Stereoselective Propargylations with Transition-Metal-Stabilized Propargyl Cations

Thomas J. J. Müller

Dedicated to Prof. Dr. Günter Szeimies on the occasion of his 65th birthday

Keywords: Asymmetric synthesis / Alkynes / Carbocations / Chromium / Cobalt

Cationic propargylations have been known for quite some time but only the advent of transition metal stabilization has initiated their stereoselective applications. The introduction of nucleophilic additions to dicobalthexacarbonyl-complexed propargyl cations, known as the Nicholas reaction, has led to widespread applications in the synthesis of complex molecules. Besides the stabilization by direct complexation of the triple bond, the complementary mode, i.e. transition metal complex substituents as propargyl cation stabilizing functional groups, is almost unknown. However, upon ionization, ferrocenyl- and (arene)chromiumcarbonyl-substituted propargyl derivatives give the desired cationic species, and these cations can be regarded as quite reactive propargyl cations without simultaneous complexation of the triple bond, thus enabling highly diastereoselective nucleophilic additions with the potential of exploiting the ambident nature of propargyl cations.

1. Introduction

Propargyl cations[1] have been known in organic chemistry for quite some time both as the reactive intermediates in Meyer−Schuster and Rupe rearrangements,[2] as well as persistent species in solution[3] and in the solid state.[4] Due to their unsymmetrical constitution they are an interesting class of ambident electrophiles that furnish either propargyl derivatives or allenes upon nucleophilic trapping. Interestingly, propargyl cations can act as two- or four-electron systems in stepwise [2+2], [3+2],[5] [4+2][6] and [4+3] cycloadditions[7] with cyclic and acyclic 1,3-dienes giving rise to several polycyclic frameworks. Heteroatomic donor substituents at the sp^2-hybridized position additionally stabilize the cationic charge and, for example, alkynyl-substituted iminium and amidinium salts[8] have found broad synthetic application in heterocyclic and cyanine chemistry.[9]

The electronic ground state of propargyl cations is represented by propargylium and allenylium resonance structures (Scheme 1) distributing the positive charge over sp- and sp^2-hybridized carbon atoms.[10] Both the electronic and structural features of propargyl cations have been extensively investigated in the past, leading to the conclusion that propargyl cations can be considered as alkynyl-substituted carbenium ions with their ambident reactivity largely depending on the substitution pattern at the α- and the γ- positions.[3b,3e] This classifies them as an intriguing class of reactive species that can open the way to highly unsaturated structures for the elaboration of syntheses of complex molecules.[1]

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MICROREVIEWS: This feature introduces the readers to the authors' research through a concise overview of the selected topic. Reference to important work from others in the field is included.

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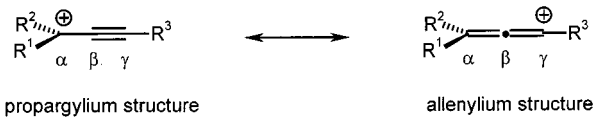
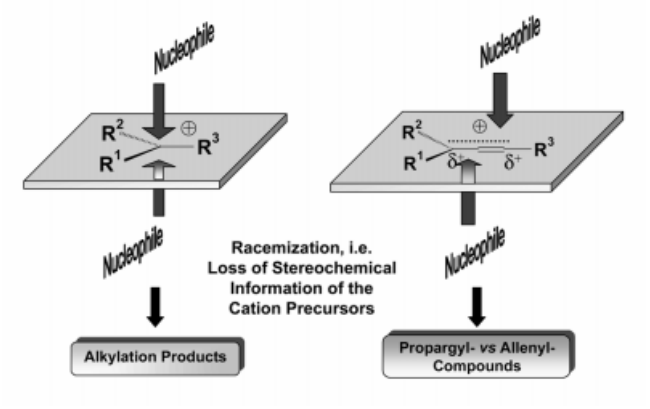


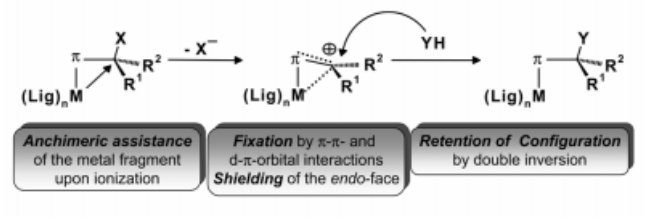
Scheme 1. Canonical structures of propargyl cations

Nucleophilic substitutions following the S_N1 mechanism proceed through a prochiral trigonal planar carbenium ion intermediate. The initial stereochemical information at the substitution center is therefore lost in the ionization step and causes the formation of racemic products. Only a very few cases of neighboring group participation, in particular with rigid bicyclic frameworks, have been found to give rise to stereocontrolled substitutions.[11] The same holds true for propargyl cations that can be considered as alkynyl-substituted carbenium ions with an additionally ambident nature furnishing propargyl derivatives or allenes (Scheme 2). Therefore, the crucial question arises as to whether stereoselective propargylations with propargyl cations can be envisioned at all.



Scheme 2. Nucleophilic attack to prochiral carbenium and propargyl cations

Fortunately, the advent of transition metal π-complex stabilization of α-carbenium ions[12] has revolutionized the synthetic application of often-elusive reactive carbocation intermediates. In particular, stereoselective nucleophilic additions with retention of configuration have become feasible (Scheme 3).



Scheme 3. Concept of neighboring group participation in stereocontrolled cationic nucleophilic substitutions

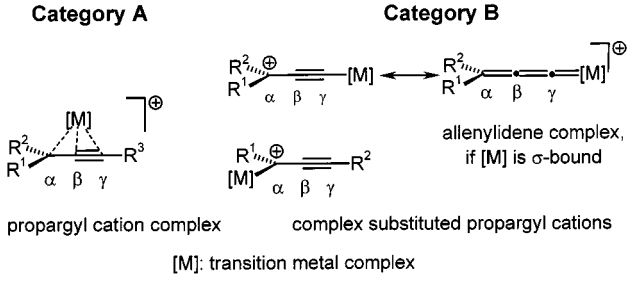
A pronounced neighboring group effect arises from an ideal overlap of occupied d-orbitals on the metal and the vacant p-orbital at the carbenium center in α-position.[12] In detail, the anchimeric assistance of the transition metal fragment enhances the rate of ionization in S_N1 reactions and stabilizes the newly formed carbenium ion by intraligand π-p and metal−ligand d-p interactions. Stereochemically, this carbenium ion is now conformationally fixed and the *endo* face is sterically shielded. The conservation of the stereochemical information at the former sp^3 center after the nucleophilic attack is now reflected as a consequence of an overall retention of configuration due to a double inversion mechanism.[12c,12d,12f]

For the stabilization and conformational fixation of propargyl cations two modes of transition metal stabilization (Scheme 4) can be realized:

Category A: the propargyl cation moiety is directly complexed to a transition metal in the sense of an η^2/η^3 coordination.[13]

Category B: the propargyl cation is substituted with a transition metal π complex at either the α- or the γ-position.

Formally, cationic allenylidene complexes also belong to category B even though their reactivity pattern significantly deviates from propargylation or allenylation products. Although allenylidene complexes represent interesting stable species with great significance as catalysis intermediates and metathesis catalyst precursors[14] they will not be considered further here.



