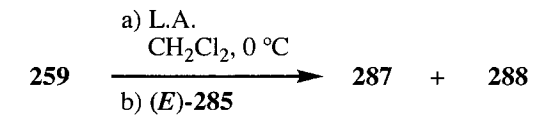
259 **287** **288**

L.A. (eq.)	**285** eq.	**287** (dr)	**288**	**237**	Yield
BF_3•OEt_2 (2)	3	61% (83:17)	37%	2%	
TMSOTf (2)	1.5	-	45%	55%	
$TiCl_4$ (1.1)	6.4	82% (95:5)	3%	15%	
$TiCl_4$ (2)	3	84% (87:13)	8%	8%	
$TiCl_4$ (2)	6.3	91% (89:11)	-	9%	
$TiCl_4$ (2)	6	93% (90:10)	-	7%	
$TiCl_4$ (2) [a]	6	90% (90:10)	-	10%	
$TiCl_4$ (4)	6	(91:9)	-	-	67%
$TiCl_4$ (4) [b]	6.5	(91:9)	-	-	69%

[a] Reaction run at room temperature.
[b] Reaction run at -10 °C.

Scheme 174

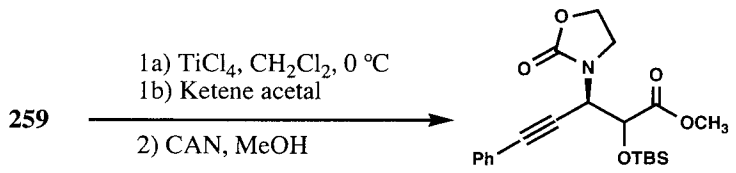
Reactions with **(*E*)-285** proved less selective (Scheme 175).



Entry	L.A. (eq.)	**285** eq.	**287** (dr)	**288**	**237**	Yield
1	BF_3•OEt_2 (1.1)	1.2	-	100%	-	
2	BF_3•OEt_2 (2)	3	-	100%	-	
3	$TiCl_4$ (1.1)	1.4	-	68%	32%	
4	$TiCl_4$ (2)	3.1	(80:20)	-	-	81%

Scheme 175

The aldol/cluster oxidation reaction sequences leading to **289** reflected these results (Scheme 176).

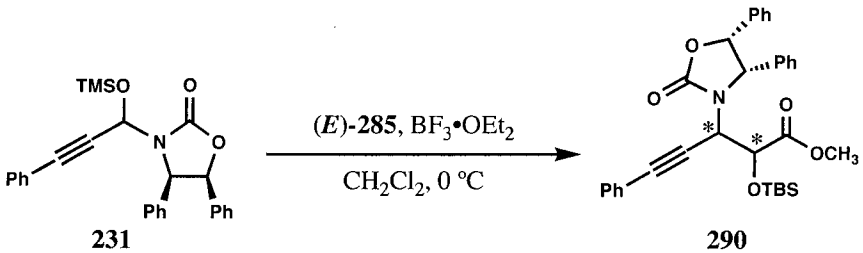


289

Ketene acetal	Crude dr	Yield
(*E*)-285	78:22	58%
(*Z*)-285	92:8	84%

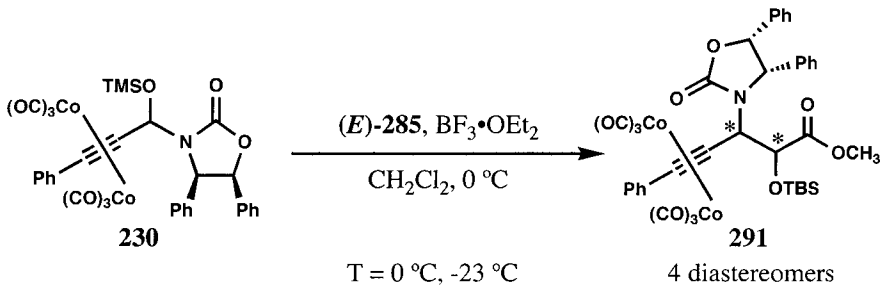
Scheme 176

The addition of ketene silyl acetal **(*E*)-285** to chiral **231** served as a benchmark for determining diastereoselectivity in subsequent reactions; all four possible diastereomers of **290** were isolated (Scheme 177).



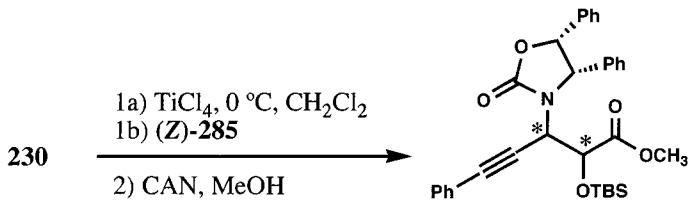
Scheme 177

Reaction of **(*E*)-285** with chiral complex **230** led to a crude mixture of 4 diastereomers (Scheme 178). Temperature did not have an effect on the diastereomeric ratio of **291**.



Scheme 178

Surprisingly, only three diastereomers of **290** could be detected in reactions of **(*Z*)-285** with **230** (Scheme 179).



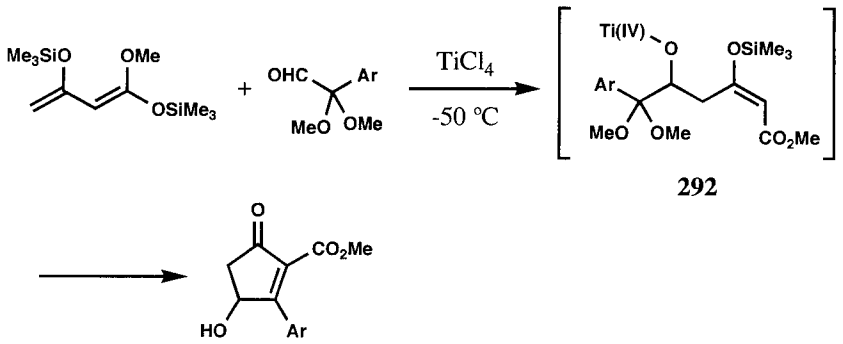
$TiCl_4$ eq.	**285** eq.	Crude	Yield
1.1	1.4 [a]	3 diast. + **216**	
2.1	6	3 diast.	
4	6.1	3 diast.	85%

[a] Reaction ran at -10 °C.

Scheme 179

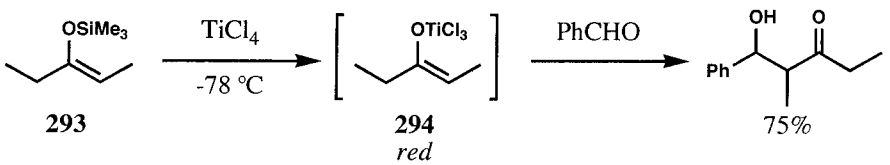
Discussion

Titanium tetrachloride. Interesting reactivity observations warrant discussion. Chan reported the ^{29}Si NMR analysis of a $TiCl_4$-mediated aldol reaction (Scheme 180).[210] No titanium enolate was detected; the only visible intermediates were **292** and trimethylchlorosilane. It should be noted that this study was undertaken with a catalytic amount of $TiCl_4$ (0.5 eq.).



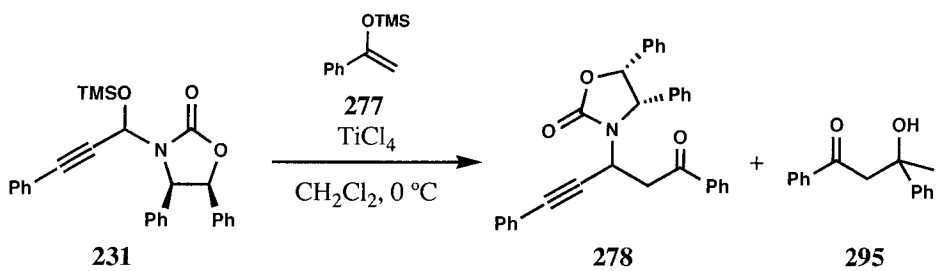
Scheme 180

The addition of an equimolar amount of $TiCl_4$ to silyl enol ether **293** led to the unequivocal synthesis of titanium enolate **294** which reacted with benzaldehyde (Scheme 181).[211] Its preparation was detected by the red color of the solution.



Scheme 181

Although it remains unclear whether a titanium enolate is uniformly involved in our system, on one occasion the addition of $TiCl_4$ (1.1 eq.) to a solution of **231** and **277** (1.1 eq.) at 0 °C led to a red color change of the reaction mixture. Upon quench, **278** and aldol product **295** were detected in the crude mixture (Scheme 182).



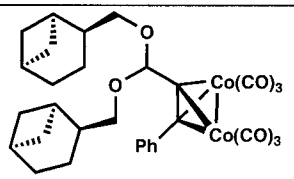
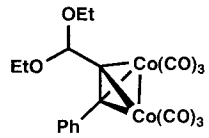
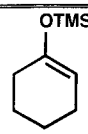
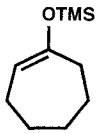
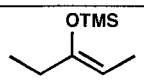
Scheme 182

Further evidence of a metal-enol ether interaction include: 1) the addition of the nucleophile at 0 °C had a beneficial effect on the diastereoselectivity of the reaction (see entry 7, Scheme 166); and 2) Lewis basic solvents (THF, Et_2O) inhibited the reaction (see Scheme 168). The former was not observed with allylsilanes. Therefore, several extenuating variables may be accounting for the varied reactivity patterns observed.

Silyl ketene acetals. Ketene acetal **(*Z*)-285**, upon addition to **259**, afforded the adduct **287** with high selectivity (91:9 dr, see Scheme 174). Yet reaction with its chiral counterpart, **230**, led to an equimolar mixture of 3 diastereomers. The discrepancy in reaction selectivity between achiral oxazolidinone (**259**) and chiral diphenyl-oxazolidinone (**230**) systems can be attributed to several causes: 1) each substrate follows a different stereochemical pathway; 2) the ketene acetal is isomerizing during the reaction; or 3) the product is epimerizing.

Since propiophenone trimethylsilyl ether **280** added to **230** and **259** with comparable selectivity (see Scheme 169 and Scheme 170), it seems counter-intuitive that chiral **230** would confer *less* stereocontrol than **259** when reacting with ketene acetals. However, a comparison of the Nicholas (achiral acetal) and Montana (chiral acetal) results is apt (Table 12). While *syn:anti* ratios are comparable, in none of the cases did Montana's chiral group effect any significant chiral induction within a *syn/syn* or *anti/anti* pair.

Table 12: Comparison of chiral and achiral acetal complexes.

	Montana [122]		Nicholas [205a]	
				
	95%	85:15 *syn:anti* 50:50 *anti:anti*	91%	90:10 *syn:anti*
	95%	72:28 *syn:anti* 60:40 *syn:syn* 50:50 *anti:anti*	72%	63:37 *syn:anti*
	70%	>99:1 *syn:anti* 50:50 *syn:syn*	93%	>95:5 *syn:anti*

Therefore, if the stereochemical pathways do not diverge, the chiral elements in **230** may not be adequate contributors to the stereodifferentiation of **291**.

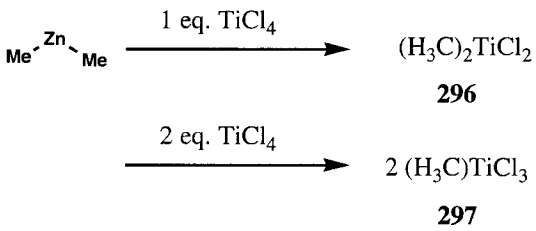
Although ketene acetal isomerization is plausible, it seems unlikely that it would impact reaction with achiral **259** to a lesser extent than with **230**.

The near statistical distribution of three or four products would require an epimerization that scrambles both nascent stereocenters. Conceivably, the presence of bulky phenyls on the oxazolidinone and the TBS ether on the molecule may contribute to unfavorable interactions with the dicobalt cluster. A subsequent $TiCl_4$-catalyzed equilibration could drive the epimerization.

Methylation

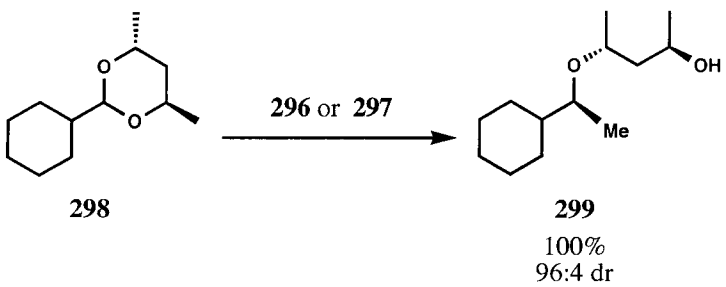
The methylation of N,O-acetals can be accomplished by reagents incorporating aluminum,[212] copper,[213] and magnesium.[214] In 1980 Reetz reported the preparation of

methyl- and dimethyltitanium(IV) chloride, **296** and **297** respectively (Scheme 183).[215] These mild reagents proved more selective than their Li or Mg counterparts.



Scheme 183

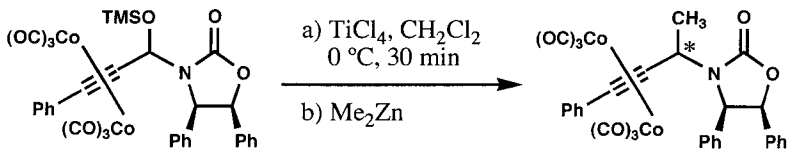
The acetal **298** was cleaved with either reagent, affording **299** in high yield (Scheme 184).[216] Critically, the same result is obtained in the *sequential* addition of $TiCl_4$ and dialkylzinc reagent.



Scheme 184

Chiral N,O-acetal template

Results of the sequential addition of $TiCl_4$ and dimethylzinc to **230** are described in Scheme 185. Dimethylzinc alone was unreactive (entry 1), and the 2:1 $TiCl_4$ to Me_2Zn ratio (see Scheme 183) was not an effective mixture (entries 2 and 3) for conversion to **300**.



