CHEMICAL REVIEWS

REVIEW

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Catalytic Asymmetric Propargylation

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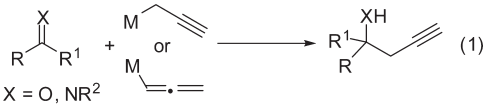
CONTENTS

1. Introduction 1914
2. Asymmetric Propargylation Involving Addition Reactions 1914
   2.1. Enantioselective Propargylation of Carbonyls Using Stoichiometric Amounts of Chiral Sources 1915
   2.2. Enantioselective Propargylation of Imines Using Stoichiometric Amounts of Chiral Sources 1916
   2.3. Catalytic Asymmetric Propargylation Using Allenyl Metals 1917
3. Chromium-Catalyzed Asymmetric Propargylation 1922
4. Asymmetric Propargylic Substitution Reaction 1924
   4.1. Catalytic Asymmetric Propargylic Substitution Using Carbon Nucleophiles 1925
   4.2. Catalytic Asymmetric Propargylic Substitution Using Heteroatom Nucleophiles 1932
5. Coupling Reactions of Metal Reagents with Propargylic Halides 1933
6. Summary and Perspective 1934
Author Information 1934
Biographies 1934
Acknowledgment 1935
References 1935

1. INTRODUCTION

The propargylation reaction is one of the most important fundamental reactions in organic synthesis. It features mild reaction conditions, a tolerance of a diverse range of functional groups, and the easy construction of carbon−carbon and carbon−heteroatom bonds.[1] The high density of functional groups of the resulting products renders them exceptionally versatile synthetic intermediates.

The propargylation reactions covered in this review mainly refer to those reactions that incorporate a propargyl functional group into the product. This involves the propynyl equivalent acting as either a nucleophile or an electrophile. These reactions can be roughly classified into two types. The first involves the propargylation of carbonyl compounds and imines with organometallic reagents such as propargyl or allenyl metal species (eq 1). The second involves the direct propargylic substitution of propargyl alcohols or their derivatives with nucleophiles (eq 2).



Catalytic asymmetric reactions play a prominent role in modern organic synthesis. They allow efficient access to a variety of important enantiomerically rich molecules to meet the growing demands of both industry and academic researchers.[2] Catalytic asymmetric reactions can produce large quantities of optically active products with a very high efficiency using small amounts of chiral catalysts. Consequently, this particular research area has great economic potential and is becoming increasingly attractive. Although asymmetric propargylation has received continuous attention from the chemical community in recent decades, only limited attention had been paid to catalytic asymmetric propargylation compared to the tremendous advances in asymmetric catalysis. However, more recently this situation has been changing with significant progress being made in this area. Some examples are the Cu-catalyzed asymmetric propargylation of aldehydes and ketones using organoboron reagents, the transition metal-catalyzed asymmetric propargylic substitution of propargyl alcohols with various nucleophiles, and last the transition metal-catalyzed asymmetric coupling reaction of propargyl halides.

This review will survey the literature in the area of catalytic asymmetric propargylation, with a focus on recent achievements using metal catalysts. In addition, some other developments of propargylation reactions will also be discussed.

2. ASYMMETRIC PROPARGYLATION INVOLVING ADDITION REACTIONS

The reaction of carbonyl compounds with propargyl, as well as other allenyl metal reagents, affords homopropargyl alcohols. As one of the most important propargylation reactions, it has received attention for many years. As far as we can ascertain, the earliest report of the propargylation of carbonyl compounds with organometallics dates back as far to 1950. Prévost et al.

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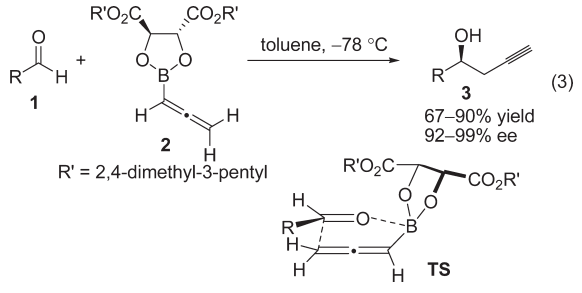
found that the reaction of allenic Grignard reagents with carbonyl compounds afforded mixtures of β-acetylenic and α-allenic carbinols.[3] Since then, a wide variety of organometallic reagents including those derived from lithium,[4] magnesium,[5] aluminum,[6] zinc,[7] titanium,[8] tin,[9] silicon,[10] and boron reagents[11] have all been successfully applied to propargylation reactions. Usually, these reactions suffer problems of selectivity because the propargylic organometallics can easily rearrange to the corresponding allenic analogues. This results in mixtures of the two reagents, which in turn react with the carbonyl substrates to afford mixtures of β-acetylenic and α-allenic carbinols.[1a,c,12] The reaction of the propargylic organometallics or their allenic analogues can proceed either by a S_E2 or a S_E2' pathway to give the carbinol mixtures. In addition, other factors, such as the nature of the metal center, any steric hindrance of the α- and γ-carbon of the propargylic reagent, and the reactivity of the electrophile can all influence the selectivity.