Scheme 4. Categories of transition-metal-stabilized propargyl cations with (category A) and without (category B) simultaneous complexation of the triple bond

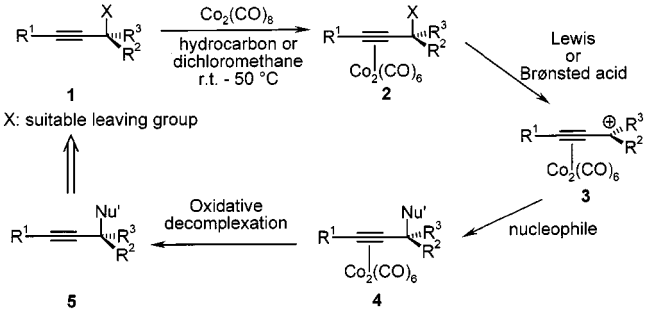
Stabilized propargyl cations with a fixed configuration are *per se* ideal electrophiles for stereoselective cationic propargylations. This Microreview encompasses the recent developments in the generation and structures of transition-metal-stabilized propargyl cations (categories A and B) and their stereoselective nucleophilic trapping reactions.

2. Propargyl Cation Complexes (With Complexation of the Triple Bond)

2.1. Synthesis and Structure of Triple-Bond-Complexed Propargyl Cations

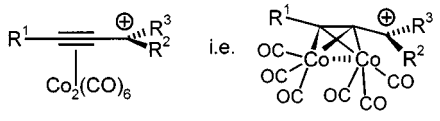
Among various transition-metal-stabilized systems, dicobalthexacarbonyl-complexed propargyl cations[15] have found elegant applications in asymmetric organic synthesis.[16] A major advantage of cobalt-complexed propargyl cations is their straightforward generation. Thus, the propargyl compounds **1** are complexed with dicobaltoctacarbonyl under mild conditions giving rise to the dico-

balthexacarbonyl-complexed propargyl derivatives **2** (Scheme 5). Here the propargylic position is considerably activated towards ionization with Lewis or Brønsted acids to furnish the stabilized carbenium ions **3**. The structure of these organometallic carbenium ions has been studied in detail by ^{13}C NMR spectroscopy.[17] The generated cation stabilized by the adjacent cobalt(0) fragment, with simultaneous protection of the alkyne, can be easily reacted with a number of nucleophiles to give the complexes **4** and furnish the functionalized propargylic derivatives **5** after oxidative demetallation.



Scheme 5. Propargyl activation by cobalt complexation (Nicholas reaction)

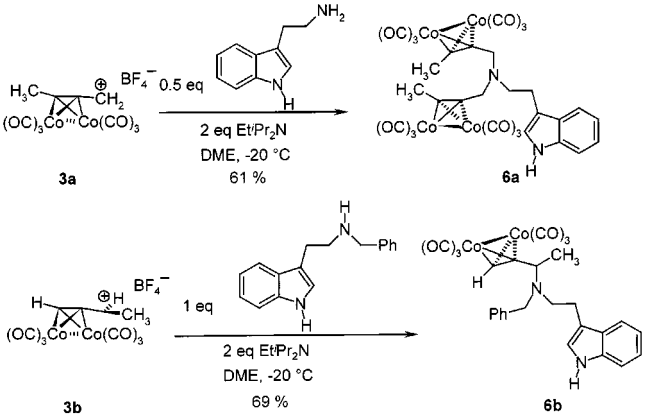
However, the so called "Nicholas' cations" should be regarded as cobalt-cluster-stabilized carbenium ions rather than propargyl cations, especially since the triple bond is permanently complexed by the dicobalthexacarbonyl fragment and even the precursors for ionizations display bond lengths for the "triple bond" that strongly deviate from those of alkynes (Scheme 6).[15,17]



Scheme 6. Nicholas' cations *are not* propargyl cations

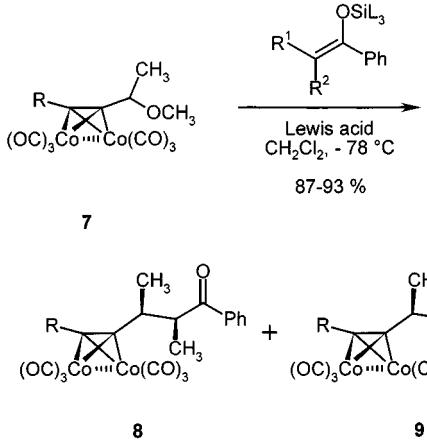
2.2. Stereoselective Additions to Triple-Bond-Complexed Propargyl Cations

Roth et al.[18] have found that primary and secondary amines react smoothly with Nicholas' cations **3** to give the expected cobalt-complexed propargylamines **6** in good yields (Scheme 7). Primary aliphatic amines give rise to the formation of bis(propargylamine) derivatives due to the enhanced nucleophilicity of the deprotonated primary adduct, i.e. the initially formed secondary amine. The propargylamine ligands can be easily liberated by oxidative decomplexation with CAN (cerium ammonium nitrate) or trimethylamine *N*-oxide.



Scheme 7. Nucleophilic additions of amines to Nicholas' cations

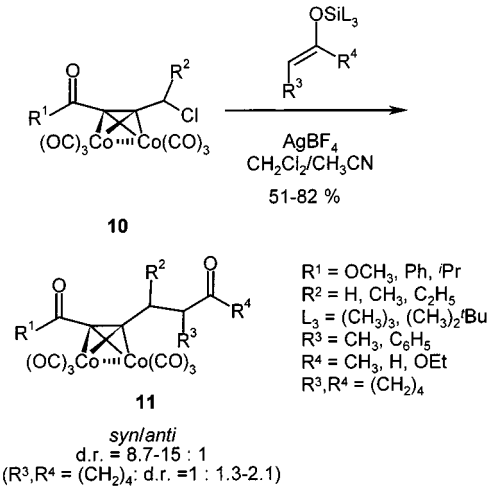
The stereochemistry of the Nicholas reaction of the *E*- and the *Z*-trimethylsilyl enol ether of propiophenone and several cobalt-complexed propargyl ethers **7** in the presence of Lewis acids has been investigated by Schreiber et al. and several important features of the facial selection were determined (Scheme 8).[19] Surprisingly, both geometric silyl enol ether isomers result in the preferential formation of the *syn* (**8**) over the *anti* (**9**) diastereomer; however, the *Z*-trimethylsilyl enol ether provides a higher level of diastereoselectivity. Furthermore, the remote acetylenic substituent exerts a significant steric impact on the degree of diastereoselectivity: large substituents result in an increased selectivity whereas a proton only leads to a slight *syn* selectivity.



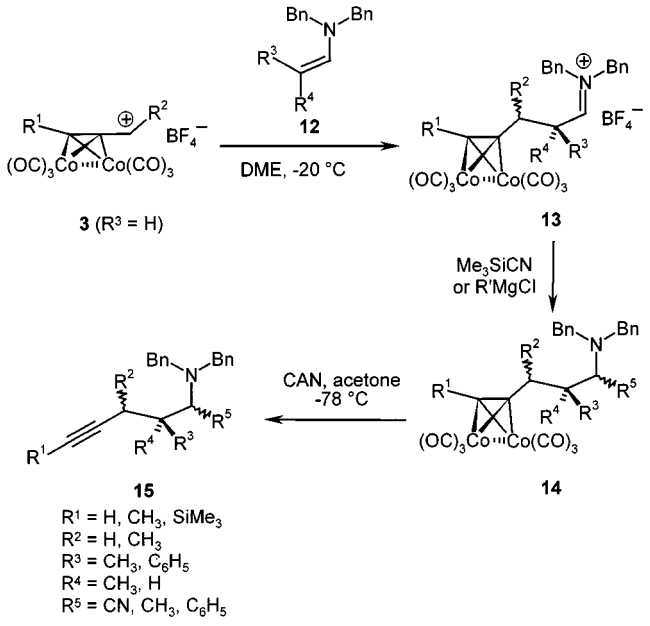
R	R¹	R²	Lewis acid	8/9
TMS	Me	H	BF_3 OEt_2	15 : 1
Ph	Me	H	$EtAlCl_2$	18 : 1
Ph	H	Me	$EtAlCl_2$	9 : 1
Me	Me	H	BF_3 OEt_2	6.8 : 1
Me	H	Me	BF_3 OEt_2	3.5 : 1
H	Me	H	$EtAlCl_2$	1.6 : 1