230
2.7:1 dr

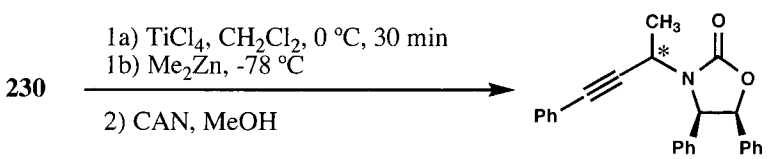
300

Entry	$TiCl_4$ eq.	Me_2Zn eq.	Temp.	Time	Recovered **230** (dr)	**237**	**300** (dr)	Yield
1	-	2	-78 °C	2 h	1:2.8	-	-	
2	1.1	0.55	-78 °C	0.25 h	21% (**1:1.6**)	62%	17%	
3	1.1	0.55	-42 °C	0.25 h	16% (**1:1.2**)	60%	24%	
4	2	3	-78 °C	0.3 h	-	-	(>20:1)	51%
5	2	3	-42 °C	0.3 h	-	-	(>20:1)	
6	2	3	0 °C	0.3 h	-	-	(>20:1)	
7[a]	2	3	0 °C	2 h	89% (5:1)	-	11%	
8[b]	2	3	0 °C	2 h	84% (>20:1)	-	16%	

[a] Reaction run in Et_2O.
[b] Reaction run in THF.

Scheme 185

The methyl propargylamide **301** was then produced directly from **230** as a single diastereomer (Scheme 186). Attempts to grow X-ray quality crystals of the product have so far failed.



301
54%
>95:5

Scheme 186

Discussion

The $TiCl_4$ and Me_2Zn stoichiometries determine whether the mono- or dimethylated titanium reagent is formed (see Scheme 183). The mixture of 2 equivalents of $TiCl_4$ and Me_2Zn has been shown to produce **297**, an alkylating species. However, under reaction conditions where $TiCl_4$ is premixed with **230** (entries 2 and 3, Scheme 185) prior to addition of Me_2Zn the conversion to **300** is low. Since dimethylzinc alone was unreactive (entry 1), alkylation must be proceeding via a methylated titanium species. However, the exact nature of this compound cannot be elucidated from this data alone. The subdued conversion observed in ether and THF is indicative of subdued formation of the alkylating reagent. Octahedral titanium(IV) complexes have been prepared, including one bearing THF ligands (Figure 27).[217]

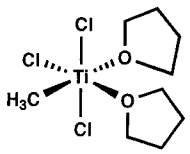
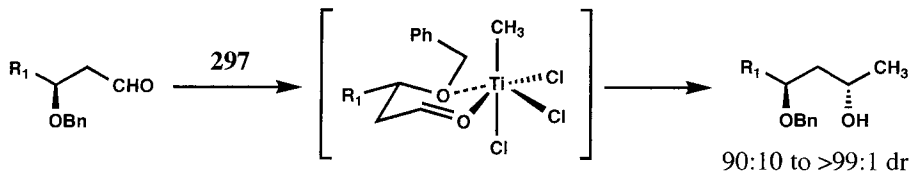


Figure 27

Therefore, it can be postulated that solvent coordination may interfere with approach of Me_2Zn to effect alkylation of titanium.

Methyl trichlorotitanium (**296**) alkylated β-alkoxy aldehydes with a high degree of selectivity (Scheme 187).[190a] The stereochemical outcome was rationalized by chair transtition state **302**.



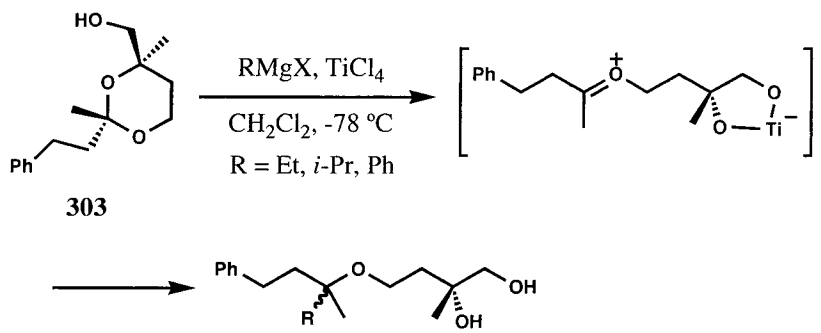
302

Scheme 187

Since the stereochemistry of the resolved acetal (***epi*-230**) is unknown, this hypothesis cannot be extended to this substrate.

Vinylation

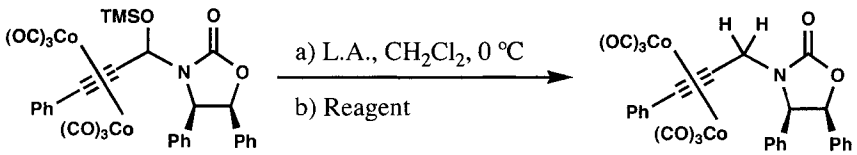
The reaction of *N,O*-acetals with Grignard reagents is a well established diastereoselective transformation.[214, 218] Wipf cleaved chiral acetal **303** with Et- *i*-Pr- and PhMgBr in the presence of $TiCl_4$ (Scheme 188).[219] The lack of stereocontrol in the addition was attributed to an acyclic oxocarbenium ion intermediate.



Scheme 188

Chiral N,O-acetal template

Dicobalt cluster **230** was subjected to several vinylation protocols with no success (Scheme 189). The formation of **304** cannot be explained at this time.



230 **304**

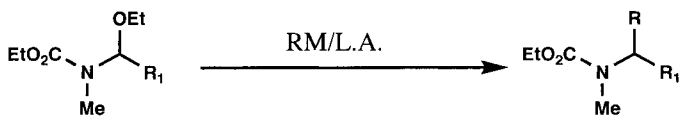
L.A. (eq.)	Reagent (eq.)	Temp.	Recovered **230**	**237**	**304**
-	VinylMgBr (4)	-78 °C to rt	-	-	-
$TiCl_4$ (1.1)	VinylMgBr (1.5)	-78 °C	+ (>95:5 dr)	-	+
$TiCl_4$ (1.1)	VinylMgBr (4)	-78 °C	+ (>95:5 dr)	-	+
$TiCl_4$ (2)	VinylMgBr (3)	0 °C	+ (>95:5 dr)	-	-
$TiCl_4$ (1)	VinylTMS (3)	-78 °C	-	+	-
$ZnCl_2$ [a] (2)	VinylMgBr (3)	-78 °C to rt	+	-	-
Et2AlCl (2)	VinylMgBr (2)	-78 °C to 0 °C	+	-	-

[a] Added following vinylMgBr.

Scheme 189

Ethylation

The addition of simple alkyl substituents to acetals is facilitated by $TiCl_4$.[220] Yamamoto alkylated α-ethoxycarbamate **305** with organolead, zin, and copper reagents (Scheme 190).[221] In entries 1 and 2, $TiCl_4$ was added to the starting material prior to the alkylating reagent.

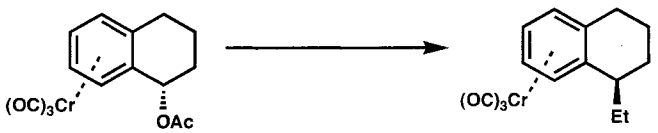


305

Entry	RM/L.A.
1	$Et_4Pb/TiCl_4$
2	$Et_2Zn/TiCl_4$
3	$(n\text{-}Bu)_2CuLi{\bullet}BF_3$

Scheme 190

Arene tricarbonylchromium complexes **306** underwent stereoselective alkylation at the benzylic position (Scheme 191).[222]



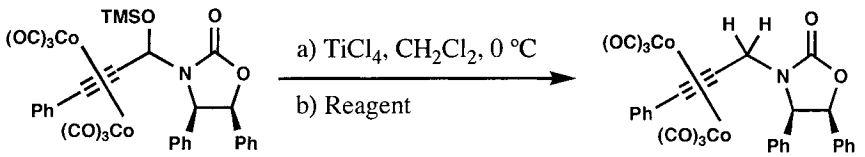
306

Reagent(s)	Yield
Et_3Al	60%
$Et_2Zn/TiCl_4$	62%

Scheme 191

Chiral N,O-acetal template

Analogous conditions failed to alkylate **230** (Scheme 192).



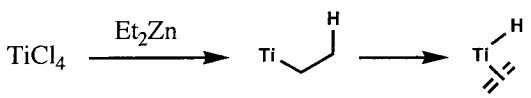
230 **304**

$TiCl_4$ eq.	Reagent (eq.)	Temp.	Recovered **230**	**304**
2	Et_2Zn (3)	-78 °C	-	+
2	Et_3Al [a] (3)	-78 °C to 0 °C	+	-
-	Et_3Al [a] (3)	-78 °C to 0 °C	+	-
-	Et_3Al (3)	-78 °C to rt	+	-

[a] Reaction run in THF.

Scheme 192

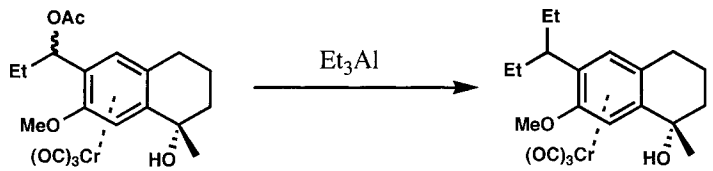
The complete conversion of the starting material to **304** is postulated to occur via a titanium hydride species arising from a β-hydride elimination of an alkylated titanium (Scheme 193). It is noteworthy that neither references utilizing the $Et_2Zn/TiCl_4$ blend reported reduction products.[221, 222]



Scheme 193

In comparison to $TiCl_4$'s methylation of **230** (see Scheme 185), it can be postulated that the delivery of a hydride may be proceeding via an analogous mechanism.

The inability of Et_3Al to alkylate **230** is surprising, considering its success with cluster-stabilized **306**. The recovery of hydrolysis product, however, alludes to a possible sterric factor interfering with delivery of the ethyl group. In support of this hypothesis, Uemura effected the ethylation of **307** with complete chemoselectivity (Scheme 194).[222]



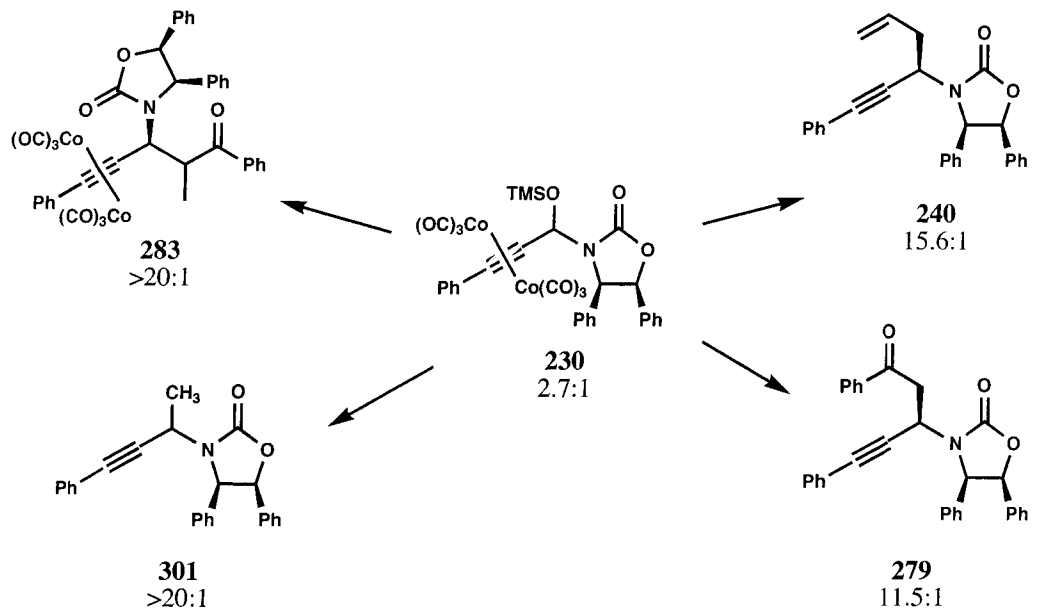
307

Scheme 194

IV. Conclusion

The formation of carbon-carbon bonds is a fundamental operation in organic chemistry. In scaffolds lacking structural rigidity (e.g., acyclic systems), *intermolecular* stereo-controlled elaborations are hampered.[223] For example, the synthesis of nucleoside analog **51** by Vorbrüggen coupling of silylated thymine (**50**) to **49** is not facially selective (~ 1:1 β:α diastereomers), owing to the near-planarity of the electrophile (see Scheme 24, Chapter 1). However, intermolecular stereocontrol can been achieved via strict control of transition state geometries (with enolates,[224] allyl organometallics,[173] and cycloadditions,[225] among others) or by reliance on diastereomeric kinetic factors (e.g., dynamic resolutions).[139]

Since Nicholas' first report of a dicobalt cluster-stabilized propargyl cation in 1971, [110, 79c] the nature of the cation has been shown to comprise four equilibrating diastereomers (see Scheme 63),[102] and the motif has been extended to cationic propargyl ethers (see Scheme 174).[122] The methodology reported herein extends the scope of cationic dicobalt clusters to propargyliminium scaffolds, generated from precursor *N,O*-acetals in the presence of Lewis acids. Clustered acetal **230** was alkylated with allyl trimethylsilane, silyl enol ethers, and dimethylzinc. By effecting an equilibration of diatereomers, a mixture of **230** diastereomers was selectively converted to **240**, **279**, **283**, and **301** (Scheme 195). The absence of a pendent cluster led to products with low diastereomeric ratios.



Scheme 195

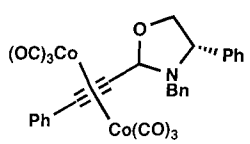
These results indicate the intermediacy of a cationic species, as exemplified by the equilibration of a diastereomeric mixture of **230** to ***epi*-230** (see Scheme 139).

However, it cannot be ascertained whether the cation is cluster-based (Schreiber model) or nitrogen-based (iminium model).

Reactions with prochiral nucleophiles (see Scheme 155, Scheme 178, and Scheme 179) led to mixtures of multiple products. The addition of vinyl (see Scheme 189) and ethyl (see Scheme 190) groups to the acetal failed as well.