One possible solution to obtaining a more selective propargylation reaction is to use allenyl metal reagents.The reason is because they add to carbonyl compounds via a chelate transition state (S_E2' process), thus providing the desired β-acetylenic alcohols with regioselectivity control (Figure 1).[8a,12]

2.1. Enantioselective Propargylation of Carbonyls Using Stoichiometric Amounts of Chiral Sources

Although research into the enantioselective propargylation of carbonyls with allenyl reagents has lagged somewhat behind that on the asymmetric addition of allylic nucleophiles to carbonyl compounds, there has still been some significant progress achieved in recent decades.

Early asymmetric propargylation reactions relied heavily on the use of chiral allenyl organometallic derivatives. The first asymmetric propargylation of a carbonyl compound was reported by Yamamoto and co-workers in 1982, who realized the addition reaction of chiral allenylboronic esters **2** derived from modified tartrates to aldehydes. This reaction provided β-acetylenic alcohols with excellent regioselectivity and enantioselectivity (eq 3).[13,14] The reaction can occur either at the α- or γ-position of the allenyl boron reagent because of its ambident nucleophilic properties. However, it was found that the regioselectivity was controlled by the addition of the reagent to the aldehyde via a cyclic transition state. According to the favored transition state (TS), the presence of a bulky tartrate ester in the allenyl boronic ester **2** has important implications for the stereoselectivity, because the alkoxy group of the tartrate ester can shield the *re* face of the aldehyde. It was shown that the allenyl boronic ester **2** derived from 2,4-dimethyl-3-pentanol was the most effective propargylation reagent. The homopropargylic alcohols **3** were obtained with a yield of up to 99% ee.



Marshall's group made an impressive contribution to the enantioselective propargylation of carbonyls.[15] Using an *anti*-S_N2'

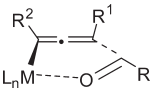
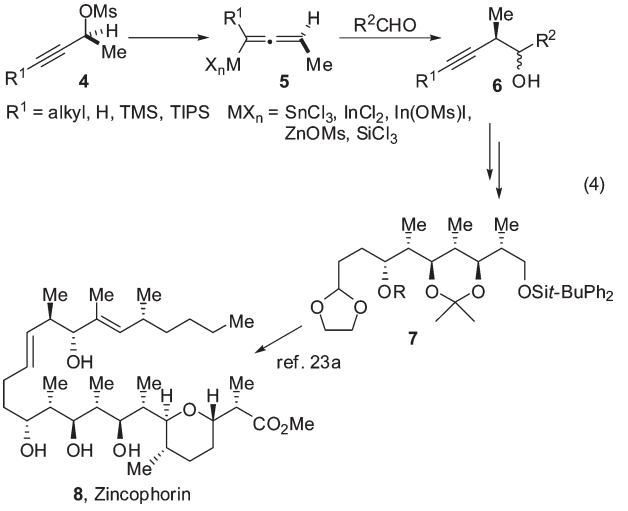


Figure 1. Proposed transition state for propargylation of aldehydes with an allenyl metal.

process, this group developed many efficient routes for preparing a range of axially chiral allenic organometallic compounds **5** such as allenylstannanes,[16] allenylsilanes,[17] allenylzinc,[18] and allenylindium[19] from chiral propargylic mesylate **4** and the corresponding metal reagents. These chiral allenyl metal reagents **5** reacted with various aldehydes in the presence of metal catalysts to afford the homopropargylic alcohols **6** with multiple chiral centers with excellent diastereoselectivities (eq 4). Of particular note is the fact that the diastereoselectivity (*syn*/*anti*) and the configuration (*R*/*S*) of the resulted homopropargylic alcohols **6** are controllable by adjusting the structures of the substrates and the Lewis acids.