Scheme 8. Facial diastereoselectivity of the nucleophilic addition of silyl enol ethers to Nicholas' cations

Complexed γ-chloroalkynones and γ-chloroalkynoates **10** are suitable precursors for silver-mediated Nicholas reactions with silyl enol ethers and silyl ketene acetals



Scheme 9. Silyl enol ether additions to complexed γ-chloro ynoates and ketones



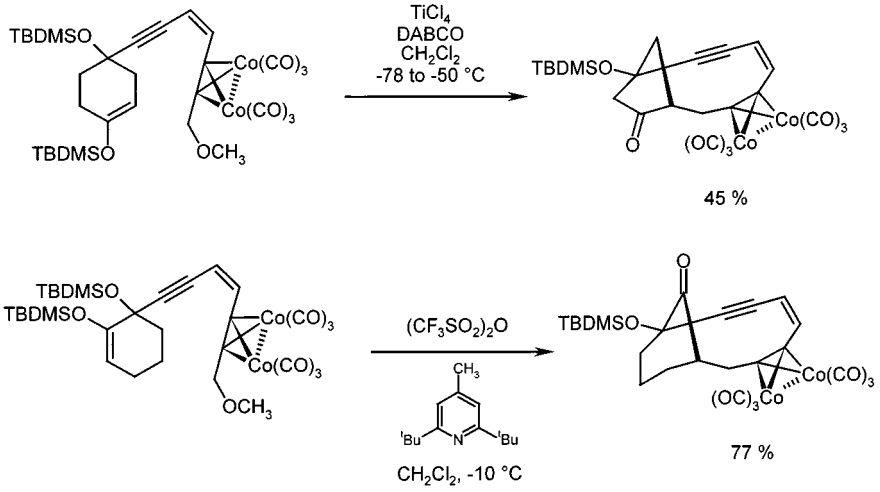
Scheme 11. Nucleophilic addition of enamines to Nicholas' cations

(Scheme 9).[20] Substrates with γ-alkyl substitution give rise to the diastereomeric products **11** with β-substituted silyl enol ethers. In particular, propiophenone trimethylsilyl enol ether gave good levels of *syn* diastereoselectivity, whereas reactions with trimethylsiloxy cyclohexene were only slightly diastereoselective, favoring the formation of the *anti* diastereomer.

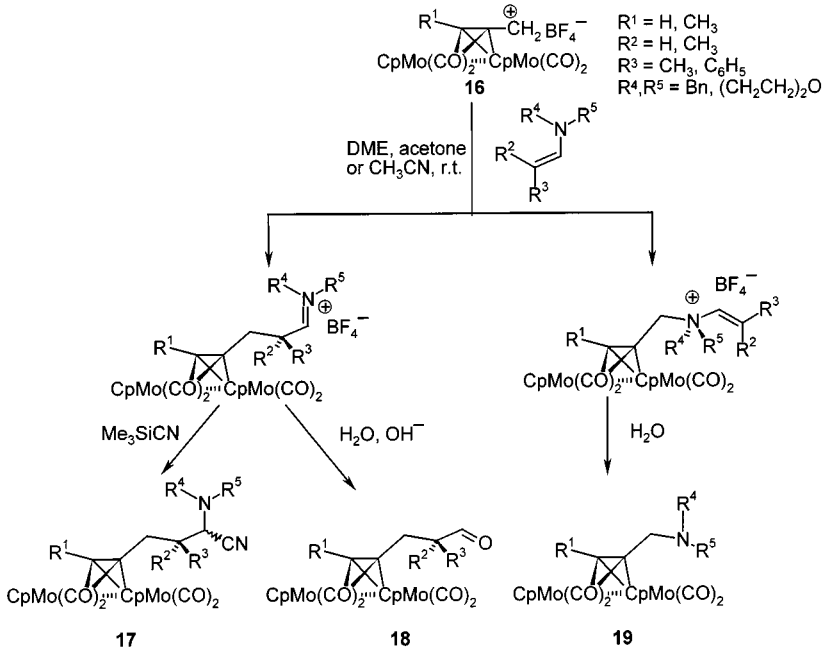
The reactions of silyl enol ethers with Nicholas' cations have found their most prominent application in Magnus' syntheses of the enediyne antibiotics esperamicin A and calicheamicin γ_1.[21] Here, in model studies, the bicyclic framework of the enediyne chromophore was established by an intramolecular addition of an in-situ-generated cobalt-complexed propargyl cation to a silyl enol ether functionality (Scheme 10).

Roth showed that the nucleophilic addition of the aldehyde *N*,*N*-dibenzyl enamines **12** to Nicholas' cations **3** furnishes organometallic derivatives of iminium salts **13** which were subsequently reacted in the same pot with Grignard reagents or trimethylsilyl cyanide (Scheme 11) to give the highly substituted complexes **14** and, after decomplexation, the corresponding propargyl derivatives **15**.[22] This consecutive nucleophilic trapping of Nicholas' cation **3** and the iminium salt **13** is a highly interesting cascade reaction since it not only takes advantage of nucleophiles with specific reactivity, with simultaneous formation of two new carbon−carbon bonds, but it also establishes three contiguous stereogenic centers in a one pot process with decent to good diastereoselectivity.