V. Experimental

General Methods. THF and Et_2O was distilled from sodium-benzophenone ketyl, CH_2Cl_2, and Et_3N were distilled from CaH_2. Commercially available reagents were used as received except as indicated. ^1H NMR, ^{13}C NMR (75 MHz), and HMQC (400 ^1H MHz) spectra were recorded in $CDCl_3$, unless otherwise noted, and chemical shifts are given in ppm relative to $CDCl_3$ (7.27 ppm). With dicobalt hexacarbonyl complexes, the presence of cobalt derived paramagnetic impurities required a low NMR sample concentration, and the passing of the sample through a plug of oven-dried neutral Al_2O_3. Column chromatography was performed with ICN 32-66 nm, 60 Å silica gel using flash column techniques. Elemental analyses were performed by M-H-W Laboratories, Phoenix, AZ. FAB high-resolution mass spectro-metry (HRMS) was obtained with a Fisons VG AutoSpec mass spectrometer with a Cs ion gun, *m*-nitrobenzyl alcohol was used for the matrix, and the resolution was set to 10000. All reactions were performed in flame-dried glassware under an atmosphere of argon or nitrogen, unless otherwise noted. The following compounds were prepared according to published methods: 3-phenyl-propriolaldehyde,[175] **215**,[176] **236**,[182] **(*E*)/(*Z*)-254**,[197] **263**,[157] **277**,[206] **280**,[207] **(*E*)/(*Z*)-285**.[209]

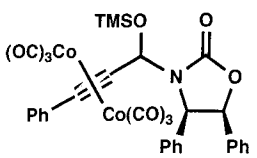


218

(4*S*)-3-Benzyl-4-phenyl-2-(phenylethynyl)oxazolidine-dicobalt hexacarbonyl complex (218). To a CH_2Cl_2 solution (35 mL) of starting material, (4*S*)-3-benzyl-4-phenyl-2-(phenylethynyl)oxazolidine **215** (2.08 g, 6.12 mmol, 2.6:1 dr), was added dicobalt octacarbonyl (2.50 g, 7.31 mmol). After stirring the reaction for 80 min at room temperature, no starting material was apparent by TLC analysis (4:1 pentane/ether). The reaction was filtered through a

plug of neutral Al_2O_3, and the filtrate washed twice with CH_2Cl_2. Removal of the solvent in vacuo afforded a dark brown oil. Purification by flash chromatography (15:1 pentane/ether) provided a dark red oil comprising an inseperable 5.4:1 mixture of diastereomers (3.27 g, 5.22 mmol, 85%). ^{1}H NMR δ 7.67-7.61 (m, 1.75H), 7.54-7.48 (m, 0.38H), 7.40-7.16 (m, 11.1H), 7.06-6.97 (m, 1.77H), 5.99 (s, 0.16H), 5.85 (s, 0.84H), 4.65 (app t, 0.16H), 4.48 (dd, J = 5.8 Hz, 7.7 Hz, 0.16H), 4.22 (dd, J = 4.7 Hz, 7.7 Hz, 0.16H), 4.17-4.05 (m, 1.7H), 3.99 (d, J = 14.3 Hz, 0.85H), 3.93 (d, J = 14.3 Hz, 0.85H), 3.86 (d, J = 14.6 Hz, 0.16H), 3.78 (dd, J = 5.8 Hz, 6.9 Hz, 0.85H), 3.46 (d, J = 13.9 Hz, 0.16H).

General procedure for the allylation studies of **215** (Scheme 106) and **218** (Scheme 108). To a solution of (±)-(4*S*)-3-benzyl-4-phenyl-2-(phenyl-ethynyl)oxazolidine **215** or (±)-(4*S*)-3-benzyl-4-phenyl-2-(phenylethynyl)oxazolidine-dicobalt hexacarbonyl complex **218** in CH_2Cl_2 (0.1 M) cooled to the appropriate temperature was added allyltrimethyl-silane followed by the Lewis acid. The reaction was quenched with $NaHCO_3$(aq), warmed to room temperature, and extracted twice with CH_2Cl_2. The organic layers were combined and dried with $MgSO_4$ prior to removal of the solvent in vacuo.

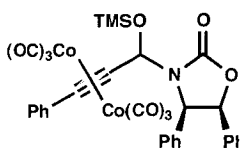


230

(4*R*,5*S*)-4,5-Diphenyl-3-(3-phenyl-1-(trimethylsilyloxy)prop-2-ynyl)oxazolidin-2-one-dicobalt hexacarbonyl complex (230). Procedure A: Starting material (4*R*,5*S*)-4,5-diphenyl-3-(3-phenylpropioloyl)oxazolidin-2-one **233** (269 mg, 0.732 mmol) was dissolved in CH_2Cl_2 (8 mL) then the solution cooled to -78 °C. Dibal-H (878 μL, 0.878 mmol, 1 M in

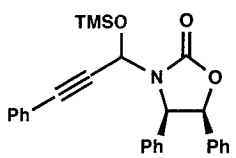
toluene) was added dropwise, and the reaction was allowed to stir for 1 h. Pyridine (89 μL, 1.098 mmol) and TMSOTf (200 μL, 1.098 mmol) were added, the cold bath was removed, and the reaction was stirred for an additional 50 min. The reaction was poured into a mixture of 20% Rochelle's salt (20 mL) and ether (20 mL), and stirred vigorously. After separating the layers, the aqueous layer was extracted again with ether (20 mL). The organic layers were combined and dried with $MgSO_4$. The removal of the solvent in vacuo afforded a viscous brown oil (379 mg) which was dissolved in CH_2Cl_2 (15 mL). Dicobalt octacarbonyl (313 mg, 0.915 mmol) was added, and the reaction stirred at room temperature for 2 h. The solvent was removed in vacuo to give a brown foam. Purification by flash chromatography (10:1 hexane/ether) provided a brown foamy solid comprising an inseperable 2.1:1 mixture of diastereomers (291 mg, 0.399 mmol, 55%). ^{1}H NMR δ 7.54-7.46 (m, 1H), 7.44-7.28 (m, 4H), 7.08-6.94 (m, 5H), 6.92-6.62 (m, 5H), 5.72 (d, J = 7.8 Hz, 0.38H), 5.60 (d, J = 7.6 Hz, 0.62H), 5.17 (d, J = 8.0 Hz, 0.38H), 4.99 (d, J = 7.8 Hz, 0.62H), 0.24 (s, 3.4H), -0.09 (s, 5.6H); ^{13}C NMR δ 199.30, 157.97, 156.82, 137.65, 136.86, 134.51, 134.22, 130.10, 129.39, 129.11, 128.69, 128.48, 128.32, 128.24, 128.09, 127.96, 127.90, 126.41, 126.18, 81.99, 80.99, 80.78, 79.48, 61.98, 61.82, 0.25, -0.13; IR (neat) 3066, 3036, 2958, 2093, 2055, 2025, 1759 cm^{-1}.

Procedure B: To a solution of (4*R*,5*S*)-4,5-diphenyl-3-(3-phenyl-1-(trimethylsilyloxy)-prop-2-ynyl)oxazolidin-2-one **231** (1.05 g, 2.37 mmol) in CH_2Cl_2 (20 mL) was added dicobalt octacarbonyl (1.22 g, 3.56 mmol) at room temperature. After stirring for 1 h, the reaction was filtered through Celite, and the solvent was removed in vacuo to afford a viscous brown oil (1.84 g). Purification by flash chromatography (12:1 pentane/ether) provided the product as a brown glassy foam (1.50 g, 2.06 mmol, 3.5:1 dr, 87%).



epi-230

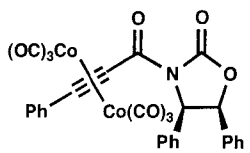
(4*R*,5*S*)-4,5-Diphenyl-3-(3-phenyl-1-(trimethylsilyloxy)prop-2-ynyl)oxazolidin-2-one-dicobalt hexacarbonyl complex (*epi*-230). A solution of (4*R*,5*S*)-4,5-diphenyl-3-(3-phenyl-1-(trimethylsilyl-oxy)prop-2-ynyl)oxazolidin-2-one-dicobalt hexacarbonyl complex **230** (274 mg, 0.376 mmol) in THF (2.5 mL) was cooled to -78 °C and treated with $TiCl_4$ (83 μL, 0.753 mmol). After warming the mixture to 0 °C and stirring for 1 h, the reaction was quenched with water and extracted with ether. The organic layer was dried with $MgSO_4$. Removal of the solvent in vacuo afforded a 92:8 mixture of resolved starting material and hydrolysis product **237** as a dark brown oil. Resolved starting material: ^{1}H NMR δ 7.53-7.47 (m, 2H), 7.41-7.35 (m, 3H), 7.06-6.99 (m, 6H), 6.96 (s, 1H), 6.88-6.79 (m, 4H), 5.90 (d, J = 7.6 Hz, 1H), 5.00 (d, J = 7.6 Hz, 1H), -0.10 (s, 9H).



231

(±)-(4*R*,5*S*)-4,5-Diphenyl-3-(3-phenyl-1-(trimethylsilyloxy)-prop-2-ynyl)oxazolidin-2-one (231). A solution of (4*R*,5*S*)-4,5-diphenyl-3-(3-phenylpropioloyl)oxazolidin-2-one **233** (70 mg, 0.190 mmol) in CH_2Cl_2 (1.2 mL) was cooled to -78 °C. Dibal-H (228 _L, 0.228 mmol, 1 M in toluene) was added dropwise, and the reaction was allowed to stir for 40 min. Pyridine (23 _L, 0.286 mmol) followed by TMSOTf (57 _L, 0.286 mmol) were added, and the cold bath was removed as the reaction stirred for an additional 90 min. The reaction was poured into a mixture of 20% Rochelle's salt and ether, and stirred vigorously. After separating the layers, the aqueous layer was extracted again with ether. The organic layers were combined and dried with $MgSO_4$. The removal of the solvent in vacuo afforded a viscous brown oil (79 mg) comprising an

inseperable 2.2:1 mixture of product diastereomers. Purification by flash chromatography on Davisil™ silica gel (15:1 hexane/ethyl acetate) afforded a white solid (47 mg, 0.106 mmol, 1.5:1 dr, 56%). ^{1}H NMR δ 7.64-7.59 (m, 0.26H), 7.50-7.32 (m, 4.18H), 7.20-6.94 (m, 9.66H), 6.74-6.68 (m, 0.90H), 6.46 (s, 0.39H), 6.42 (s, 0.61H), 5.88 (d, J = 8.2 Hz, 1.2H), 5.44 (d, J = 8.2 Hz, 0.70H), 5.41 (d, J = 7.1 Hz, 0.45H), 0.30 (s, 4.01H), 0.05 (s, 6.35H); ^{13}C NMR δ 168.53, 157.14, 135.86, 134.67, 132.17, 131.78, 129.45, 128.87, 128.79, 128.24, 128.14, 128.11, 127.77, 126.62, 126.49, 121.94, 85.10, 81.67, 80.78, 70.29, 69.05, 63.84, 61.22, 0.48, 0.20; IR (neat) 3064, 3035, 2957, 2245, 2189, 1760 cm^{-1}; mp 127-128 °C (major diastereomer); HRMS-FAB (*m/z*): M^+ calcd for $C_{27}H_{27}NO_3Si$, 441.1760; found, 441.1759.



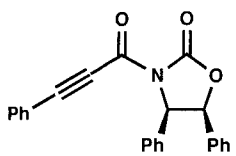
232

(±)-(4*R*,5*S*)-4,5-Diphenyl-3-(3-phenylpropioloyl)oxazolidin-2-one-dicobalt hexacarbonyl complex (232). To a solution of (4*R*,5*S*)-4,5-diphenyl-3-(3-phenylpropioloyl)oxazolidin-2-one **233** (323 mg, 0.87 mmol) in CH_2Cl_2 (10 mL) was added dicobalt octacarbonyl (366 mg, 1.07 mmol) at room temperature. After stirring for 1 h, the solvent was removed in vacuo to afford a dark red oil. Purification by flash chromatography (5:1 pentane/ether) provided the product as a brown foamy solid (501 mg, 0.76 mmol, 87%). ^{1}H NMR δ 7.59-7.52 (m, 2H), 7.39-7.32 (m, 3H), 7.16-7.09 (m, 6H), 7.02-6.90 (m, 4H), 6.00 (d, J = 7.7 Hz), 5.90 (d, J = 7.3 Hz).

General procedure for the Dibal-H reduction studies of **232** (Scheme 121), $NaHCO_3$(aq) /1 N HCl/15% Rochelle's salt quench. A solution of (4*R*,5*S*)-4,5-diphenyl-3-(3-

phenylpropioloyl)oxazolidin-2-one-dicobalt hexacarbonyl complex **232** in CH_2Cl_2 or THF (~ 0.1 M) was cooled to the requisite temperature prior to the addition of Dibal-H (1.0 M in toluene). After stirring for the appropriate time, the reaction was quenched, warmed to room temperature, and extracted twice with CH_2Cl_2 (filtered through Celite in case of emulsion formation). The organic layers were combined and dried with $MgSO_4$. The solvent was subsequently removed in vacuo.

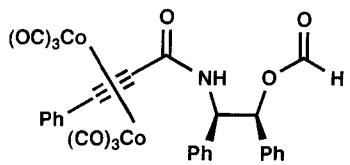
$Na_2SO_4(H_2O)_{10}$(s) quench. The reaction was quenched with $Na_2SO_4(H_2O)_{10}$(s), diluted with CH_2Cl_2, then warmed to room temperature and filtered through Celite. The cake was washed with CH_2Cl_2 until the filtrate was clear. The solvent was removed in vacuo.