These homopropargylic alcohols are particularly valuable with their multiple chiral centers. They have been widely applied to the total synthesis of a host of polyketides. For example, the alcohol **6** was readily transformed into an acetonide acetal **7**, which is an intermediate in Danishefsky's synthesis of zincophorin **8** (eq 4).[20c] The reactions of the chiral allenyl metal reagent **5** with aldehydes also play an important role in the total synthesis of bafilomycin,[21] (−)-callystatin A,[22] membrenone C,[23] vancosamine,[24] amphidinolide X,[25] and 19-*epi*-amphidinolide X.[26]

Optically active α-oxazolidinonylallenylstannane **9**, prepared from *N*-propargyloxazolidinone[27] via a lithiation/stannylation sequence, is an efficient reagent for the asymmetric propargylation of carbonyl compounds. The reagent **9** reacted with various aldehydes in the presence of $BF_3 \cdot OEt_2$ to produce the β-hydroxypropargylamines **10** with high *syn* diastereoselectivity.[28a] A wide range of aldehydes, including aromatic, linear-chain, and branched-chain aliphatic, as well as α,β-unsaturated aldehydes, are all suitable substrates for the reaction. The diastereoselectivity of the reaction can be predicted using the Felkin−Ahn transition state model.[16c] The allenylstannane **9** attacks the *si* face of the aldehyde with the large oxazolidinone of **9** *anti* to the large R group of the aldehyde (eq 5). This particular methodology was subsequently applied as

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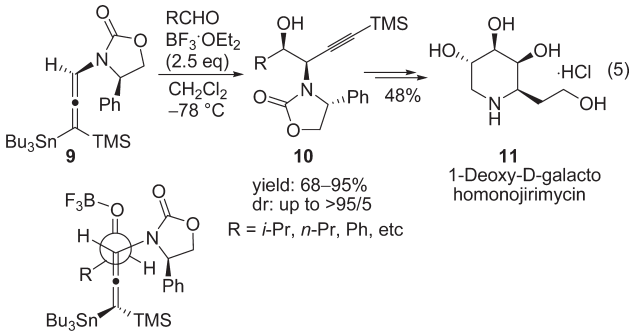
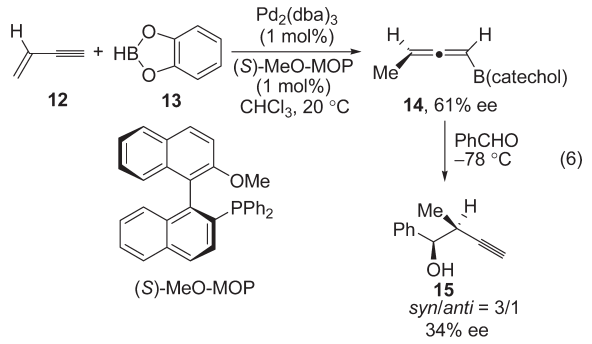
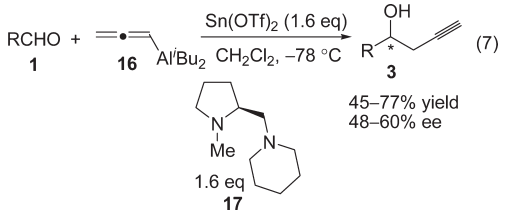
one of the key steps in the synthesis of 1-deoxy-D-galactohomonojirimycin (**11**).[29]



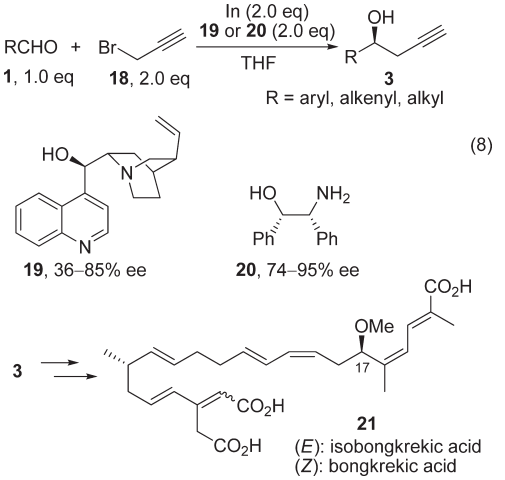
Hayashi and co-workers reported an indirect catalytic asymmetric propargylation reaction with moderate enantioselectivity. It proceeded via the catalytic asymmetric formation of the optically active allenyl borane **14** through the reaction of but-1-en-3-yne (**12**) with catecholborane **13** in the presence of a catalytic amount of a chiral palladium complex with a chiral monodentate phosphine ligand, (*S*)-(−)-MeO−MOP. The resulting allenyl borane **14** reacted with benzaldehyde by a *syn* attack to give the corresponding optically active but-3-ynyl alcohol **15** in 34% ee (eq 6).[30]



The use of stoichiometric amounts of an external chiral source represents another strategy in the asymmetric propargylation of aldehydes. The earliest example of such a reaction is that between benzaldehyde and prop-2-ynyl bromide in the presence of a Sn(IV)/(+)-diethyl tartrate complex. It afforded the 1-phenylbut-3-yn-1-ol as a byproduct in 8% yield. However, the optical purity of the product was not reported.[31] The asymmetric propargylation of aldehydes with allenic aluminum **16** with moderate enantioselectivities (48−60% ee) was realized in the presence of an excess amount of the chiral diamine **17** and tin triflate.[32] In this reaction, excellent regioselectivity was achieved and allenic alcohols were not observed (eq 7).