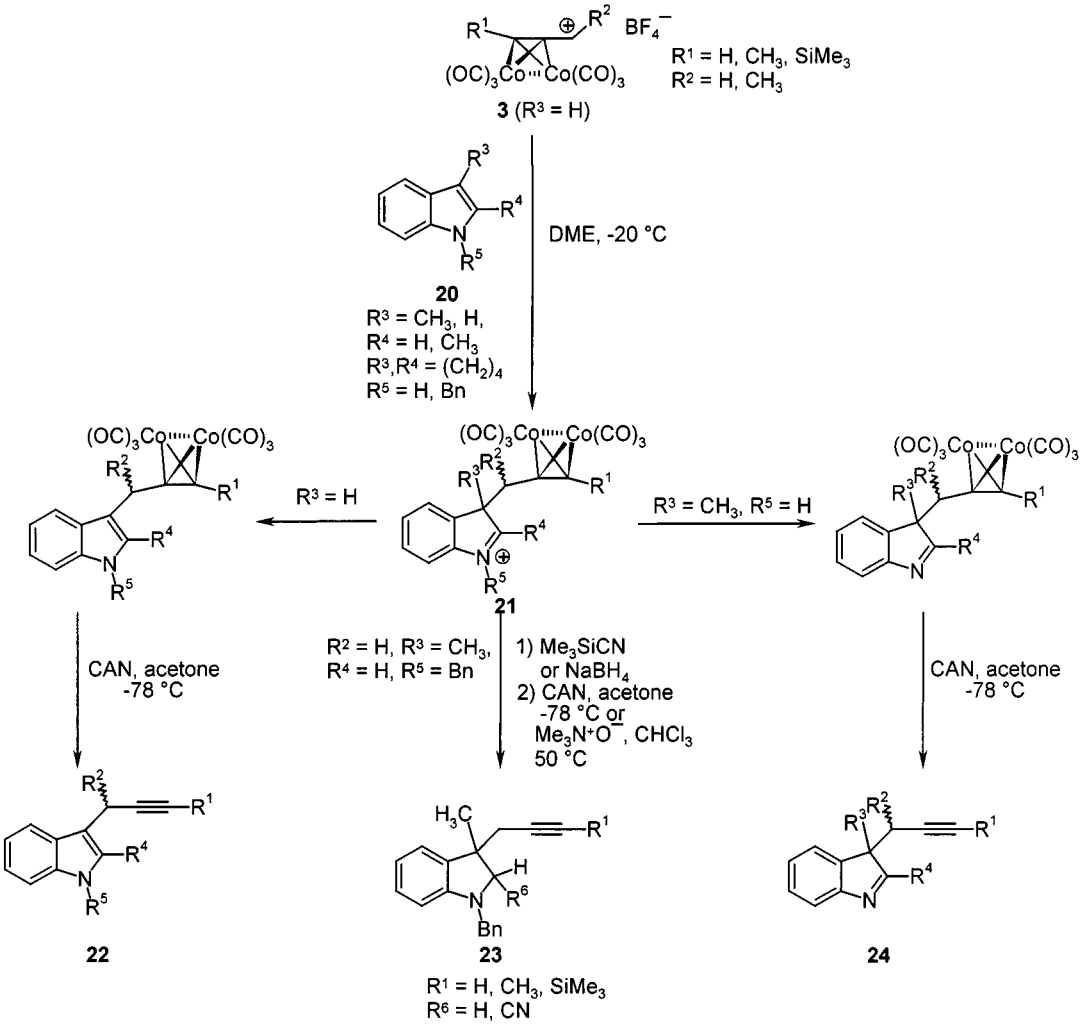
In a related study, Roth has applied $[CpMo(CO)_2]_2$ analogues of Nicholas' cations **16**[23] in propargylation reactions of enamines as well as consecutive transformations to give organometallic derivatives of the highly functionalized complexed propargyl derivatives **17** and **18** (Scheme 12).[24] However, in several examples a competing *N*-attack has



Scheme 10. Intramolecular Nicholas reactions as key steps in establishing the core structures of esperamicin A and calicheamicin γ_1



Scheme 12. Nucleophilic addition of enamines to bis(cyclopentadienyldicarbonyl molybdenum)-complexed propargyl cations

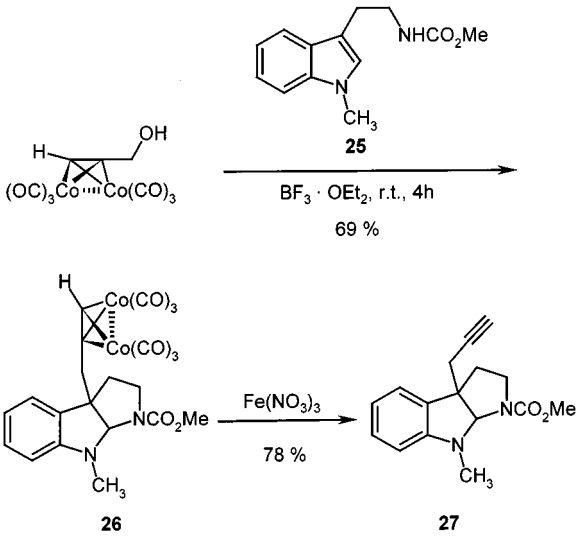


Scheme 13. Nucleophilic aromatic substitutions with Nicholas' cations at the indole core

been observed as well as the more normal C-β attack, resulting in a Hofmann degradation to give the complexed propargylamines **19**.

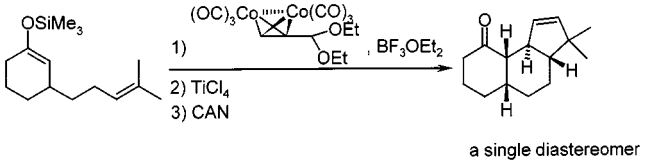
Indoles are an interesting class of nucleophilic heterocycles since they are constituents of quite a number of alkaloid families. Hence, the application of indoles **20** as suitable trapping nucleophiles for Nicholas' cations represents, after demetallation, an elegant access to the 3-propargylated indoles **22** and 3-propargylated indolenines **24**.[25] Like enamines, indoles react with the cobalt-complexed propargyl cations to give an iminium salt intermediate **21** that is readily trapped in a consecutive reaction with hydride or cyanide nucleophiles to give highly functionalized indolenine derivatives **23** with modest diastereoselectivity (Scheme 13).

Likewise, the presence of a weakly nucleophilic functionality within the indole derivative as in *N*-methyl-*N*′-methoxycarbonyl tryptamine (**25**) can be readily exploited for a domino reaction.[26] An iminium salt intermediate is formed, initiated by the electrophilic attack of Nicholas' cation, that is now trapped intramolecularly by the pendant amide functionality to furnish the organometallic pyrrolo[2,3-b]indole derivative **26** in good yield (Scheme 14). Decomplexation of **26** then gives rise to the formation of the propargyl pyrrolo[2,3-b]indole **27**.

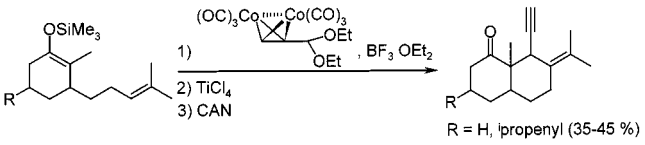


Scheme 14. Consecutive nucleophilic additions and trapping reactions with Nicholas' cations at the indole core

A nice combination of two subsequent Nicholas reactions terminated by a cyclization reaction, demonstrated by Tyrrell et al., was the result of a highly diastereoselective tandem cyclization of a silylenol ether with a pendant isopropylidene side-chain.[27] As a consequence of its nucleophilicity the silylenol ether is alkylated first, before a second ionization step regenerates the carbenium ion which then attacks the isopropenylidene moiety in an intramolecular fashion (Scheme 15). The mechanism of the final cyclization step that constitutes the tricyclic framework has not been elucidated yet. However, this cyclopentene formation is completely suppressed if a β-methyl group is present in the silylenol ether (Scheme 16).

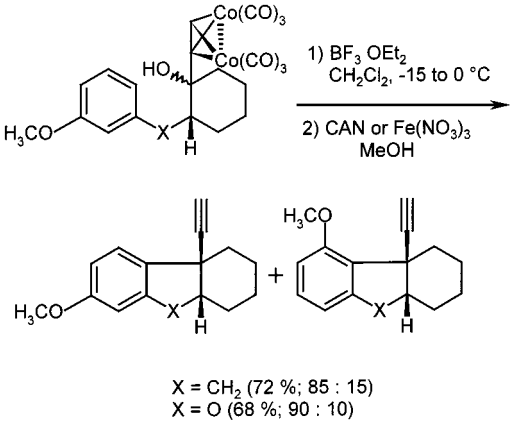


Scheme 15. A cyclization based upon a double Nicholas reaction



Scheme 16. Cyclizations based upon subsequent Nicholas reactions

Finally, the Nicholas reaction also provided an entry to the synthesis of oligocyclic aromatic compounds such as hexahydrofluorenes and their corresponding benzofuran derivatives.[28] Here, Nicholas' cations react with an appended electron-rich arene in the sense of a Friedel−Crafts alkylation to give, in a stereoconvergent fashion, solely the *cis*-fused five-membered rings in the tricyclic products (Scheme 17). The remarkably high regioselectivity in the cyclization step can be largely explained on steric grounds.