233

(+)-(4*R*,5*S*)-4,5-Diphenyl-3-(3-phenylpropioloyl)oxazolidin-2-one (233). A solution of (4*R*,5*S*)-4,5-diphenyloxazolidin-2-one **234** (919 mg, 3.84 mmol) in THF (50 mL) was cooled to -78 °C. *n*-BuLi (2.6 mL, 4.19 mmol, 1.6 M in hexane) was added, and the reaction was stirred for 5 min before removing the cold bath and stirring for an additional 30 min. This solution was cannulated into a solution of 3-phenylpropioloyl chloride **236** (575 mg, 3.49 mmol) in THF (15 mL) cooled to -78 °C. After stirring for 5 min, the cold bath was removed and the reaction allowed to stir for an additional 3 h. After pouring the reaction into water (150 mL), the mixture was extracted with ether (100 mL, 3 times). The organic layers were combined and dried with $MgSO_4$. The removal of the solvent in vacuo afforded an off-white solid (1.23 g). Recrystalization from benzene provided a white solid (1.01 g, 2.77 mmol, 79%). ^{1}H NMR δ 7.74-7.66 (m, 2H), 7.52-7.34 (m, 3H), 7.18-7.08 (m, 6H), 7.04-6.88 (m, 4H), 5.95 (d, J = 7.6 Hz, 1H), 5.74 (d, J = 7.3 Hz, 0.62H; ^{13}C

NMR δ 133.64, 131.37, 128.84, 128.64, 128.36, 126.91, 126.45, 80.71, 63.23; IR (neat) 3032, 2920, 2358, 2340, 2215, 1785, 1662, 1653 cm^{-1}; m.p. 202 – 204 °C; $[\alpha]^{25}_{D}$ +236.91° (*c* 2.3, $CHCl_3$); anal. Calcd for $C_{24}H_{17}NO_3$: C, 78.46; H, 4.66; N, 3.81. Found: C, 78.58; H, 4.50; N, 3.84.

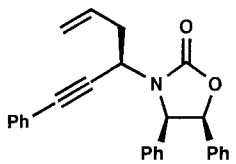


238

(±)-(1*S*,2*R*)-1,2-diphenyl-2-(3-phenylpropiolamido)-ethyl formate-dicobalt hexacarbonyl complex (238). Procedure A: A solution of (4*R*,5*S*)-4,5-diphenyl-3-(3-phenylpropiol-oyl)oxazolidin-2-one-dicobalt hexacarbonyl complex **232** (22 mg, 0.033 mmol) in CH_2Cl_2 (500 μL) was cooled to -78 °C prior to the addition of Dibal-H (40 μL, 0.040 mmol, 1.0 M in hexane). After stirring for 3 h, the reaction was quenched with $NaHCO_3$ (aq), diluted with CH_2Cl_2 (5 mL), then warmed to room temperature. The layers were separated, and the aqueous phase was extracted again with CH_2Cl_2 (5 mL). The organic layers were combined and dried with $MgSO_4$. Removal of the solvent in vacuo afforded a brown oil (20 mg) comprising a 1:1.4 mixture of aldehyde **237** and formate **238**. Purification by flash chromatography (8:1 pentane/ether) afforded a dark brown oil (7 mg). ^1H NMR δ 8.14 (s, 1H), 7.67-7.61 (m, 2H), 7.36-7.26 (m, 9H), 7.14-7.06 (m, 4H), 6.54 (d, J = 8.7 Hz, 1H), 6.32 (d, J = 4.4 Hz, 1H), 5.68 (dd, J = 4.7 Hz, 8.7 Hz, 1H); IR (neat) 2097, 2061, 2031, 1713, 1654 cm^{-1}.

Procedure B: A solution of (4R,5S)-4,5-diphenyl-3-(3-phenylpropiol-oyl)oxazolidin-2-one-dicobalt hexacarbonyl complex **232** (31 mg, 0.047 mmol) in CH_2Cl_2 (500 μL) was cooled to -78 °C prior to the addition of Dibal-H (104 μL, 0.104 mmol, 1.0 M in toluene). After stirring for 3 h, the reaction was quenched with $Na_2SO_4(H_2O)_{10}$(s), diluted with

CH_2Cl_2 (5 mL), then warmed to room temperature and filtered through Celite. The cake was washed with CH_2Cl_2 until the filtrate was clear. Removal of the solvent in vacuo afforded a brown oil (51 mg) comprising a crude 1:3.4 mixture of aldehyde **237** and formate **238**. Crude mixture: see Appendix B for HMQC spectrum; HRMS-FAB (*m/z*): $[M+H]^+$ calcd for $C_{30}H_{19}Co_2NO_9$ (**238**), 655.9802; found, 655.9825.



240

(4*R*,5*S*)-4,5-Diphenyl-3-(1-phenylhex-5-en-1-yn-3-yl)oxazolidin-2-one (240). Procedure A (Scheme 125): To a solution of (4*R*,5*S*)-4,5-diphenyl-3-(3-phenyl-1-(trimethylsilyloxy)prop-2-ynyl)oxazolidin-2-one **231** (62 mg, 0.140 mmol) in CH_2Cl_2 (1 mL) was added allyltrimethylsilane (67 μL, 0.421 mmol) followed by BF_3•OEt_2 (20 μL, 0.154 mmol) at 0 °C. After stirring for 30 min the reaction was quenched with $NaHCO_3$ (aq), warmed to room temperature, and extracted twice with CH_2Cl_2. The organic layers were combined and dried with $MgSO_4$. Removal of the solvent in vacuo provided an oil (59 mg, 1.4:1 dr). Purification by flash chromatography afforded an off-white solid comprising an inseparable 1.4:1 mixture of diastereomers (46 mg, 0.122 mmol, 84%). Major diastereomer: ^{1}H NMR δ 7.24-6.86 (m, 15H), 6.05-5.92 (m, 1H), 5.81 (d, J = 7.6 Hz, 1H), 5.31-5.22 (m, 2H), 5.15 (d, J = 7.6 Hz, 1H), 5.10-4.96 (m, 1H), 2.90-2.70 (m, 2H); ^{13}C NMR: d 157.90, 135.45, 134.41, 133.66, 131.81, 128.55, 128.26, 128.13, 126.53, 122.39, 119.26, 88.68, 85.59, 80.94, 64.17, 46.40, 39.18. Minor diastereomer: ^{1}H NMR δ 7.48-7.42 (m, 2H), 7.38-7.33 (m, 3H), 7.16-6.98 (m, 10H), 5.92 (d, J = 8.4 Hz, 1H), 5.82-5.67 (m, 1H), 5.36 (d, J = 8.7 Hz, 1H), 5.10-4.96 (m, 3H), 2.42-2.26 (m, 1H), 2.10-1.96 (m, 1H); ^{13}C NMR δ 157.85, 136.14, 134.92, 133.72, 132.17, 129.08, 128.80, 128.73, 128.31, 128.20, 128.13,

126.27, 122.57, 118.71, 86.68, 85.53, 80.36, 64.30, 48.64, 39.77; mixture: IR (neat) 3064, 3034, 2979, 2921, 2240, 1953, 1747, 1641, 1598 cm^{-1}; HRMS-FAB (*m/z*): $[M+H]^+$ calcd for $C_{27}H_{23}NO_2$, 394.1807; found, 394.1817.

Procedure B (Scheme 124): A solution of (4*R*,5*S*)-4,5-diphenyl-3-(3-phenylpropioloyl)-oxazolidin-2-one **233** (56 mg, 0.152 mmol) in CH_2Cl_2 (1.4 mL) was cooled to -78 °C and treated with Dibal-H (183 μL, 0.183 mmol, 1 M in toluene). After stirring for 1 h, pyridine (15 μL, 0.183 mmol) and TMSOTf (37 μL, 0.183 mmol) were sequentially added. The cold bath was removed, and the mixture was allowed to stir for 1 h. The reaction was quenched by pouring it into a mixture of 20% Rochelle's salt (aq) (10 mL) and ether (10 mL). After vigorously stirring for 1 h, the layers were separated, and the aqueous layer was extracted again with ether (10 mL). The organic layers were combined and dried with $MgSO_4$. Removal of the solvent in vacuo afforded crude **231** which was dissolved in CH_2Cl_2 (1.4 mL). After adding allyltrimethylsilane (73 μL, 0.357 mmol), the mixture was cooled to -78 °C and treated with $TiCl_4$ (305 μL, 0.305 mmol, 1 M in CH_2Cl_2). After stirring for 1 h, the reaction was quenched with $NaHCO_3$ (aq) (5 mL) and warmed to room temperature. The mixture was diluted with CH_2Cl_2 (5 mL) and water (5 mL), stirred vigorously, and filtered through Celite to remove the emulsion. The layers were separated, and the aqueous layer was extracted again with CH_2Cl_2 (5 mL, twice). The organic layers were combined and dried with $MgSO_4$. Removal of the solvent in vacuo provided an orange oil (64 mg, 1.8:1 dr). Purification by flash chromatography (10:1 hexane/ethyl acetate) afforded the product as an inseperable 1.8:1 mixture of diastereomers (37 mg, 0.094 mmol, 62%).

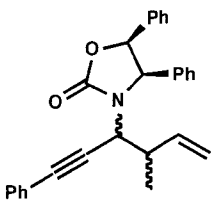
Procedure C (Scheme 130): A solution of optically active (4*R*,5*S*)-4,5-diphenyl-3-(3-

phenyl-1-(trimethyl-silyloxy)prop-2-ynyl)oxazolidin-2-one **231** (216 mg, 0.297 mmol) in CH_2Cl_2 (2 mL) was cooled to -78 °C and treated with $TiCl_4$ (594 μL, 0.594 mmol, 1 M in CH_2Cl_2). After warming the mixture to 0 °C and stirring for 30 min, it was recooled to -78 °C and allyltrimethylsilane (142 μL, 0.890 mmol) was added. The reaction was warmed to 0 °C and allowed to stir for 30 min before quenching with 10% KF (aq) and warming to room temperature. After extracting the mixture twice with CH_2Cl_2, the solvent was removed in vacuo to afford crude **241** (203 mg) as a dark brown oil. It was dissolved in methanol (5 mL), and ammonium cerric nitrate (589 mg, 1.074 mmol) was added portion-wise at room temperature until gas evolution ceased and the solution turned clear orange. After quenching with water (10 mL), the mixture was extracted with ether (10 mL, 3 times). The organic layers were combined and dried with $MgSO_4$. Removal of the solvent in vacuo yielded an off-white solid (119 mg, 94:6 dr). Purification by flash chromatography (10:1 hexane/ethyl acetate) afforded the product as a white solid (88 mg, one diastereomer by ^1H NMR, 0.223 mmol, 73%). $[\alpha]^{20}_D$ -176.0° (*c* 0.35, $CHCl_3$); mp 148-149 °C. Recrystallization from CH_2Cl_2/hexane provided crystals for X-ray analysis (see Appendix A).

General procedure for the allylation studies of **230** (Scheme 126). A solution of (4*R*,5*S*)-4,5-diphenyl-3-(3-phenyl-1-(trimethylsilyloxy)prop-2-ynyl)oxazolidin-2-one-dicobalt hexacarbonyl complex **230** in CH_2Cl_2 (~ 0.1 M) was cooled to -78 °C and treated with allyltrimethylsilane (3 eq.) followed by Lewis acid. After warming to the appropriate temperature and stirring for the prescribed time, the reaction was quenched with $NaHCO_3$ (aq) and warmed to room temperature. After extracting the mixture twice with ether, the

organic layers were combined and dried with $MgSO_4$. Removal of the solvent in vacuo afforded the crude product **241** as a dark brown oil.

General procedure for the equilibration/allylation studies of **230** (Scheme 129). A solution of (4*R*,5*S*)-4,5-diphenyl-3-(3-phenyl-1-(trimethylsilyloxy)prop-2-ynyl)oxazolidin-2-one-dicobalt hexacarbonyl complex **230** in CH_2Cl_2 (~ 0.1 M) was cooled to the reported temperature and treated with Lewis acid. After stirring for the prescribed time, allyltrimethylsilane (3 eq.) was added and the mixture was allowed to stir for 0.5 h. The reaction was quenched with $NaHCO_3$ (aq) and warmed to room temperature. After extracting the mixture twice with CH_2Cl_2, the organic layers were combined and dried with $MgSO_4$. Removal of the solvent in vacuo afforded the crude product **241** as a dark brown oil.



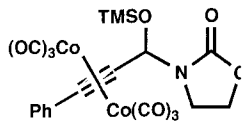
255-258

(4*R*,5*S*)-3-(4-Methyl-1-phenylhex-5-en-1-yn-3-yl)-4,5-diphenyloxazolidin-2-one (255-258). Procedure A (Scheme 154): To a solution of (4*R*,5*S*)-4,5-diphenyl-3-(3-phenyl-1-(trimethylsilyloxy)-prop-2-ynyl)-oxazolidin-2-one **231** (98 mg, 0.222 mmol) in CH_2Cl_2 (1.6 mL) was cannulated a solution of (*E*)-crotyltrimethyl-silane **254** (89 mg, 0.694 mmol) in CH_2Cl_2 (400 μL). After cooling the mixture to 0 °C, BF_3•OEt_2 (56 μL, 0.443 mmol) was added, and the reaction was allowed to stir for 30 min. Following an aqueous quench, the mixture was extracted twice with CH_2Cl_2. The organic layers were combined and dried with $MgSO_4$. Removal of the solvent in vacuo afforded a viscous yellow oil (110 mg). Purification by flash chromatography (9:1 hexane/ethyl acetate) provided an off-white

solid comprising an inseparable mixture of four diastereomers (74 mg, 0.182 mmol, 82%). ^{1}H NMR δ 7.48-7.41 (m), 7.38-7.30 (m), 7.23-6.75 (m), 6.12-5.94 (m), 5.94-5.82 (m), 5.79 (d, J = 7.6 Hz), 5.43-5.19 (m), 5.16 (d, J = 7.3 Hz), 5.10 (d, J = 7.6 Hz), 5.00-4.88 (m), 4.91 (d, J = 5.8 Hz), 4.82 (d, J = 8.7 Hz), 4.62 (d, J = 9.8 Hz), 4.51 (d, J = 10.6 Hz), 3.10-2.88 (m), 2.21-2.06 (m), 1.28 (d, J = 6.5 Hz), 1.24 (d, J = 6.9 Hz), 1.20 (d, J = 6.9 Hz), 1.07 (d, J = 6.5 Hz); ^{13}C NMR δ 158.57, 158.16, 157.85, 140.53, 139.67, 139.50, 136.31, 135.69, 135.56, 135.24, 134.32, 134.17, 132.10, 131.73, 129.29, 129.06, 128.95, 128.69, 128.58, 128.48, 128.27, 128.22, 128.19, 128.11, 128.04, 127.67, 126.59, 126.52, 126.36, 126.25, 126.59, 126.52, 126.36, 126.25, 122.75, 122.41, 122.27, 117.29, 116.78, 116.14, 88.49, 87.41, 85.21, 84.87, 83.46, 81.26, 81.02, 80.03, 79.89, 65.05, 64.03, 54.07, 51.93, 51.32, 44.83, 43.15, 42.84, 42.20, 17.74, 17.69, 17.35; IR (neat) 3064, 3034, 2973, 2928, 2359, 2340, 2248, 1951, 1750 cm^{-1}; HRMS-FAB (*m/z*): $[M+H]^{+}$ calcd for $C_{28}H_{25}NO_2$, 408.1963; found, 408.1961.