Loh et al. reported an indium-mediated asymmetric propargylation of both aromatic and aliphatic aldehydes with good enantioselectivity. They used stoichiometric amounts of cinchona alkaloid **19** under Barbier-reaction conditions (eq 8).[33] Commercially available (1*S*,2*R*)-(+)-2-amino-1,2-diphenylethanol (**20**) is another chiral auxiliary that proved useful in the reaction. It showed better stereocontrol ability than (−)-cinchonidine and afforded the products **3** with higher enantioselectivity (eq 8).[34] Although the indium-mediated propargylation method needs 2 equiv of chiral reagent, it still has some advantages such as mild reaction conditions, good functional group compatibility, experimental simplicity, and the commercial availability of inexpensive chiral reagents. All these advantages make it a useful protocol in organic synthesis. The total synthesis of both bongkrekic and isobongkrekic acids **21** serves as an example of where the method proved useful for installing the C17 chiral center.[35]



2.2. Enantioselective Propargylation of Imines Using Stoichiometric Amounts of Chiral Sources

As discussed in the previous section, although to date the enantioselective propargylation of carbonyls has been well developed, the use of imines, however, as the electrophile in such reactions has received much less attention. Among the possible reasons are the fact that imines are less reactive compared to carbonyl compounds because of the difference in electronegativity of the N and O atoms. Also, because imines have an *E* or *Z* geometry caused by the presence of the substituent on the N atom, this can result in difficulties in controlling the stereochemistry of the reaction. In addition, imines are also easily hydrolyzed. In spite of these difficulties, however, several successful examples of the enantioselective propargylation of imines have been reported in recent years.

Lai and Soderquist successfully extended the use of chiral organoborane regents containing the 10-trimethylsilyl-9-borabicyclo[3.3.2]-decane (10-TMS-9-BBD) ring system,[14d] which they developed, to the asymmetric propargylation of imines. The reaction of enantiomerically pure allenylborane **22** and the imine **23** afforded the propargyl amine **24** in 91% yield with 73% ee (eq 9). The lower selectivity may result from the small size difference between the allenyl group attached to the boron atom and the incoming imine. In an effort to improve it, *B*-allenyl-10-TMS-9-BBD **25** with the bulkier allenyl group was used in the addition reaction of the imine. The ee value of the resulting α-TMS propargylic carbamines **26** was as high as 99%

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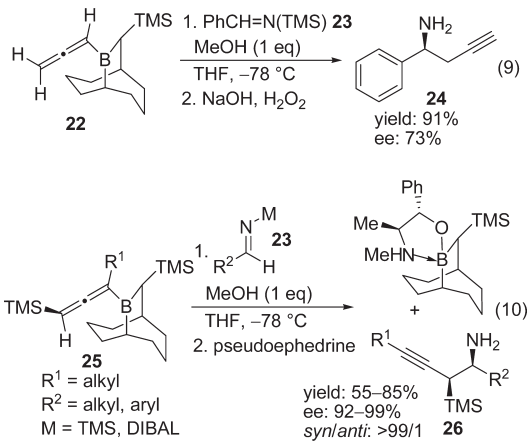
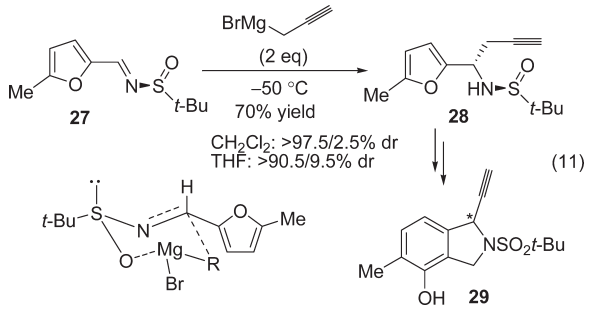
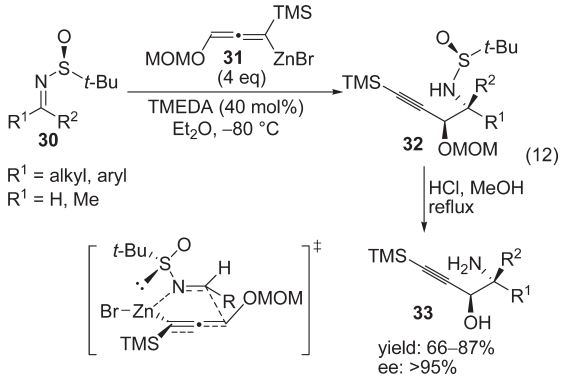
(eq 10).[36] This addition reaction represents a facial access to the chiral homopropargylic amines.