Scheme 17. Intramolecular nucleophilic aromatic substitutions with Nicholas' cations

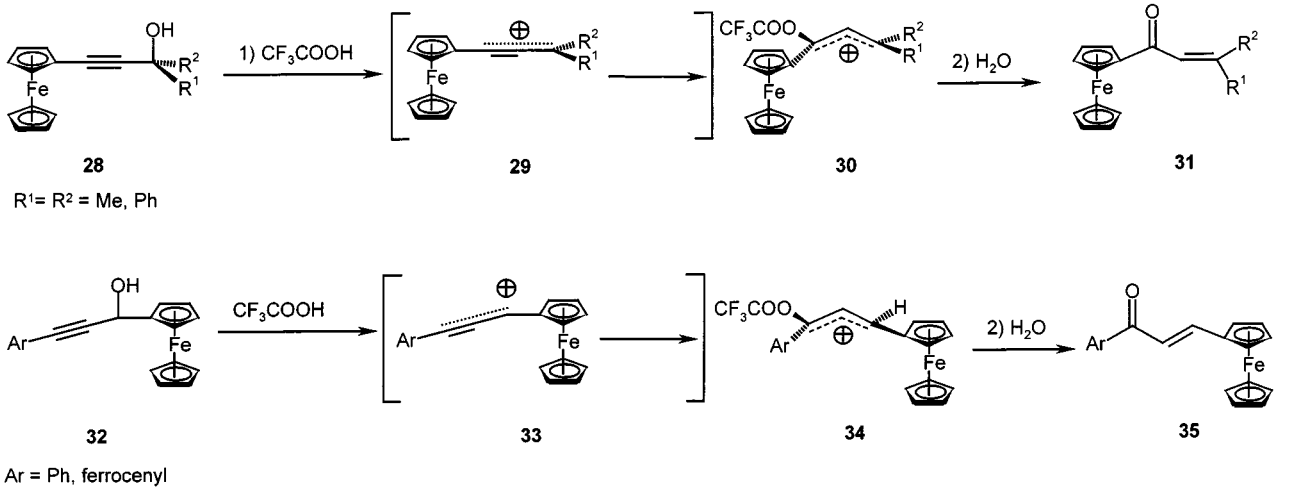
3. Complex-Substituted Propargyl Cations (Without Complexation of the Triple Bond)

Although Nicholas' cations have found widespread applications in the synthesis of complex molecules they still cannot be regarded as propargyl cations since the triple bond is completely complexed by a dicobalt cluster.[15] However, "true" propargyl cations, i.e. without simultaneous complexation of the triple bond, can be highly interesting species for tackling stereochemical issues of cationic propargylations with these ambident electrophiles. Facing this apparent problem of triple-bond-complexed propargyl

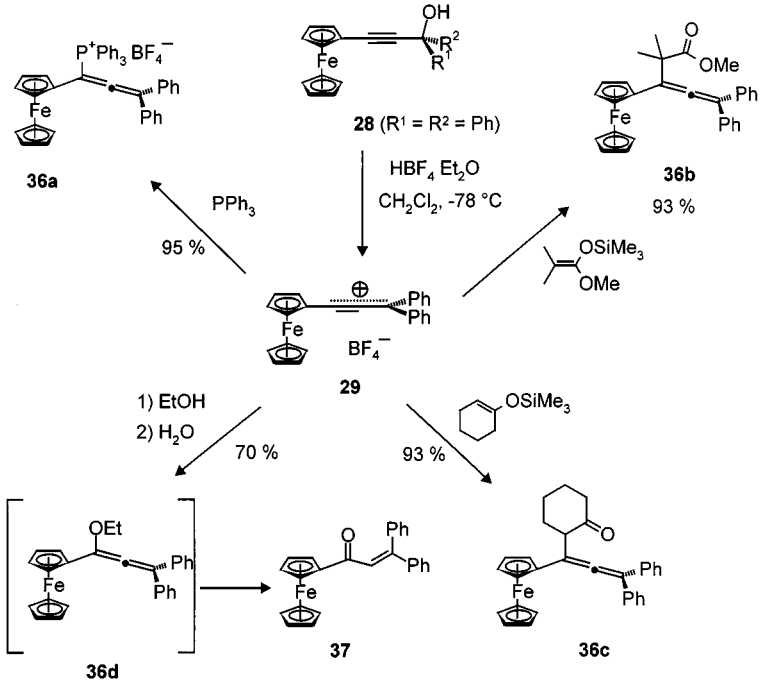
cations, we have suggested that the chromiumcarbonyl stabilization of benzylic cations[12f,29] could well be transposed to the stabilization of propargyl cations, simultaneously fixing their configuration without complexation of the triple bond. Furthermore, the chromiumcarbonyl fragment is as easily removed as the dicobalt hexacarbonyl group under very mild oxidative conditions (irradiation with sunlight in the presence of air).[12f] In the course of our studies directed to synthesize and to explore the chemical, structural and physical properties of (arene)chromiumcarbonyl complexes with conjugated side-chains[30,31] we have recently begun to investigate the novel class of organometallically substituted propargyl cations.[32,33]

3.1. Synthesis and Structure of Complex-Substituted Propargyl Cations

Before our studies the only examples of complex-substituted propargyl cations were realized with ferrocenyl substituents.[34] The in situ ionization of the α- or γ-ferrocenyl-substituted propargyl alcohols **28** and **32** gave rise to the isolation of the ferrocenyl-substituted enones **31** and **35**, formally as the result of a Meyer−Schuster rearrangement (Scheme 18).[34a] This transformation was rationalized on the basis that the ionization of the propargyl alcohols **28** and **32** was facilitated by the ferrocenyl stabilization of the intermediate propargyl-allenyl cations **29** and **33**. Addition



Scheme 18. Generation of ferrocenyl-substituted propargyl cations as intermediates in the solvolysis of propargyl alcohols

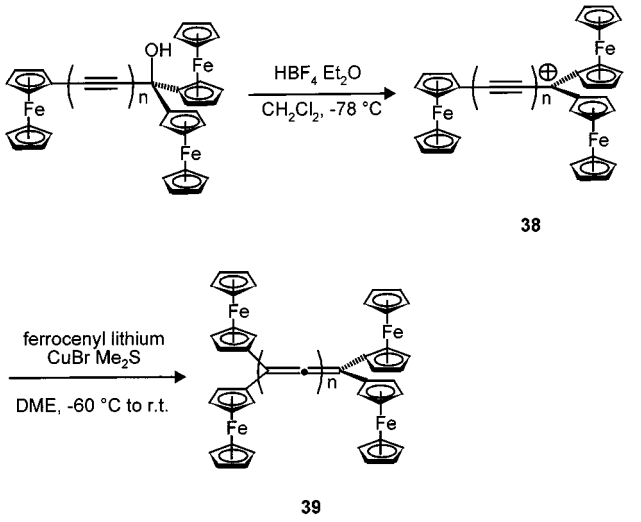


Scheme 19. Generation and nucleophilic trapping reactions of a stable ferrocenyl-substituted propargyl cation

of trifluoroacetic acid furnished the highly stabilized allyl cations **30** and **34**, which could be identified by ^{1}H NMR spectroscopy. Upon aqueous work up the trifluoroacetoxy allyl cations were hydrolyzed to give the enones **31** and **35**.

Recently, we have shown that even the above-mentioned propargyl cation **29** is easily accessible by ionization of the propargyl alcohol **28** with only a slight excess of tetrafluoroboric acid.[35] The trapping of **29** with several nucleophiles gave rise to the formation of the ferrocenyl-substituted allenes **36** and the hydrolysis product **37** (Scheme 19).