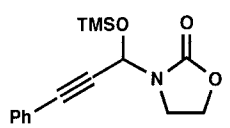
Procedure B (Scheme 155): A solution of (4*R*,5*S*)-4,5-diphenyl-3-(3-phenyl-1-(trimethylsilyloxy)prop-2-ynyl)oxazolidin-2-one-dicobalt hexacarbonyl complex **230** (265 mg, 0.364 mmol) in CH_2Cl_2 (2.4 mL) was cooled to -78 °C and treated with $TiCl_4$ (80 μL, 0.728 mmol). After warming the mixture to 0 °C and stirring for 30 min, a solution of (*E*)-crotyltrimethylsilane **254** (166 mg, 1.294 mmol) in CH_2Cl_2 (400 μL) was cannulated into the vessel, and the reaction was allowed to stir for 70 min. Following an aqueous quench and warming to room temperature, the mixture was extracted with ether. The organic layer was dried with $MgSO_4$, and the solvent was removed in vacuo to afford a dark brown residue (267 mg) which was dissolved in methanol (5 mL) and treated with ammonium cerric nitrate (664 mg, 1.211 mmol). After quenching with water (10 mL),

the mixture was extracted with ether (10 mL, 3 times). The organic layers were combined and dried with $MgSO_4$. Removal of the solvent in vacuo yielded the crude product (162 mg), comprising two diastereomers. Purification by flash chromatography (10:1 hexane/ethyl acetate) afforded the product as a white solid comprising two diastereomers (66 mg, 0.162 mmol, 44%).



259

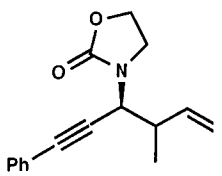
3-(3-Phenyl-1-(trimethylsilyloxy)prop-2-ynyl)oxazolidin-2-one-dicobalt hexacarbonyl complex (259). Dicobalt octacarbonyl (1.53 g, 4.474 mmol) was added in two portions to a solution of 3-(3-phenyl-1-(trimethylsilyloxy)-prop-2-ynyl)oxazolidin-2-one **260** (670 mg, 2.315 mmol) in CH_2Cl_2 (15 mL) at room temperature. After stirring the reaction for 1 h, the solvent was removed in vacuo. Purification by flash chromatography (5:1 hexane/ether, 4:1 hexane/ether) yielded the product as a dark brown, viscous oil (0.99 g, 1.721 mmol, 74%). ^{1}H NMR δ 7.62-7.56 (m, 2H), 7.40-7.30 (m, 3H), 6.74 (s, 1H), 4.31 (m, 1H), 4.19 (dd, J = 8.4 Hz, 16.8 Hz, 1H), 3.73 (dd, J = 8.7 Hz, 17.2 Hz, 1H), 3.36 (m, 1H), 0.25 (s, 9H); ^{13}C NMR δ 157.06, 137.51, 130.13, 129.27, 128.40, 78.88, 62.59, 40.03, -0.03; IR (neat) 2958, 2916, 2244, 1758 cm^{-1}; anal. Cacld for $C_{21}H_{19}Co_2NO_9Si$: C, 43.84; H, 3.33; N, 2.43. Found: C, 43.79; H, 3.41; N, 2.42.



260

3-(3-Phenyl-1-(trimethylsilyloxy)prop-2-ynyl)oxazolidin-2-one (260). A solution of 3-(3-phenylpropioloyl)oxazolidin-2-one **263** (58 mg, 0.272 mmol) in CH_2Cl_2 (1.8 mL) was cooled to -78 °C. Dibal-H (326 μL, 0.326 mmol) was added dropwise, and the reaction was stirred for 1 h.

Pyridine (88 μL, 1.088 mmol) then TMSOTf (109 μL, 0.544 mmol) were added; the reaction was warmed to 0 °C and allowed to stir for 15 min. The reaction was quenched with 20% aqueous Rochelle's salt solution, warmed to room temperature, then extracted twice with Et_2O. The organic layers were combined and dried with $MgSO_4$. The solvent was removed in vacuo to give an oil. Purification by flash chromatography (6:1 hexane/ethyl acetate) afforded the product (34 mg, 0.117 mmol, 43%). ^1H NMR δ 7.48-7.41 (m, 2H), 7.37-7.28 (m, 3H), 6.25 (s, 1H), 4.39 (t, J = 8.06 Hz, 2H), 3.82 (app t, 2H), 0.25 (s, 9H); ^{13}C NMR δ 132.03, 129.27, 128.62, 121.83, 85.54, 84.99, 69.44, 62.78, 40.29, 0.41; IR (neat) 2958, 2916, 2244, 1758 cm^{-1}.

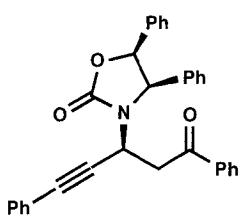


264

3-(4-Methyl-1-phenylhex-5-en-1-yn-3-yl)oxazolidin-2-one (264). A solution of 3-(3-phenyl-1-(trimethylsilyloxy)prop-2-ynyl)oxazolidin-2-one **260** (56 mg, 0.194 mmol) in CH_2Cl_2 (1.2 mL) was cooled to -78 °C. (*Z*)-crotylsilane (76 mg, 0.592 mmol, in 200 μL CH_2Cl_2) then $TiCl_4$ (42 μL, 0.387 mmol) were added. After stirring for 10 min at -78 °C the reaction was quenched with water, warmed to room temperature, and extracted twice with CH_2Cl_2. The organic layers were combined and dried with $MgSO_4$. The solvent was removed in vacuo to give the crude product as an oil (66 mg, 1.8:1 dr). Purification by flash chromatography (4:1 hexane/ethyl acetate) afforded an off-white solid comprising an inseperable 2:1 mixture of diastereomers (40 mg, 0.156 mmol, 80%). ^1H NMR δ 7.46-7.39 (m, 2H), 7.36-7.29 (m, 3H), 5.97 (ddd, J = 8.0 Hz, 9.7 Hz, 17.7 Hz, 0.67H), 5.79 (ddd, J = 8.4 Hz, 9.5 Hz, 17.9 Hz, 0.33H), 5.26-5.04 (m, 2H), 4.75 (d, J = 7.3 Hz, 0.67H), 4.71 (d, J = 9.5 Hz, 0.33H), 4.44-4.26 (m, 2H), 3.82 (m, 1H), 3.72-3.50

(m, 1H), 2.70-2.50 (m, 1H), 1,26 (d, J = 6.6 Hz, 0.33H), 1.15 (d, J = 6.9 Hz, 0.67H); ^{13}C NMR δ 158.18, 139.74, 139.52, 131.99, 128.88, 128.58, 122.48, 116.81, 116.36, 84.80, 84.04, 62.56, 62.50, 51.99, 51.51, 43.08, 42.88, 42.49, 41.56, 18.16, 17.67; IR (neat) 3079, 2974, 2925, 1747 cm^{-1}; HRMS-FAB (m/z): $[M + H]^+$ calcd for $C_{16}H_{17}NO_2$, 256.1337; found 256.1337.

General procedure for the achiral crotylation studies of **259** (Scheme 153). A solution of 3-(3-phenyl-1-(trimethylsilyloxy)prop-2-ynyl)oxazolidin-2-one-dicobalt hexacarbonyl complex **259** in CH_2Cl_2 (~ 0.15 M) was cooled to 0 °C and treated with $TiCl_4$. After stirring for 10 min, an (*E*)/(*Z*)-crotyltrimethylsilane solution in CH_2Cl_2 (200 μL) was cannulated to the mixture, and the reaction was allowed to stir for 30 min. Following a quench with water, the mixture was warmed to room temperature and extracted with ether, which was subsequently dried with $MgSO_4$. The solvent was removed in vacuo to afford a dark brown residue which was immediately dissolved in methanol (~ 0.05 M) and treated with ammonium cerric nitrate until gas evolution ceased, and TLC analysis indicated the disappearance of starting material. The product was purified by flash chromatography (4:1 hexane/ethyl acetate).



278

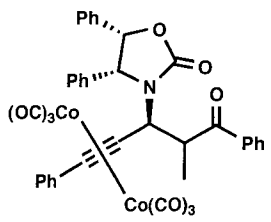
(4*R*,5*S*)-3-(5-Oxo-1,5-diphenylpent-1-yn-3-yl)-4,5-diphenyl-oxazolidin-2-one (278). To a solution of (4*R*,5*S*)-4,5-diphenyl-3-(3-phenyl-1-(trimethylsilyloxy)prop-2-ynyl)oxa-zolidin-2-one **231** (42 mg, 0.095 mmol) in CH_2Cl_2 (600 μL) was added trimethyl(1-phenylvinyloxy)silane **277** (21 μL, 0.104 mmol) followed by $BF_3 \cdot OEt_2$ (13 μL, 0.104

mmol). The reaction was allowed to stir for 2 h at room temperature. After quenching with $NaHCO_3$ (aq), the solution was extracted twice with CH_2Cl_2. The organic layers were combined and dried with $MgSO_4$. The removal of the solvent in vacuo afforded a 1.8:1 mixture of product diastereomers (46 mg). Purification by flash chromatography (6:1 hexane/ethyl acetate) afforded a white solid comprising a 1.8:1 mixture of diastereomers (36 mg, 0.076 mmol, 80%). Major diastereomer: ^{1}H NMR δ 7.84 (m, 2H), 7.66-7.00 (m, 18H), 5.88 (d, J = 8.4 Hz, 1H), 5.45 (d, J = 8.4 Hz, 1H), 5.26 (dd, J = 5.8 Hz, 8.0 Hz, 1H), 3.92 (dd, J = 8.4 Hz, 17.5 Hz, 1H), 3.15 (dd, J = 5.6 Hz, 17.7 Hz, 1H). Minor diastereomer: ^{1}H NMR δ 8.4 (m, 2H), 7.66-6.86 (m, 18H), 5.81 (d, J = 8.0 Hz, 1H), 5.37 (d, J = 8.0 Hz, 1H), 5.14 (t, J = 6.5 Hz, 1H), 3.87 (dd, J = 3.3 Hz, 6.6 Hz, 2H). ^{13}C NMR δ 196.47, 158.08, 156.92, 136.75, 136.36, 135.41, 134.82, 134.63, 133.79, 132.09, 131.98, 129.03, 128.90, 128.84, 128.71, 128.58, 128.51, 128.35, 128.25, 128.21, 128.13, 128.06, 126.41, 126.22, 122.56, 122.22, 85.94, 85.71, 85.27, 85.16, 80.48, 80.14, 66.17, 65.42, 43.83, 43.18, 42.42; IR (neat) 3063, 3034, 2923, 2249, 1750, 1685, 1597, 1580 cm^{-1}; HRMS-FAB (*m/z*): $[M+H]^+$ calcd for $C_{32}H_{25}NO_3$, 472.1912; found, 472.1898.

General procedure for the alkylation studies of **230** with trimethyl(1-phenylvinyloxy)-silane **277** (Scheme 166). A solution of (4*R*,5*S*)-4,5-diphenyl-3-(3-phenyl-1-(trimethyl-silyloxy)prop-2-ynyl)oxazolidin-2-one-dicobalt hexacarbonyl complex **230** in CH_2Cl_2 (~ 0.15 M) was cooled to -78 °C and treated with Lewis acid. After warming the mixture to 0 °C and stirring for 30 min, it was recooled to -78 °C, treated with trimethyl(1-phenyl-vinyloxy)-silane **277**, then rewarmed to 0 °C. Aqueous quench, ether extraction, and removal of the solvent in vacuo afforded a dark brown residue.

Procedure for the alkylation studies of **259** with (*Z*)-trimethyl(1-phenylprop-1-enyl-oxy)silane **280** (Entries 1 and 3, Scheme 169). A solution of 3-(3-phenyl-1-(trimethylsilyloxy)prop-2-ynyl)oxazolidin-2-one-dicobalt hexacarbonyl complex **259** in CH_2Cl_2 (~ 0.1 M) and (*Z*)-trimethyl(1-phenylprop-1-enyloxy)silane **280** was cooled to -78 °C and treated with Lewis acid. After stirring at 0 °C, the reaction was quenched with water and extracted with ether. Removal of the solvent in vacuo afforded a dark brown residue.

Procedure for the alkylation studies of **259** with (*Z*)-trimethyl(1-phenylprop-1-enyloxy)silane **280** (Entry 2, Scheme 169). A solution of 3-(3-phenyl-1-(trimethylsilyloxy)prop-2-ynyl)oxazolidin-2-one-dicobalt hexacarbonyl complex **259** in CH_2Cl_2 (0.16 M) was cooled to -78 °C and treated with $TiCl_4$ (2 eq.). The mixture was warmed to 0 °C and stirred for 30 min. After recooling to -78 °C, (*Z*)-trimethyl(1-phenylprop-1-enyloxy)silane **280** (3 eq., in CH_2Cl_2) was cannulated into the vessel, and the reaction was allowed to stir at 0 °C for 40 min. Following an aqueous quench and an ether extract, the solvent was removed in vacuo.