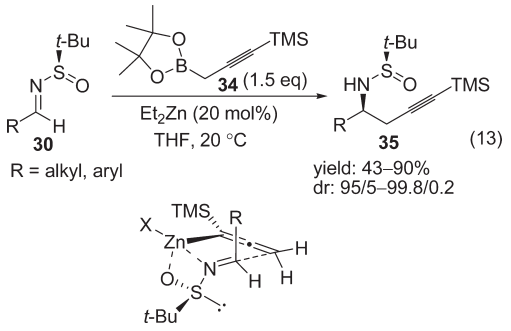
The enantioselective propargylation of imines has also been realized by using chiral imines. Undoubtedly, the enantiomerically pure sulfinyl imines are among the most widely used.[37] The addition of pregenerated propargylmagnesium to enantiomerically pure Ellman's *N*-*tert*-butanesulfinimine, which contains a furan group **27**, delivered the homopropargylic amine **28**. The selectivity of the reaction was influenced by the solvent as evidenced by the fact that the diastereoselectivity in CH_2Cl_2 was better than that in tetrahydrofuran (THF) (eq 11).[38] A transition state, supporting the less polar solvent, for the addition reaction based on the observed newly formed chiral centers in the product was proposed.[39] The products were then converted into chiral dihydroisoindole **29**, which is found in some bioactive compounds.[40]



Chemla and Ferreira reported that the racemic 3-alkoxy allenylzinc species **31** reacted with enantiomerically pure Ellman's *N*-*tert*-butanesulfinimines **30** efficiently, leading to the corresponding diastereomerically enriched acetylenic (S_S,3*S*,4*R*)-α-*N*-*tert*-butanesulfinamidoalkyl methoxymethyl ethers **32** (eq 12). The reaction mechanism postulated involved a monochelate-type transition state based on the observed stereochemistry of the product.[41] The compounds **32** were treated with dry methanolic hydrochloric acid under reflux to yield the *anti*-(3*S*,4*R*)-4-aminoalk-1-yn-3-ols **33** with excellent enantioselecitvity.[42] This protocol offers a convenient access to functionalized acetylenic 1,2-amino alcohols, which are useful building blocks for the synthesis of a range of biologically active compounds such as (−)-α-conhydrone[43a] and (−)-1-hydroxyquinolizidinone.[43b] A drawback of the protocol is the use of excess amounts of the preformed allenylzincs.



Fandrick et al. developed a highly diastereoselective zinc-catalyzed propargylation of *tert*-butanesulfinyl imines **30** (eq 13). Both aliphatic and aryl homopropargylic amines **35** were afforded with up to 99.8:0.2 diastereoselectivity.[44] The proposed mechanism was depicted as involving a chelated six-membered transition state to rationalize the stereochemistry.



2.3. Catalytic Asymmetric Propargylation Using Allenyl Metals

Although asymmetric catalysis using chiral organometal complexes and chiral organomolecules has shown many advantages and a range of catalytic asymmetric reactions have been well documented, the catalytic version of the asymmetric propargylation of carbonyls only first appeared in 1994 when Keck et al. reported the first example of a chiral Lewis acid-catalyzed addition of allenylstannane to aldehydes. Keck et al. showed that the chiral Lewis acid prepared from (*R*)-BINOL and $Ti(O^iPr)_4$ could serve as a catalyst in the propargylation of aldehydes with allenyltri-*n*-butylstannane (**36**). The reaction afforded the homopropargylic alcohols **3** with 82 to >99% enantiomeric excess (ee).[45] However, the method suffers from high catalyst loading (50−100 mol %) and long reaction times (72−100 h). By employing a similar catalyst (the 1:1 mixture of (*S*)-BINOL−$Ti(O^iPr)_4$ or (*S*)-BINOL−$Zr(O^iPr)_4$), Yu et al. developed a catalytic asymmetric propargylation of a range of aldehydes in the presence of the bifunctional synergetic reagent Et_2BS^iPr.[46] This in fact was a key for the success of the reaction.[47] The enantioselectivity using a Zr^{IV} complex as catalyst (68−92% ee; entries 2, 6, 9, 12, and 14, Table 1) was found to be slightly lower than that using the Ti^{IV} complex (88−94% ee; entries 1, 5, 8, 11, and 13, Table 1). The reaction also produced trace amounts of isomeric allenyl alcohols (<2% for Ti^{IV} complex; < 3% for Zr^{IV} complex). The authors suggest that the acceleration of Et_2BS^iPr in the catalytic process may involve the dissociation of the product from