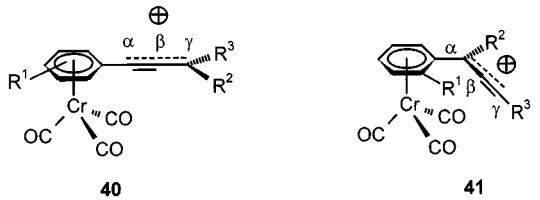
In impressive studies, Bildstein et al. showed that the perferrocenylated propargyl cations **38** and their higher homologues can be synthesized and trapped with organometallic nucleophiles such as ferrocenyl copper to give a convenient access to highly electron-rich perferrocenylated cumulenes **39**, an interesting class of novel organometallic NLO-active chromo- and electrophores (Scheme 20).[36]



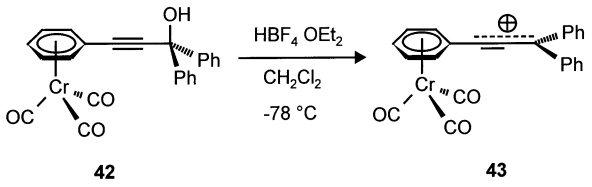
Scheme 20. Ferrocenyl propargyl cations and their homologues as building blocks for perferrocenylated cumulenes

Although, ferrocenyl-substituted carbenium ions have been applied in several stereoselective transformations,[37] there are no comparable studies of the above-mentioned substituted propargyl cations.

Arene chromiumcarbonyl complexes are well suited to stabilize benzyl cations,[29] and therefore we have extended this feature to the stabilization of propargyl cations. Basically, two different modes of propargyl cations **40** and **41** stabilized by arene complex substituents can be conceived: a propargyl cation center in the α- or the γ-position with respect to the organometallic substituent. Ionization of the corresponding propargyl alcohols or acetates leads to the realization of both types of systems.[32,33]

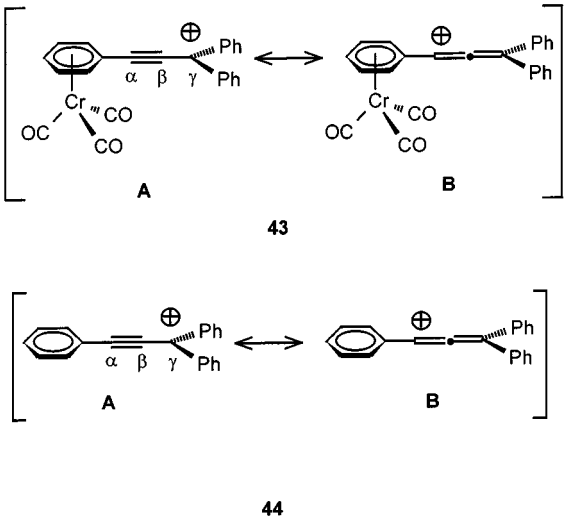


At low temperatures (−78 °C) the ionization of the (arene)Cr(CO)$_3$-substituted propargyl alcohol **42** with only a slight excess of tetrafluoroboric acid−diethyl ether leads to the formation of a deep green species.[33] The complexed 1,1,3-triphenyl propargyl cation (**43**) (cation **40** with R^1 = H and R^2 = R^3 = Ph) was formed as a stable intermediate (< 20 °C) (Scheme 21) that could be characterized in solution by NMR and UV/Vis spectroscopy.[33]



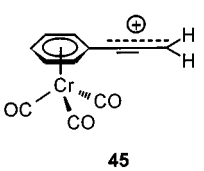
Scheme 21. Generation of a stable (phenyl)chromiumcarbonyl γ-substituted propargyl cation

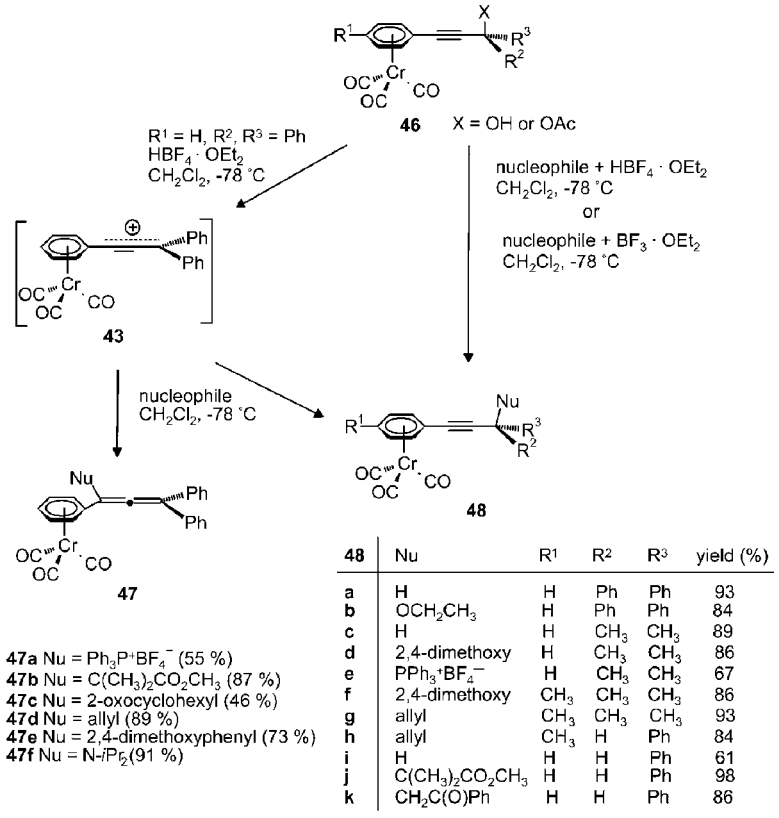
In comparison to the free ligand, i.e. the propargyl cation **44**, which was studied quite some time ago in a superacidic medium by ^{13}C NMR spectroscopy,[3b] the weighted contribution of the allenylium resonance structure **B** (Scheme 22) to the electronic ground state of **43** can be estimated to be 60% (**44**, **B**: 10%) as a consequence of the chromium tricarbonyl complex stabilization.[33,35]



Scheme 22. Canonical structures of the chromiumtricarbonyl-complexed triphenylpropargyl cation **43** and the hydrocarbon ligand **44**

According to MO calculations at the extended Hückel level of theory with an η^6-phenylCr(CO)$_3$-substituted γ-propargyl cation (**45**) as a model, the bending of the propargyl cation side-chain by 4° towards the chromiumcarbonyl tripod results in a small gain of energy (≈ 0.33 kcal/mol).[33]





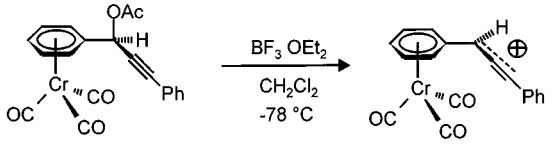
48	Nu	R1	R2	R3	yield (%)
a	H	H	Ph	Ph	93
b	OCH_2CH_3	H	Ph	Ph	84
c	H	H	CH_3	CH_3	89
d	2,4-dimethoxy	H	CH_3	CH_3	86
e	$PPh_3^+BF_4^-$	H	CH_3	CH_3	67
f	2,4-dimethoxy	CH_3	CH_3	CH_3	86
g	allyl	CH_3	CH_3	CH_3	93
h	allyl	CH_3	H	Ph	84
i	H	H	H	Ph	61
j	$C(CH_3)_2CO_2CH_3$	H	H	Ph	98
k	$CH_2C(O)Ph$	H	H	Ph	86

Scheme 23. Nucleophilic trapping reactions of **43** (allenes **47** and propargyl derivatives **48**)

The regioselectivity of the nucleophile-trapping reactions strongly depends on the substitution pattern at the γ position. Thus, only the highly stable complexed triphenylpropargyl cation (**43**) gives rise to the regioselective formation of allenes **47** with π- and soft n-nucleophiles in good yields.[33] Other propargyl alcohols or acetates **46** leading to the less-stable propargyl cations **40** have to be subsequently trapped under in situ ionization conditions and furnish exclusively the propargyl compounds **48** (Scheme 23).