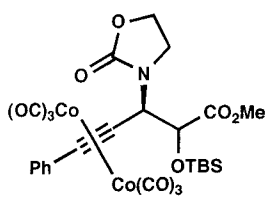


282

3-(4-Methyl-5-oxo-1,5-diphenylpent-1-yn-3-yl)oxazolidin-2-one-dicobalt hexacarbonyl complex (282). A solution of 3-(3-phenyl-1-(trimethyl-silyloxy)prop-2-ynyl)oxazolidin-2-one-dicobalt hexacarbonyl complex **259** (78 mg, 0.107 mmol) and (*Z*)-trimethyl(1-phenylprop-1-enyloxy)silane **280** (32 mg, 0.155 mmol) in CH_2Cl_2 (1 mL)

was cooled to -78 °C and treated with BF_3•OEt_2 (43 μL, 0.339 mmol). After warming to room temperature and stirring for 1 h, the mixture was quenched with water and extracted with ether. Drying of the organic layer with $MgSO_4$ followed by removal of the solvent in vacuo afforded an oil (86 mg, >95:5 dr). Purification by flash chromatography (neutral Al_2O_3, 12:1 hexane/ethyl acetate) afforded the product as an oil comprising one diastereomer (32 mg, 0.041 mmol, 39%). ^{1}H NMR (C_6D_6) δ 8.00-7.93 (m, 2H), 7.45-7.39 (m, 2H), 7.11-6.84 (m, 6H), 6.83-6.71 (m, 10H), 5.45 (d, J = 10.2 Hz, 1H), 5.36-5.27 (m, 1H), 5.25 (d, J = 9.1 Hz, 1H), 5.11 (d, J = 9.1 Hz, 1H).

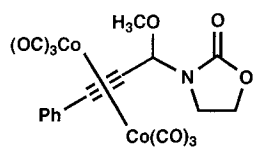
Procedure for the alkylation studies of **259** with (*Z*)-silylketene acetal **286** (Scheme 174) and (*E*)-silylketene acetal (Scheme 175). A solution of of 3-(3-phenyl-1-(trimethylsilyl-oxy)prop-2-ynyl)oxa-zolidin-2-one-dicobalt hexacarbonyl complex **259** in CH_2Cl_2 (~ 0.1 M) was cooled to 0 °C and treated with Lewis acid. After stirring for 10 min, (*Z*)-silyl-ketene acetal **286** (solution in CH_2Cl_2) was cannulated into the flask, and the reaction was stirred at that temperature. The reaction was quenched by the addition of water, and the mixture was extracted with ether. The organic layer was dried with $MgSO_4$, and the solvent removed in vacuo.



287

Methyl 2-(tert-butyldimethylsilyloxy)-3-(2-oxooxazolidin-3-yl)-5-phenylpent-4-ynoate-dicobalt hexacarbonyl complex (287). A solution of 3-(3-phenyl-1-(trimethylsilyloxy)prop-2-ynyl)oxa-zolidin-2-one-dicobalt hexacarbonyl complex **259** (103 mg, 0.179 mmol) in CH_2Cl_2 (1.2 mL) was cooled to 0 °C. After adding $TiCl_4$ (39 mL, 0.358 mmol)

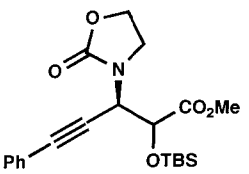
the reaction was stirred at 0 °C for 10 min. (*E*)-silylketene acetal (154 mg, 0.557 mmol, in 200 μL CH_2Cl_2) was cannulated into the flask, and the reaction was stirred at 0 °C for 75 min before quenching with water and extracting the mixture with ether. The organic phase was dried with $MgSO_4$. The solvent was removed in vacuo to give the crude product (174 mg) as a 4.1:1 mixture of diastereomers. Purification by flash chromatography (4:1 hexane/ether) afforded major (80 mg, 0.116 mmol, 65%) and minor (20 mg, 0.029 mmol, 16%) diastereomers as dark brown oils. Major diastereomer: ^{1}H NMR δ 7.43-7.28 (m, 5H), 5.46 (br s, 1H), 4.62 (br s, 1H), 4.34-4.14 (m, 2H), 3.80-3.62 (m, 2H), 3.25 (s, 3H), 0.88 (s, 9H), 0.06 (s, 3H), 0.02 (s, 3H); ^{13}C NMR δ 199.28, 171.22, 158.08, 137.86, 129.60, 129.06, 128.16, 73.64, 62.32, 52.40, 25.96, 18.45, -4.87, -4.96; IR (neat) 2954, 2930, 2858, 2359, 2093, 2055, 2025, 1755 cm^{-1}; HRMS-FAB (*m/z*): $[M + H]^+$ calcd for $C_{27}H_{29}Co_2NO_{11}Si$, 690.0207; found 690.0236. Minor diastereomer: ^{1}H NMR δ 7.51-7.45 (m, 2H), 7.38-7.29 (m, 3H), 5.91 (d, J = 4.0 Hz, 1H), 4.80 (d, J = 3.6 Hz, 1H), 4.21 (dd, J = 8.4 Hz, 16.4 Hz, 1H), 4.14-4.04 (m, 1H), 3.90-3.79 (m, 1H), 3.60 (s, 3H), 3.45 (dd, J = 8.7 Hz, 16.4 Hz, 1H), 0.90 (s, 9H), 0.12 (s, 3H), 0.01 (s, 3H); ^{13}C NMR δ 170.96, 158.00, 138.15, 129.63, 129.22, 128.24, 76.75, 62.51, 59.44, 52.47, 43.47, 26.23, 18.95, -4.59, -4.70; IR (neat) 2954, 2928, 2857, 2093, 2056, 2025, 1755 cm^{-1}; HRMS-FAB (*m/z*): $[M + H]^+$ calcd for $C_{27}H_{29}Co_2NO_{11}Si$, 690.0207; found 690.0282.



288

3-(1-Methoxy-3-phenylprop-2-ynyl)oxazolidin-2-one-dicobalt hexacarbonyl complex (288). See procedure above for Scheme 175 (entry 2). Purification by flash chromatography (2:1 hexane/ether) afforded a dark brown oil (22 mg). ^{1}H NMR δ 7.61-7.51 (m, 2H), 7.40-

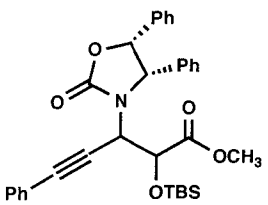
7.31 (m, 3H), 6.30 (s, 1H), 4.39 (dt ,J = 5.6 Hz, 8.9 Hz, 1H), 4.24 (app q, 1H), 3.66 (app q, 1H), 3.58 (s, 3H), 3.38 (dt, J = 5.8 Hz, 9.1 Hz, 1H); see Appendix C for HSQC spectrum; LRMS *m/z* (relative intensity): 485.85 (40.4%), 460.90 (90.1%), 404.98 (100.0%), 377.00 (36.1%).



289

Methyl 2-(tert-butyldimethylsilyloxy)-3-(2-oxooxazolidin-3-yl)-5-phenylpent-4-ynoate (289). To a solution of 3-(3-phenyl-1-(trimethylsilyloxy)prop-2-ynyl)oxazolidin-2-one **260** (62 mg, 0.214 mmol) at 0 °C was added (*Z*)-silylketene acetal (210 mg, 0.659 mmol, in 200 μL CH_2Cl_2), followed by BF_3•OEt_2 (54 μL, 0.428 mmol). After stirring for 30 min at 0 °C, the reaction was quenched with water, warmed to room temperature, and extracted twice with CH_2Cl_2. The organic layers were combined and dried with $MgSO_4$. The solvent was removed in vacuo to give the crude product as an oil (175 mg, 1.2:1 dr). Purification by flash chromatography (6:1 hexane/ethyl acetate) afforded major (42 mg, 0.104 mmol, 49%) and minor (37 mg, 0.092 mmol, 43%) diastereomers. Major diastereomer: ^{1}H NMR δ 7.45-7.40 (m, 2H), 7.36-7.31 (m, 3H), 5.38 (d, J = 2.9 Hz, 1H), 4.58 (d, J = 2.9 Hz, 1H), 4.38-4.28 (m, 2H), 4.00-3.90 (m, 1H), 3.88-3.77 (m, 1H), 3.76 (s, 3H), 0.95 (s, 9H), 0.13 (s, 3H), 0.12 (s, 3H); ^{13}C NMR δ 170.64, 158.19, 132.01, 129.05, 128.62, 122.19, 86.94, 82.90, 75.41, 63.06, 52.77, 50.78, 43.58, 25.99, 18.70, -4.62, -5.06; IR (neat) 2953, 2929, 2894, 2857, 2359, 2341, 1755;; HRMS-FAB (*m/z*): $[M + H]^+$ calcd for $C_{21}H_{29}NO_5Si$, 404.1893; found 404.1888. Minor diastereomer: ^{1}H NMR δ 7.45-7.38 (m, 2H), 7.36-7.29 (m, 3H), 5.22 (d, J = 6.2 Hz, 1H), 4.54 (d, J = 6.2 Hz, 1H), 4.44-4.26 (m, 2H), 3.92-3.76 (m, 2H), 3.76 (s, 3H), 0.94 (s, 9H), 0.11 (s, 3H), 0.09 (s, 3H); ^{13}C NMR δ

170.75, 157.73, 132.08, 129.07, 128.58, 122.19, 87.39, 82.14, 74.44, 62.82, 52.66, 50.86, 43.32, 26.03, 18.64, -4.64; IR (neat) 2953, 2929, 2896, 2857, 1755 cm^{-1}; HRMS-FAB (*m/z*): $[M + H]^+$ calcd for $C_{21}H_{29}NO_5Si$, 404.1893; found 404.1894.



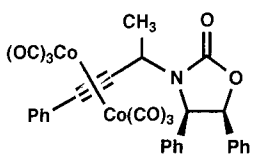
290

Methyl 2-(*tert*-butyldimethylsilyloxy)-3-((4*S*,5*R*)-2-oxo-4,5-diphenyloxazolidin-3-yl)-5-phenylpent-4-ynoate (290).

Procedure A: To a solution of (±)-(4*R*,5*S*)-4,5-diphenyl-3-(3-phenyl-1-(trimethylsilyl-oxy)-prop-2-ynyl)oxazolidin-2-one **231** (101 mg, 0.228 mmol) in CH_2Cl_2 (1.6 mL) was cannulated a solution of (*E*)-crotyl-trimethylsilane **285** (197 mg, 0.712 mmol) in CH_2Cl_2 (400 μL). The mixture was cooled to 0 °C and treated with BF_3•OEt_2 (58 μL, 0.457 mmol). After stirring for 30 min, the reaction was quenched with water, and extracted twice with CH_2Cl_2. The organic layers were combined, dried with $MgSO_4$. Removal of the solvent in vacuo provided a viscous yellow oil (194 mg). Purification by flash chromatography (9:1 hexane/ethyl acetate) afforded an oil comprising a mixture of four product diastereomers (86 mg, 0.155 mmol, 68%). ^1H NMR δ 7.39-7.32 (m), 7.19-6.86 (m), 6.77-6.72 (m), 6.67-6.62 (m), 5.82-5.77 (m), 5.55 (d, *J* = 7.4 Hz), 5.45 (d, *J* = 2.9 Hz), 5.25 (d, *J* = 7.6 Hz), 5.24 (d, *J* = 8.5 Hz), 5.21 (d, *J* = 5.9 Hz), 4.86 (d, *J* = 2.5 Hz), 4.84 (d, *J* = 5.7 Hz), 4.81 (d, *J* = 8.5 Hz), 4.63 (d, *J* = 2.7 Hz), 4.47 (d, *J* = 8.5 Hz), 4.38 (d, *J* = 2.5 Hz), 3.77 (s), 3.73 (s), 3.72 (s), 3.64 (s), 0.94 (s), 0.90 (s), 0.90 (s), 0.12 (s), 0.11 (s), 0.10 (s), 0.09 (s), 0.02 (s); ^{13}C NMR δ 171.46, 171.24, 157.86, 157.75, 157.04, 135.80, 134.95, 134.55, 134.18, 132.20, 132.00, 131.85, 131.63, 129.34, 129.01, 128.90, 128.68, 128.65, 128.54, 128.34, 128.28, 128.17, 128.12, 128.05, 127.95, 127.79, 126.50, 126.37, 125.61, 122.58, 122.44, 122.09, 122.05,

88.25, 88.02, 87.62, 87.25, 85.81, 83.19, 82.23, 82.13, 81.84, 81.42, 80.37, 76.12, 75.58, 73.79, 73.59, 68.06, 65.53, 65.05, 64.65, 52.89, 52.60, 52.43, 51.65, 50.61, 49.75; IR (neat) 3064, 3034, 2952, 2928, 2895, 2856, 1762 cm^{-1}; HRMS-FAB (*m/z*): $[M+H]^+$ calcd for $C_{33}H_{37}NO_5Si$, 556.2519; found, 556.2533.

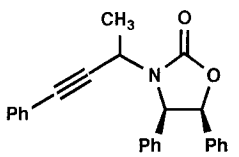
Procedure B: A solution of chiral (4*R*,5*S*)-4,5-Diphenyl-3-(3-phenyl-1-(trimethylsilyl-oxy)prop-2-ynyl)oxazolidin-2-one-dicobalt hexacarbonyl complex **230** (82 mg, 0.112 mmol) in CH_2Cl_2 (800 μL) was cooled to 0 °C and treated with $TiCl_4$ (49 μL, 0.450 mmol) for 10 min. To the mixture was cannulated a solution of (*Z*)-crotyltrimethylsilane **285** (220 mg, 0.690 mmol) in CH_2Cl_2 (400 μL). After stirring for 20 min, the reaction was quenched with water and extracted with ether. The organic layer was dried with $MgSO_4$ and the solvent removed in vacuo to afford a dark brown residue (248 mg) which was dissolved in methanol (4 mL) and treated with ammonium cerric nitrate (220 mg, 0.401 mmol). After quenching with water, the mixture was extracted with ether (3 times). The organic layers were combined and dried with $MgSO_4$. Removal of the solvent in vacuo yielded the crude product (146 mg). Purification by flash chromatography (9:1 hexane/ethyl acetate) afforded the product (53 mg, 0.095 mmol, 85%).