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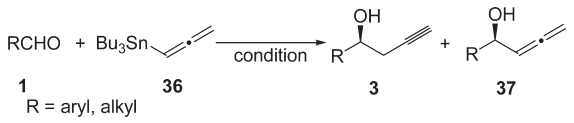
Table 1. Chiral Lewis Acid-Catalyzed Asymmetric Propargylation of Aldehydes with Allenyl Stannane 36



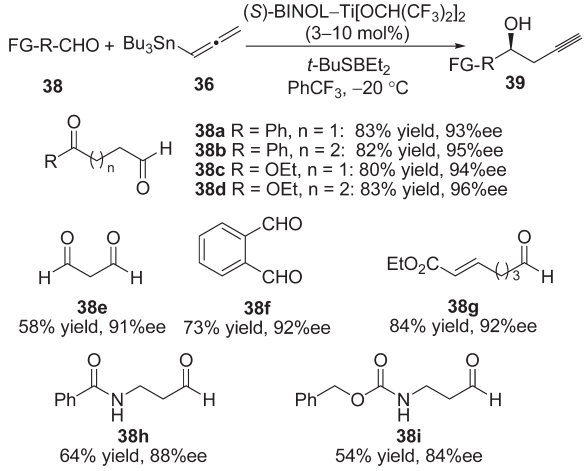
entry	R	condition[a]	3/37	yield (%)	ee (%)
1	$PhCH_2CH_2$	**A**	>98/2	86	94
2	$PhCH_2CH_2$	**B**	>97/3	72	92
3	$PhCH_2CH_2$	**C**	>98/2	72	>97
4	$PhCH_2CH_2$	**D**	15/1	64	−92
5	C_6H_{11}	**A**	>98/2	75	92
6	C_6H_{11}	**B**	>97/3	71	87
7	C_6H_{11}	**C**	94/6	71	94
8	*c*-C_6H_{11}	**A**	>98/2	73	91
9	*c*-C_6H_{11}	**B**	93/7	67	68
10	*c*-C_6H_{11}	**C**	78/22	44	95
11	Me_2CHCH_2	**A**	>98/2	61	95
12	Me_2CHCH_2	**B**	>97/3	65	91
13	Ph	**A**	>98/2	52	92
14	Ph	**B**	>97/3	44	71
15	Ph	**C**	90/10	57	92
16	Ph	**D**	10/1	69	−92

[a] Condition **A**: (*S*)-BINOL−Ti (10 mol %), Et_2BS^iPr, CH_2Cl_2, −20 °C.[47] Condition **B**: (*S*)-BINOL−Zr (10 mol %), Et_2BS^iPr, CH_2Cl_2, −20 °C.[47] Condition **C**: (*S*)-BINOL−$Ti(O^iPr)_4$ (10 mol %), $B(OMe)_3$, CH_2Cl_2, 0 °C.[48] Condition **D**: chiral bis-Ti oxide **41** (10 mol %), CH_2Cl_2, 0 °C.[52]

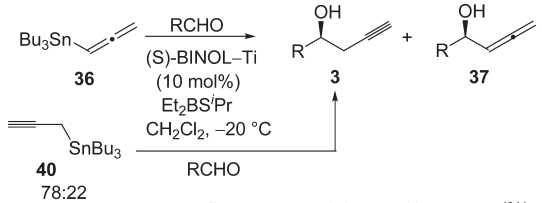
the reaction complex and the regeneration of the chiral catalyst. Also, the origin of the isomeric allenyl alcohols may result from an equilibration between the allenyl- and prop-2-ynyltin reagents or an α- and γ-orientation to tin in the transition state.[47] $B(OMe)_3$ proved to be a generally superior co-Lewis acid in the catalytic asymmetric propargylation of aldehyde mediated by (*S*)-BINOL−$Ti(O^iPr)_4$ (entries 3, 7, 10, and 15, Table 1).[48] The mechanistic behavior of $B(OMe)_3$ has been proposed as being similar to that of Et_2BS^iPr.