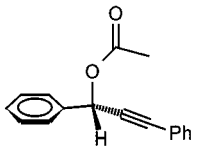
Kinetic studies on the nucleophilic trapping reactions with the stable cation **43** allowed a semi-quantitative treatment of the reactivity of **43** upon determining its electrophilicity.[38] Therefore, temperature-dependent kinetic measurements of the trapping reactions of **43** with allyl trimethylsilane, 1,3-dimethoxy benzene and allyl triphenylstannane gave rise to the extrapolated rate constant at 20 °C.[33] Thus, the averaged electrophilicity parameter Ebar = −0.36 was determined for the chromiumcarbonyl-stabilized γ-propargyl cation **43** indicating that the reactivity of **43** is lowered by two orders of magnitude relative to the free ligand **44** ($\bar{E}$ = 1.64).[39]

Likewise, the ionization of the complex-substituted α-propargyl acetate **49** can be achieved completely and irreversibly with boron trifluoride−diethyl ether in dichloromethane at −78 °C (Scheme 24). The formation of a deep purple specimen can be observed which was identified and characterized by UV/Vis and NMR spectroscopy as the phenyl$Cr(CO)_3$-stabilized propargyl cation **50** (cation **41** with $R^1 = R^2 = H$ and R^3 = Ph).[32]



Scheme 24. Generation of a stable (phenyl)chromiumcarbonyl α-substituted propargyl cation

In comparison the free ligand **51**[40] cannot be ionized either under similar conditions or in superacidic medium, where a subsequent cationic polymerization hampers the generation of the free ligand cation.[41]

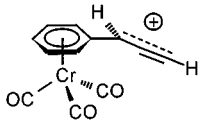


51

The splitting of the carbonyl resonances to give three signals (δ = 229.4, 227.7 and 227.6) in the ^{13}C NMR spectrum of **50** can be interpreted as a conformational fixation of the

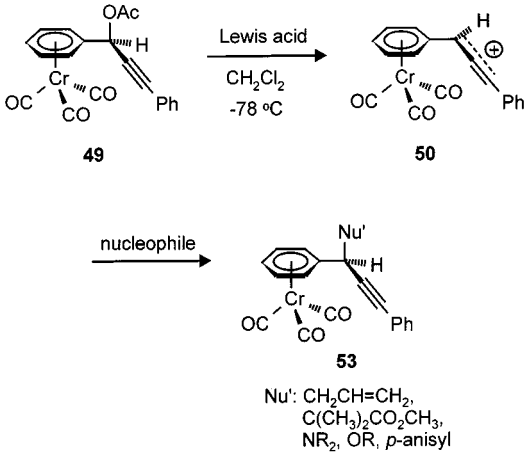
propargyl cation side-chain as a consequence of a strong backbonding of the propargyl center to the chromiumcarbonyl tripod that is now hindered in its rotation. Additionally, the assistance of the chromiumcarbonyl arene fragment in the stabilization of the propargyl cation is also manifested in the chemical shift of the propargyl carbenium nucleus, and thus an 80% contribution of the corresponding propargylium resonance structure can be estimated for the ground state stabilization of the cation **50**.[32]

According to MO calculations at the extended Hückel level of theory with an η^6-phenylCr(CO)$_3$-substituted α-propargyl cation (**52**) as a model, the bending of the propargyl cation side-chain by 10° towards the chromiumcarbonyl tripod results in a gain of energy of approximately 1.1 kcal/mol.[32]



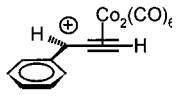
52

As a consequence of the larger orbital coefficient at the propargyl position in the LUMO a preferred propargyl selectivity can be expected for kinetically controlled nucleophilic trapping reactions. Experimentally, all π-nucleophiles and most n-nucleophiles react with excellent regioselectivity at the propargyl position to give the propargyl derivatives **53** (Scheme 25).[32] Thiols behave exceptionally and furnish allenyl thioethers.



Scheme 25. Nucleophilic trapping reactions of the propargyl cation **50**

The electrophilic reactivity of the stable cation was determined quantitatively by measuring the temperature-dependent kinetics of the trapping reactions of **50** with allyl trimethylsilane, anisole and allyl dimethylchlorosilane.[42] The averaged electrophilicity parameter of $\bar{E} = 1.24$ for the chromiumcarbonyl-stabilized α-propargyl cation **50** revealed that **50** is 2.5 orders of magnitude more reactive than the related Nicholas' cation **54** (Nicholas' cation **3** with $R^1 = R^3 = H$ and $R^2 = Ph$; $\bar{E} = -1.34$).[43]

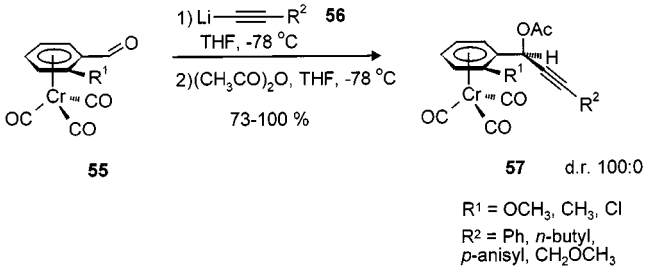


54

3.2. Stereoselective Additions to Arene Chromiumcarbonyl-Complexed Propargyl Cations

Coming back to the initially posed question on the possibility of stereoselective propargylations with conformationally fixed propargyl cations and, thus, closing the circle, we were able to answer it positively.[44] Since (phenyl)Cr(CO)$_3$-substituted α-propargyl cations are not only quite reactive electrophiles but also possess conformationally fixed propargyl side chains, studies of diastereoselective cationic propargylation were now possible.

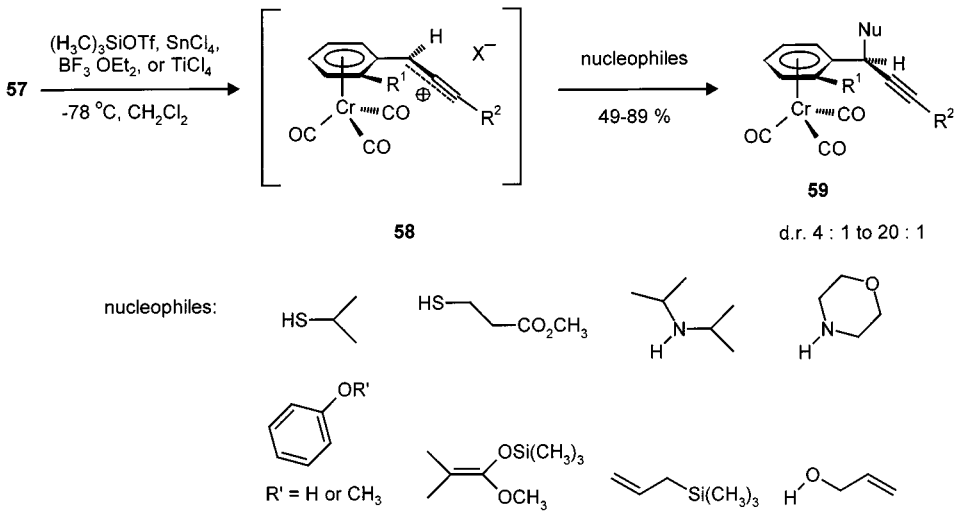
Since lithium and magnesium organic compounds add to planar chiral complexed *ortho*-substituted benzaldehydes **55** with excellent diastereoselectivity,[45] the addition of lithium acetylides **56** followed by subsequent trapping of the propargyl alcoholate with acetic anhydride furnishes the complex-substituted propargyl acetates **57** with good yields and excellent diastereoselectivity as crystalline materials (Scheme 26). In several X-ray structure analyses the relative stereochemistry could be unambiguously confirmed, revealing that the alkynyl chain and the *ortho*-substituent adopt a *syn*-conformation when the acetate fragment and the chromium atom are aligned in an *anti*-periplanar orientation.[44b,46]