300

(4*R*,5*S*)-4,5-Diphenyl-3-(4-phenylbut-3-yn-2-yl)oxazolidin-2-one-dicobalt hexacarbonyl complex (300). To a solution of (4*R*,5*S*)-4,5-diphenyl-3-(3-phenyl-1-(trimethylsilyloxy)prop-2-ynyl)oxazolidin-2-one-dicobalt hexacarbonyl complex **230** (97 mg, 0.133 mmol) in CH_2Cl_2 (1 mL) was added $TiCl_4$ (29 μL, 0.266 mmol) at 0 °C. The

solution was allowed to stir for 10 min then it was cooled to -78 °C and Me_2Zn (200 mL, 0.399 mmol, 2 M in toluene) was added. After stirring the reaction for 30 min it was quenched by the careful addition of water then warmed to room temperature. The mixture was extracted twice with ether. The organic layers were combined and dried with $MgSO_4$. After removal of the solvent in vacuo a viscous dark brown oil (76 mg, >95:5 dr) was collected. Purification by flash chromatography (5:1 hexane/ether) yielded the diastereomerically pure product as an oil (44 mg, 0.067 mmol, 51%). ^1H NMR δ 7.54-7.46 (m, 2H), 7.44-7.32 (m, 3H), 7.14-7.00 (m, 8H), 6.94-6.86 (m, 2H), 5.88 (q, J = 6.9 Hz, 1H), 5.69 (d, J = 7.3 Hz, 1H), 5.08 (d, J = 7.3 Hz, 1H), 1.17 (d, J = 6.9 Hz, 3H); ^{13}C NMR δ 199.23, 158.40, 137.88, 137.06, 134.13, 129.48, 129.45, 128.57, 128.45, 128.21, 128.15, 126.37, 99.40, 92.31, 80.99, 62.58, 53.23, 22.55; IR (neat) 3066, 3034, 2985, 2936, 2359, 2091, 2053, 2022, 1755 cm^{-1}; HRMS-FAB (*m/z*): $[M+H]^+$ calcd for $C_{31}H_{21}Co_2NO_8$, 654.0009; found, 653.9993.



301

(4*R*,5*S*)-4,5-Diphenyl-3-(4-phenylbut-3-yn-2-yl)oxazolidin-2-one (301). To a solution of (4*R*,5*S*)-4,5-diphenyl-3-(3-phenyl-1-(trimethylsilyloxy)prop-2-ynyl)oxazolidin-2-one-dicobalt hexacarbonyl complex **230** (139 mg, 0.191 mmol) in CH_2Cl_2 (1.5 mL) was added $TiCl_4$ (382 μL, 0.382 mmol, 1 M in CH_2Cl_2) at -78 °C. After warming the reaction to 0 °C and stirring for 30 min, Me_2Zn (286 μL, 0.573 mmol, 2 M in toluene) was added at -78 °C and the reaction allowed to stir for 20 min. With a careful aqueous quench, the reaction was warmed to room temperature and extracted twice with ether. The combined organic layers were dried with $MgSO_4$. Removal of the solvent in vacuo

provided a dark brown residue (122 mg) which was dissolved in methanol (5 mL) and treated with CAN portion-wise (402 mg, 0.733 mmol) until the starting material had disappeared by TLC and the solution became clear orange. Water (10 mL) was added and the reaction extracted twice with ether (10 mL). The organic layers were combined and dried with $MgSO_4$. Removal of the solvent in vacuo afforded an off-white solid (76 mg). Purification by flash chromatography (9:1 hexane/ethyl acetate) provided the product as a white solid (38 mg, 0.103 mmol, 54% for two steps). ^{1}H NMR δ 7.50-7.42 (m, 2H), 7.40-7.32 (m, 3H), 7.14-6.96 (m, 10H), 5.92 (d, J = 8.4 Hz, 1H), 5.35 (d, J = 8.4 Hz, 1H), 5.18 (q, J = 7.1 Hz, 1H), 1.17 (d, J = 6.9 Hz, 3H); ^{13}C NMR δ 157.76, 136.62, 134.85, 132.17, 129.05, 128.75, 128.62, 128.33, 128.19, 128.09, 126.30, 122.61, 86.94, 85.34, 80.47, 63.81, 43.96, 22.03; IR (neat) 3034, 2983, 2932, 1739 cm^{-1}; mp 134-135 °C; $[\alpha]^{20}_D$ -180.0° (*c* 0.17, $CHCl_3$); HRMS-FAB (*m/z*): $[M+H]^+$ calcd for $C_{25}H_{21}NO_2$, 368.1650; found, 368.1636.

Procedure for the vinylation studies of **230** (Scheme 189). A solution of (4*R*,5*S*)-4,5-diphenyl-3-(3-phenyl-1-(trimethylsilyloxy)prop-2-ynyl)oxazolidin-2-one-dicobalt hexacarbonyl complex **230** in THF (~ 0.1 M) was cooled to -78 °C and treated with Lewis acid. After warming to 0 °C and stirring for 30 min, the mixture was recooled to -78 °C and vinyl magnesium bromide (1 M, in THF) was added. The reaction was quenched with water and extracted with ether. The organic layer was dried with $MgSO_4$ and the solvent was removed in vacuo.

Procedure for the ethylation studies of **230** (Scheme 192). A solution of (4*R*,5*S*)-4,5-diphenyl-3-(3-phenyl-1-(trimethylsilyloxy)prop-2-ynyl)oxazolidin-2-one-dicobalt hexacarbonyl complex **230** in CH_2Cl_2 or THF (~ 0.1 M) was cooled to -78 °C and treated with $TiCl_4$. After stirring at 0 °C for 30 min, the ethylating reagent was added, and the mixture was stirred at the prescribed temperature. The reaction was quenched with water and extracted with ether. The organic layer was dried with $MgSO_4$, and the solvent was removed in vacuo.

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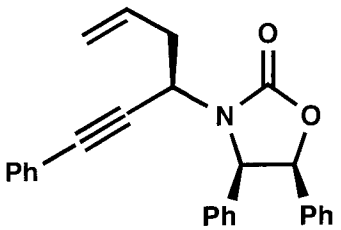
VII. Summary

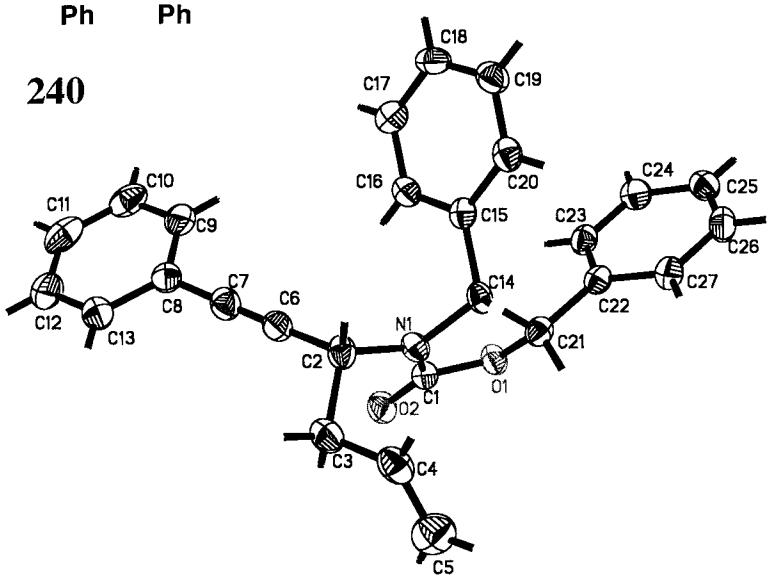
- Dicobalt cluster-stabilized α-cation methodology (*Nicholas cation*) extended to α-iminium motif.
- Dicobalt hexacarbonyl complex of propargyl *N,OTMS*-acetal diastereomers can be equilibrated to *one* diastereomer in the presence of $TiCl_4$. The nature of the cationic intermediate could not be determined.
- Equilibration/alkylation sequence of dicobalt hexacarbonyl complex of propargyl *N,OTMS*-acetal diastereomers led to the stereoselective synthesis of R-substituted propargyl amides (R = CH_3, allyl, CH_2COPh, and $CH(CH_3)COPh$).
- In the absence of a dicobalt cluster, propargyl *N,OTMS*-acetals reacted with reduced diastereoselectivity.

VIII. Appendix A

X-ray structure of (4*R*,5*S*)-4,5-Diphenyl-3-(1-phenylhex-5-en-1-yn-3-yl)oxazolidin-2-one (**240**).



240



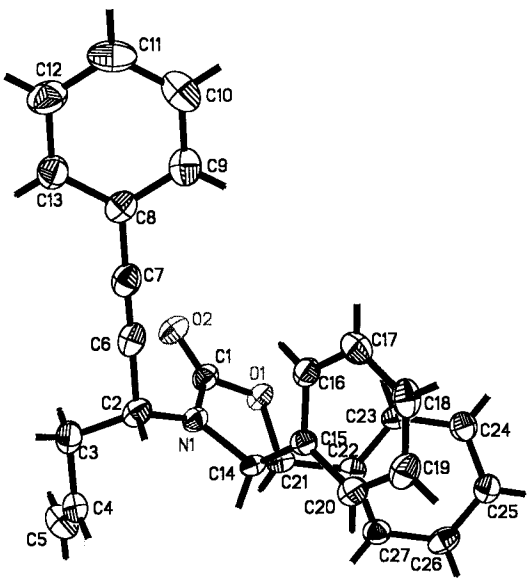


Table 1. Crystal data and structure refinement for lsh161.

Identification code	lsh161	
Empirical formula	C27 H23 N O2	
Formula weight	393.46	
Temperature	293(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P2(1)2(1)2(1)	
Unit cell dimensions	a = 6.0651(8) Å	α= 90°.
	b = 14.762(2) Å	β= 90°.
	c = 23.677(3) Å	γ = 90°.
Volume	2119.9(5) $Å^3$	
Z	4	
Density (calculated)	1.233 Mg/m^3	
Absorption coefficient	0.077 mm^{-1}	
F(000)	832	
Crystal size	0.14 x 0.06 x 0.03 mm^3	
Theta range for data collection	2.89 to 23.25°.	
Index ranges	-6<=h<=6, -16<=k<=16, -26<=l<=26	
Reflections collected	24296	
Independent reflections	3041 [R(int) = 0.0706]	
Completeness to theta = 23.25°	99.8 %	
Absorption correction	multi-scan	
Max. and min. transmission	0.9975 and 0.9892	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3041 / 0 / 272	
Goodness-of-fit on F^2	0.897	
Final R indices [I>2sigma(I)]	R1 = 0.0430, wR2 = 0.0964	
R indices (all data)	R1 = 0.0740, wR2 = 0.1176	
Extinction coefficient	0.023(2)	
Largest diff. peak and hole	0.188 and -0.191 $e.Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for lsh161. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
N(1)	-12(4)	4795(2)	1934(1)	27(1)
O(1)	1215(3)	6210(1)	1919(1)	30(1)
O(2)	3403(4)	5143(2)	2308(1)	36(1)
C(1)	1686(5)	5339(2)	2079(1)	29(1)
C(2)	-46(5)	3807(2)	2031(1)	30(1)
C(3)	-484(5)	3581(2)	2652(1)	36(1)
C(4)	-2513(5)	4035(2)	2863(2)	38(1)
C(5)	-2618(6)	4537(3)	3316(2)	49(1)
C(6)	1948(6)	3352(2)	1816(2)	33(1)
C(7)	3497(6)	2945(2)	1631(1)	34(1)
C(8)	5374(5)	2478(2)	1405(1)	31(1)
C(9)	6282(6)	2756(2)	892(2)	38(1)
C(10)	8180(6)	2345(3)	692(2)	45(1)
C(11)	9150(6)	1655(3)	992(2)	49(1)
C(12)	8241(6)	1367(3)	1496(2)	48(1)
C(13)	6363(5)	1773(2)	1702(2)	38(1)
C(14)	-1622(5)	5264(2)	1580(1)	26(1)
C(15)	-1352(5)	5049(2)	958(1)	25(1)
C(16)	603(5)	4715(2)	740(1)	29(1)
C(17)	824(5)	4509(2)	168(1)	34(1)
C(18)	-912(5)	4653(2)	-192(1)	34(1)
C(19)	-2865(6)	5007(2)	12(2)	36(1)
C(20)	-3085(5)	5198(2)	582(1)	30(1)
C(21)	-1100(5)	6250(2)	1756(1)	28(1)
C(22)	-1466(5)	6973(2)	1324(1)	25(1)
C(23)	147(5)	7209(2)	938(1)	30(1)
C(24)	-249(6)	7868(2)	535(1)	34(1)
C(25)	-2275(5)	8302(2)	513(1)	33(1)
C(26)	-3881(5)	8071(2)	900(2)	35(1)

C(27)	-3493(5)	7414(2)	1306(1)	31(1)

Table 3. Bond lengths [Å] and angles [°] for lsh161.