On the basis of the above results, Yu et al. extended the substrate scope of the (*S*)-BINOL−Ti(IV)-catalyzed propargylation to a variety of aldehydes **38** containing additional carbonyl groups such as ketone, aldehyde, ester, amide, and carbamoyl. When $Ti[OCH(CF_3)_2]_4$ was the Lewis acid, *t*-BuSBEt$_2$ as the additive and $PhCF_3$ as the solvent proved to be the optimal reaction conditions. An 84−96% ee for the corresponding homopropargylic alcohols **39** was achieved (Scheme 1).[49] These functionalized aldehydes showed increased reactivity toward the propargylation compared to normal aldehydes employing chiral Lewis acid and *t*-BuSBEt$_2$. For example, product **39a** in 83% with an isolated yield with 93% ee was obtained when the aldehyde **38a** was treated with allenyltributylstannane **36** and *t*-BuSBEt$_2$ using 3 mol % of (*S*)-BINOL−$Ti[OCH(CF_3)_2]_2$ complex as the catalyst. A yield of 80% with 92% ee was obtained when $PhCH_2CH_2CHO$ was the substrate, using 100 mol % of BINOL−Ti(IV) complex.[45] In addition, results showed a 86% yield with 94% ee using 10 mol % of (*S*)-BINOL−$Ti[OCH(CF_3)_2]_2$

Scheme 1. Asymmetric Propargylation of Functionalized Aldehydes Catalyzed by (*S*)-BINOL−$Ti[OCH(CF_3)_2]_2$



Scheme 2. Catalytic Asymmetric Propargylation with Allenyltin 36 and Propargyltin 40



	R	3:37	%	ee (%)
36:	$PhCH_2CH_2$	>98:2	86	94
	nC_6H_{13}	>98:2	75	92
40:	$PhCH_2CH_2$	89:11	71	91
	nC_6H_{13}	87:13	70	92

catalyst, *i*-PrSBEt$_2$.[47] It was found that *t*-BuSBEt$_2$ was essential for reaction to occur; no reaction occurred for BINOL−Ti(IV) alone.

During their investigations, the authors observed that the equilibrium between the allenyl- and propargylstannane reagents could be regulated in the presence of (*S*)-BINOL−Ti(IV) and *i*-PrSBEt$_2$.[50] In general, allenyl reagents afforded mainly propargylic adducts, whereas propargylic reagents provided allenyl adducts via a S_E2' addition to the aldehyde. This reaction was mediated by a Lewis acid catalyst in the absence of equilibrating reagents such as $BuSnCl_3$.[15a] However, the homopropargyl alcohols **2** were the major product with high enantioselectivity using allenyltin **36** or propargyltin **45** as the nucleophile under identical conditions (Scheme 2). These phenomena are clarified by the existence of an equilibrium between the allenyl- and propargyltin reagents under the reaction conditions. The reaction may proceed via either the transition state **A** or **B** to yield the allenyl alcohols **42** and homopropargylic alcohols **2**, respectively (Scheme 3). The transition state may be affected by several factors such as steric hindrance, orientation, and stability under kinetic control. Therefore, the authors proposed that the thermodynamic stability of the tin reagents as well as subtle geometrical preferences in orientation in the transition states might dominate the regioselectivity of these transformations.

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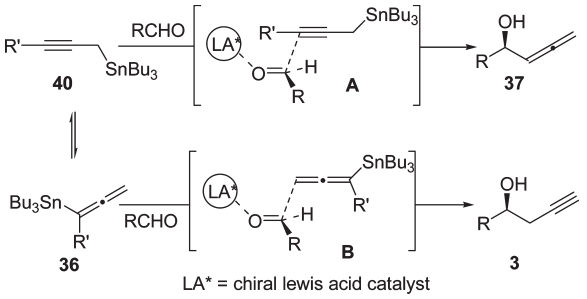
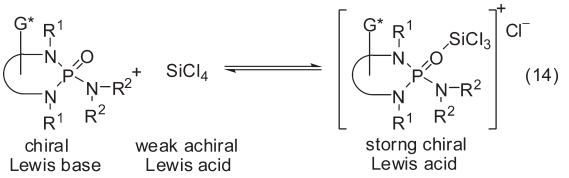
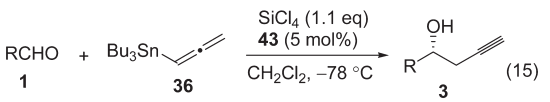
Scheme 3. Formation of 3 and 37 from the Equilibrium between 36 and 40



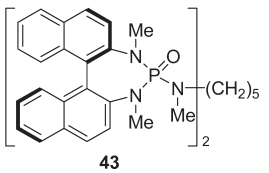
The catalytic enantioselective propargylation of aldehydes with allenyltributyltin **36** also proceeded efficiently using in situ prepared chiral bis{[(*S*)-binaphthoxy](isopropoxy)titanium} oxide **41**.[51] The corresponding homopropargylic alcohols **3** were obtained in >90% ee (entries 4 and 16, Table 1).[52] It was noted that the bis Ti^{IV} complex **41** demonstrated much better catalytic activity than the monomer of the Ti complex **42** (Figure 2). Interestingly, a better enantioselectivity was realized when the reaction proceeded at lower concentrations of substrate. However, an excess of allenyltributyltin **36** was needed to obtain good chemical yield.