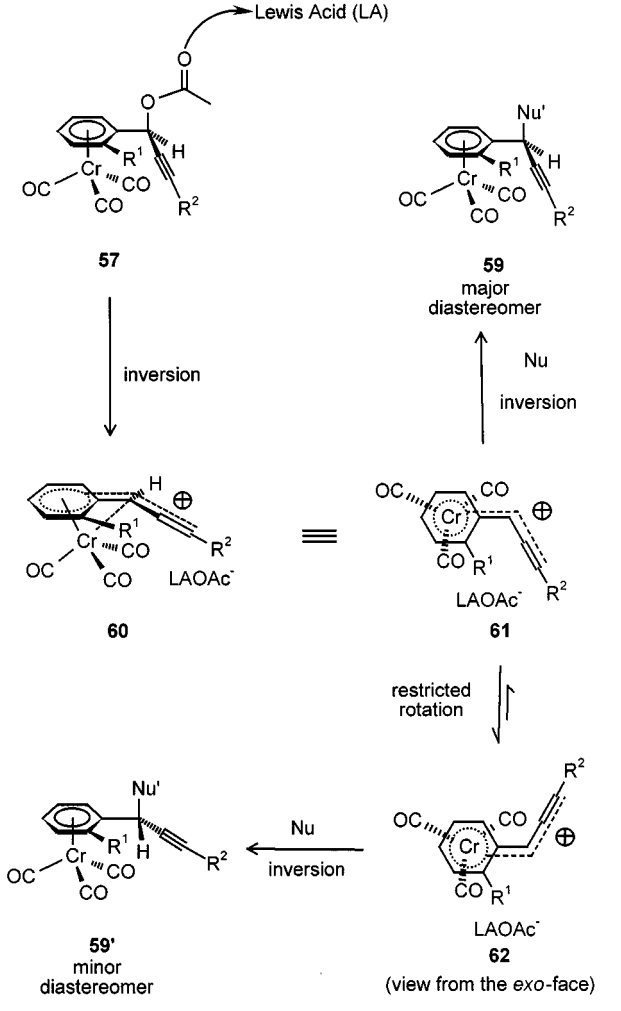
Scheme 26. Diastereoselective synthesis of planar chiral complex substituted propargyl acetates **57**

Upon ionization of the diastereomerically pure planar chiral propargyl acetates **57** with trimethylsilyl triflate (TMSOTf), tin tetrachloride or titanium tetrachloride, the formation of intensively colored (arene)Cr(CO)$_3$-substituted α-propargyl cations **58** (cation **41** with $R^2 = H$) is observed (Scheme 27). These cations can then be trapped with various π-, sulfur, oxygen and nitrogen nucleophiles to give the propargyl compounds **59** in good yields and remarkably high diastereoselectivities.[44]

The relative stereochemistry of the products **59** was elucidated by several X-ray structure analyses and correlated with the ^{1}H NMR spectra.[44,46] Assuming a double inversion mechanism[12c,12d,12f] as a consequence of an ionization of **57** with inversion followed by a nucleophilic attack with inversion, the observed diastereoselectivity can be readily

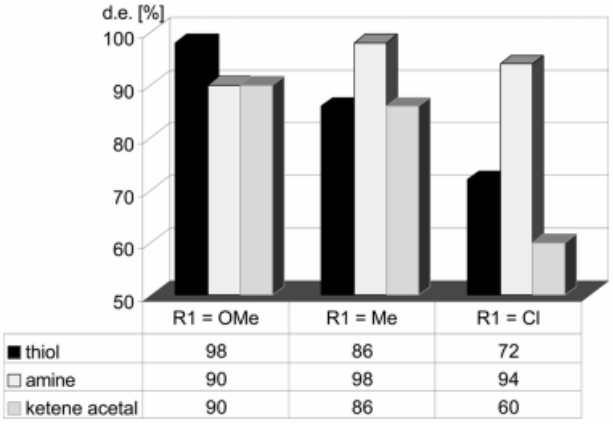


Scheme 27. Diastereoselective cationic propargylations with planar chiral complex substituted propargyl cations **58**



Scheme 28. Mechanistic pathway and origin of the loss of diastereoselectivity as a result of a *syn-anti* isomerization process on the cationic stage

explained (Scheme 28). Most crucial in this model is the configurational stability of the propargyl cation **60**. The observation of the epimeric minor diastereomer **59′** is a result of the rotation of the propargyl cation side-chain around the $C_{ispo}-C_{\alpha}$ bond from the *syn*-diastereomer **61** to give the diastereomeric *anti*-cation **62**.[44b]



	R1 = OMe	R1 = Me	R1 = Cl
thiol	98	86	72
amine	90	98	94
ketene acetal	90	86	60

Figure 1. Dependence of the $de = [(dr - 1)/(dr + 1)]\times 100$ (%) of **58** on the variation of the *ortho* substituent; R^1, R^2 = H, R^3 = Ph

The conformational stability of the cationic propargyl side-chain is significantly influenced by the substituent effect of the *ortho*-substituent (+M/+I) on the complexed phenyl ring and the neighboring-group effect of the chromiumcarbonyl tripod.[44b] Upon increasing the donor character of the *ortho*-substituent the configurational stability of the cation is enhanced, and thus the diastereoselectivity improves regardless of the trapping nucleophile (Figure 1).

Diastereoselective nucleophilic additions to stable (arene)$Cr(CO)_3$-substituted α-propargyl cations **58** are not only a simple extension of chromiumcarbonyl stabilization from benzylic cations to conjugated side chains, but, in ad-

dition, the problem of a regio- *and* stereoselective propargylation of an ambident propargyl cation *without* simultaneous complexation of the triple bond is solved for the first time. The (arene)$Cr(CO)_3$-substituted α-propargyl cations **58** are suitable novel organometallic electrophiles for future synthetic applications and, with respect to their enhanced electrophilic reactivity, they can be considered to be complementary to the well-established Nicholas cations **3**.

4. Conclusion

Besides the well-known application of the dicobalthexacarbonyl-complexed propargyl cations **3** in stereoselective synthesis, diastereoselective nucleophilic additions to configurationally stable arene chromiumcarbonyl-substituted propargyl cations **58** have now also been shown to be synthetically useful, and this concept will be extended to additions with double diastereofacial selectivity in the sense of a subsequent asymmetric induction of adjacent stereogenic centers. Further studies will be directed to enantioselective cationic propargylations with homochiral (arene)$Cr(CO)_3$ stabilized α-propargyl cations and will be developed towards highly selective and concise syntheses of aromatic sesquiterpenes and norlignans. These studies are currently in progress.

Acknowledgments

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