N(1)-C(1)	1.351(4)
N(1)-C(14)	1.461(4)
N(1)-C(2)	1.475(4)
O(1)-C(1)	1.370(4)
O(1)-C(21)	1.458(3)
O(2)-C(1)	1.209(4)
C(2)-C(6)	1.474(5)
C(2)-C(3)	1.532(5)
C(2)-H(2A)	0.9800
C(3)-C(4)	1.488(5)
C(3)-H(3A)	0.9700
C(3)-H(3B)	0.9700
C(4)-C(5)	1.304(5)
C(4)-H(4A)	0.9300
C(5)-H(5A)	0.9300
C(5)-H(5B)	0.9300
C(6)-C(7)	1.198(4)
C(7)-C(8)	1.435(5)
C(8)-C(13)	1.392(4)
C(8)-C(9)	1.395(5)
C(9)-C(10)	1.385(5)
C(9)-H(9A)	0.9300
C(10)-C(11)	1.374(5)
C(10)-H(10A)	0.9300
C(11)-C(12)	1.382(5)
C(11)-H(11A)	0.9300
C(12)-C(13)	1.376(5)
C(12)-H(12A)	0.9300
C(13)-H(13A)	0.9300
C(14)-C(15)	1.516(4)
C(14)-C(21)	1.546(4)
C(14)-H(14A)	0.9800

C(15)-C(16)	1.383(4)
C(15)-C(20)	1.394(4)
C(16)-C(17)	1.395(5)
C(16)-H(16A)	0.9300
C(17)-C(18)	1.372(4)
C(17)-H(17A)	0.9300
C(18)-C(19)	1.382(4)
C(18)-H(18A)	0.9300
C(19)-C(20)	1.386(5)
C(19)-H(19A)	0.9300
C(20)-H(20A)	0.9300
C(21)-C(22)	1.493(4)
C(21)-H(21A)	0.9800
C(22)-C(23)	1.385(4)
C(22)-C(27)	1.392(4)
C(23)-C(24)	1.384(4)
C(23)-H(23A)	0.9300
C(24)-C(25)	1.387(5)
C(24)-H(24A)	0.9300
C(25)-C(26)	1.379(5)
C(25)-H(25A)	0.9300
C(26)-C(27)	1.386(5)
C(26)-H(26A)	0.9300
C(27)-H(27A)	0.9300

C(1)-N(1)-C(14)	111.9(3)
C(1)-N(1)-C(2)	124.0(3)
C(14)-N(1)-C(2)	123.3(3)
C(1)-O(1)-C(21)	108.2(2)
O(2)-C(1)-N(1)	128.9(3)
O(2)-C(1)-O(1)	121.8(3)
N(1)-C(1)-O(1)	109.2(3)
C(6)-C(2)-N(1)	112.7(3)
C(6)-C(2)-C(3)	111.9(3)

N(1)-C(2)-C(3)	111.6(3)
C(6)-C(2)-H(2A)	106.7
N(1)-C(2)-H(2A)	106.7
C(3)-C(2)-H(2A)	106.7
C(4)-C(3)-C(2)	111.6(3)
C(4)-C(3)-H(3A)	109.3
C(2)-C(3)-H(3A)	109.3
C(4)-C(3)-H(3B)	109.3
C(2)-C(3)-H(3B)	109.3
H(3A)-C(3)-H(3B)	108.0
C(5)-C(4)-C(3)	124.9(4)
C(5)-C(4)-H(4A)	117.5
C(3)-C(4)-H(4A)	117.5
C(4)-C(5)-H(5A)	120.0
C(4)-C(5)-H(5B)	120.0
H(5A)-C(5)-H(5B)	120.0
C(7)-C(6)-C(2)	176.4(3)
C(6)-C(7)-C(8)	178.7(4)
C(13)-C(8)-C(9)	119.3(3)
C(13)-C(8)-C(7)	120.9(3)
C(9)-C(8)-C(7)	119.8(3)
C(10)-C(9)-C(8)	119.8(3)
C(10)-C(9)-H(9A)	120.1
C(8)-C(9)-H(9A)	120.1
C(11)-C(10)-C(9)	120.2(4)
C(11)-C(10)-H(10A)	119.9
C(9)-C(10)-H(10A)	119.9
C(10)-C(11)-C(12)	120.2(3)
C(10)-C(11)-H(11A)	119.9
C(12)-C(11)-H(11A)	119.9
C(13)-C(12)-C(11)	120.1(4)
C(13)-C(12)-H(12A)	119.9
C(11)-C(12)-H(12A)	119.9
C(12)-C(13)-C(8)	120.2(3)

C(12)-C(13)-H(13A)	119.9
C(8)-C(13)-H(13A)	119.9
N(1)-C(14)-C(15)	112.7(2)
N(1)-C(14)-C(21)	98.9(2)
C(15)-C(14)-C(21)	115.9(3)
N(1)-C(14)-H(14A)	109.6
C(15)-C(14)-H(14A)	109.6
C(21)-C(14)-H(14A)	109.6
C(16)-C(15)-C(20)	117.7(3)
C(16)-C(15)-C(14)	121.9(3)
C(20)-C(15)-C(14)	120.4(3)
C(15)-C(16)-C(17)	121.4(3)
C(15)-C(16)-H(16A)	119.3
C(17)-C(16)-H(16A)	119.3
C(18)-C(17)-C(16)	119.8(3)
C(18)-C(17)-H(17A)	120.1
C(16)-C(17)-H(17A)	120.1
C(17)-C(18)-C(19)	120.0(3)
C(17)-C(18)-H(18A)	120.0
C(19)-C(18)-H(18A)	120.0
C(18)-C(19)-C(20)	120.0(3)
C(18)-C(19)-H(19A)	120.0
C(20)-C(19)-H(19A)	120.0
C(19)-C(20)-C(15)	121.1(3)
C(19)-C(20)-H(20A)	119.4
C(15)-C(20)-H(20A)	119.4
O(1)-C(21)-C(22)	110.7(2)
O(1)-C(21)-C(14)	103.4(2)
C(22)-C(21)-C(14)	117.3(3)
O(1)-C(21)-H(21A)	108.4
C(22)-C(21)-H(21A)	108.4
C(14)-C(21)-H(21A)	108.4
C(23)-C(22)-C(27)	119.1(3)
C(23)-C(22)-C(21)	121.8(3)

C(27)-C(22)-C(21)	119.1(3)
C(24)-C(23)-C(22)	120.7(3)
C(24)-C(23)-H(23A)	119.7
C(22)-C(23)-H(23A)	119.7
C(23)-C(24)-C(25)	120.3(3)
C(23)-C(24)-H(24A)	119.9
C(25)-C(24)-H(24A)	119.9
C(26)-C(25)-C(24)	119.2(3)
C(26)-C(25)-H(25A)	120.4
C(24)-C(25)-H(25A)	120.4
C(25)-C(26)-C(27)	120.9(3)
C(25)-C(26)-H(26A)	119.5
C(27)-C(26)-H(26A)	119.5
C(26)-C(27)-C(22)	119.9(3)
C(26)-C(27)-H(27A)	120.0
C(22)-C(27)-H(27A)	120.0

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for lsh161. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
N(1)	23(1)	29(2)	29(2)	3(1)	-5(1)	1(1)
O(1)	28(1)	27(1)	34(1)	2(1)	-7(1)	3(1)
O(2)	32(1)	37(1)	39(1)	-3(1)	-10(1)	6(1)
C(1)	30(2)	29(2)	27(2)	-1(2)	-1(2)	6(2)
C(2)	29(2)	24(2)	37(2)	-1(2)	-6(2)	0(2)
C(3)	40(2)	33(2)	34(2)	7(2)	-4(2)	-1(2)
C(4)	36(2)	39(2)	37(2)	13(2)	2(2)	-1(2)
C(5)	52(2)	49(3)	47(3)	3(2)	11(2)	-7(2)
C(6)	39(2)	28(2)	31(2)	1(2)	-8(2)	1(2)
C(7)	37(2)	28(2)	37(2)	2(2)	-6(2)	-2(2)
C(8)	30(2)	29(2)	34(2)	-4(2)	-9(2)	-2(2)
C(9)	50(2)	28(2)	37(2)	-3(2)	-2(2)	-3(2)
C(10)	56(2)	38(2)	41(2)	-11(2)	11(2)	-16(2)
C(11)	37(2)	56(3)	56(3)	-25(2)	5(2)	2(2)
C(12)	48(2)	47(3)	48(3)	-7(2)	4(2)	16(2)
C(13)	41(2)	35(2)	37(2)	2(2)	1(2)	3(2)
C(14)	17(2)	29(2)	31(2)	4(2)	-1(1)	4(2)
C(15)	23(2)	21(2)	31(2)	1(2)	0(2)	-2(1)
C(16)	28(2)	28(2)	30(2)	3(2)	-4(2)	0(2)
C(17)	36(2)	31(2)	34(2)	0(2)	6(2)	-5(2)
C(18)	47(2)	31(2)	25(2)	0(2)	-5(2)	-8(2)
C(19)	40(2)	31(2)	37(2)	1(2)	-11(2)	-1(2)
C(20)	28(2)	24(2)	38(2)	1(2)	-4(2)	-2(2)
C(21)	22(2)	30(2)	31(2)	-5(2)	-1(2)	2(1)
C(22)	24(2)	22(2)	29(2)	-4(2)	1(2)	-3(2)
C(23)	24(2)	30(2)	35(2)	-6(2)	-1(2)	4(2)
C(24)	37(2)	30(2)	34(2)	1(2)	1(2)	-3(2)
C(25)	35(2)	31(2)	32(2)	3(2)	-3(2)	0(2)
C(26)	32(2)	27(2)	46(2)	-4(2)	-6(2)	6(2)

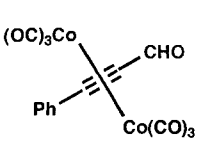
C(27)	29(2)	29(2)	35(2)	0(2)	3(2)	3(2)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for lsh161.

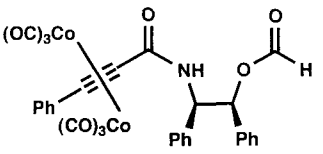
	x	y	z	U(eq)
H(2A)	-1293	3566	1815	36
H(3A)	-641	2930	2694	43
H(3B)	767	3771	2878	43
H(4A)	-3803	3956	2657	45
H(5A)	-1362	4632	3533	59
H(5B)	-3950	4799	3421	59
H(9A)	5615	3216	685	46
H(10A)	8800	2536	353	54
H(11A)	10424	1381	856	59
H(12A)	8899	898	1697	58
H(13A)	5753	1576	2041	46
H(14A)	-3117	5105	1702	31
H(16A)	1796	4627	981	35
H(17A)	2143	4274	32	40
H(18A)	-774	4513	-573	41
H(19A)	-4032	5116	-234	43
H(20A)	-4411	5429	717	36
H(21A)	-1976	6396	2091	33
H(23A)	1511	6921	949	36
H(24A)	848	8021	277	40
H(25A)	-2548	8743	242	39
H(26A)	-5242	8360	888	42
H(27A)	-4586	7268	1567	37

IX. Appendix B

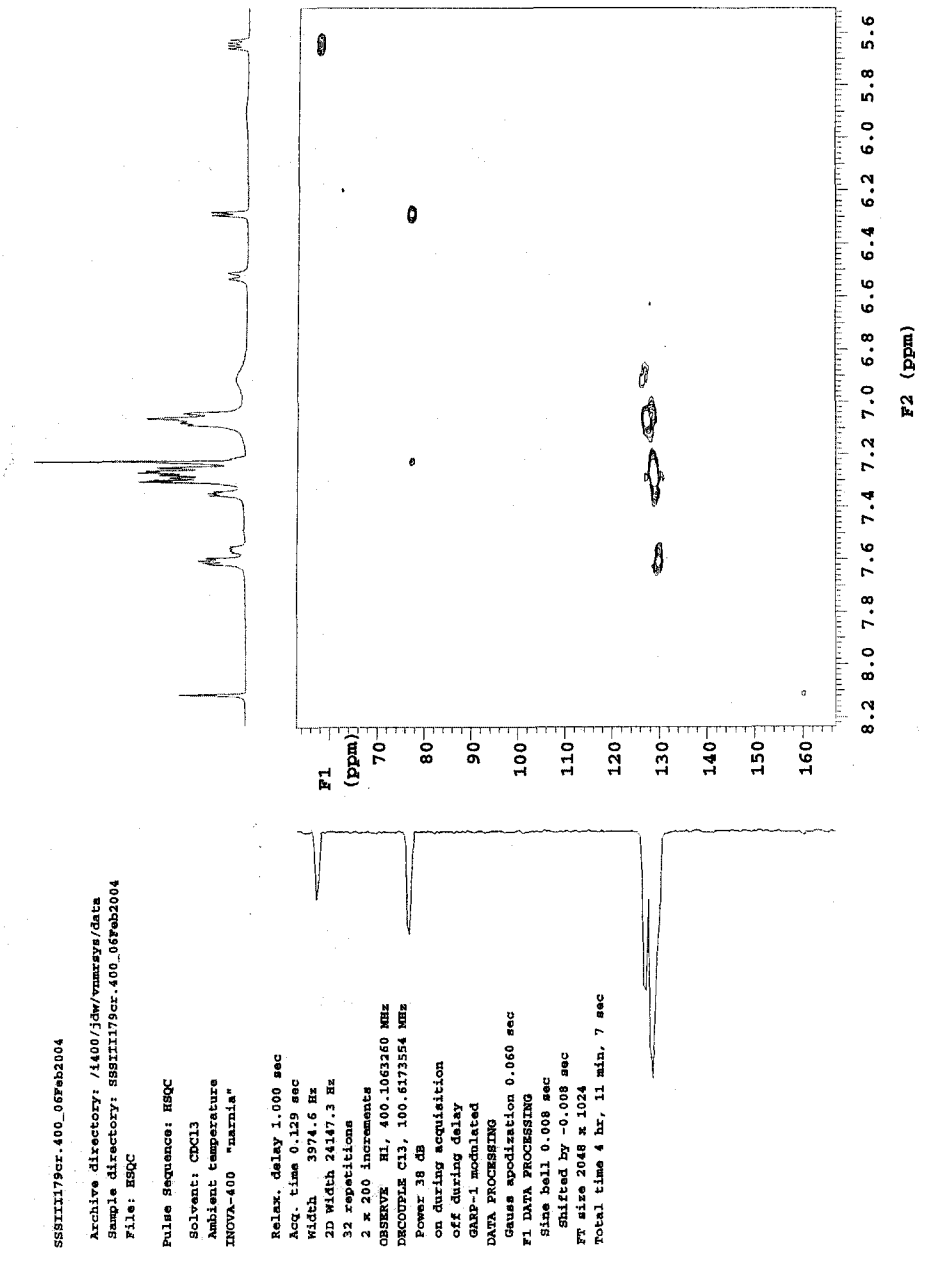
HMQC spectrum of 1:3.4 mixture of aldehyde **237** and formate **238** (procedure B).



237

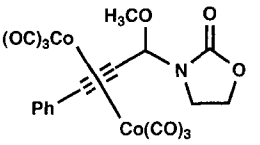


238



X. Appendix C

HSQC spectrum of **288**.



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