Lewis base activation of the Lewis acid is an efficient strategy in designing a catalyst for asymmetric catalysis.[53] A similar strategy was also applied in the development of a catalyst for asymmetric propargylation reactions. Denmark and Wynn demonstrated that a weak achiral Lewis acid such as $SiCl_4$ can be activated by a chiral Lewis base to afford a strong chiral Lewis acid (eq 14). On the basis of the above strategy, the catalyst, binaphthyl-based phosphoramide **43**·$SiCl_4$, was developed. This was used to successfully catalyze the propargylation of several aldehydes with allenyltributylstannane **36** at −78 °C. Yields of 81−95% with 87−97% ee were achieved (eq 15).[54] The reaction features excellent regioselectivity, as only 1,2-addition was observed with cinnamaldehyde and in no case was the isomeric allenyl alcohol detected.





a R = Ph, 81% yield, 97% ee (*R*)
b R = cinnamyl, 90% yield, 87% ee (*R*)
c R = 2-naphthyl, 95% yield, 93%ee (*R*)



For a long time, the reagents in catalytic asymmetric propargylation were limited to those derived from the tin analogue **36**.

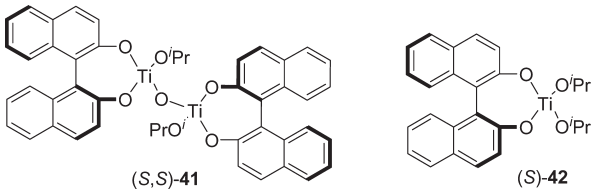
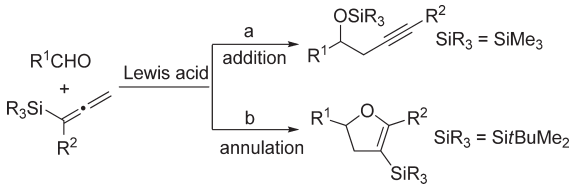
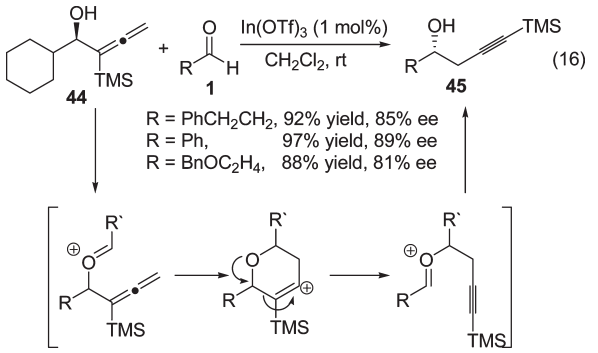


Figure 2. Chiral (*S*)-BINOL−Ti complexes.

Scheme 4. Two Reaction Paths of Allenylsilanes with Aldehydes



Evans et al. discovered that silylallenes could also serve as efficient nucleophiles in the catalytic asymmetric propargylation reaction of aldehydes. This extended the scope of nucleophiles significantly (vide infra). One of the advantages of using silylallenes over the tin analogues is their lower toxicity. It was observed that the normal propargylation pathway occurs for the reaction of trimethylsilylallenes with aldehydes (path a, Scheme 4),[10,55] while functionalized dihydrofurans are produced by the [3 + 2]-annulation in the case of sterically demanding allenylsilanes (path b, Scheme 4).[56]



In addition, homopropargylic alcohols were obtained via a propargyl transfer from 2-trimethylsilyl allenic alcohol to aldehydes in the presence of Lewis acid catalysts. The enantiomerically enriched allenic alcohol **44** in 92% ee afforded the homopropargylic alcohols **45** in 81−95% ee. They have the opposite configuration of the starting material **44** (eq 16).[57] This result suggests that the reaction may proceed via an oxonium [3,3]-sigmatropic rearrangement of an allenic alcohol.

As shown in Table 2, the addition of allenylsilanes **47** containing either linear or branched alkyl substituents to ethyl glyoxylate (**46**) using bis(oxazolinyl)pyridine−scandium triflate **48** as the catalyst afforded the products **49** with yields of 90−98% ee and 63−96% overall.[58] The presence of hexafluoro-2-propanol (HFIP) was found to improve the chemical yield but not to influence either catalyst activity or the enantioselectivity. It was proposed that rather it served to suppress the formation

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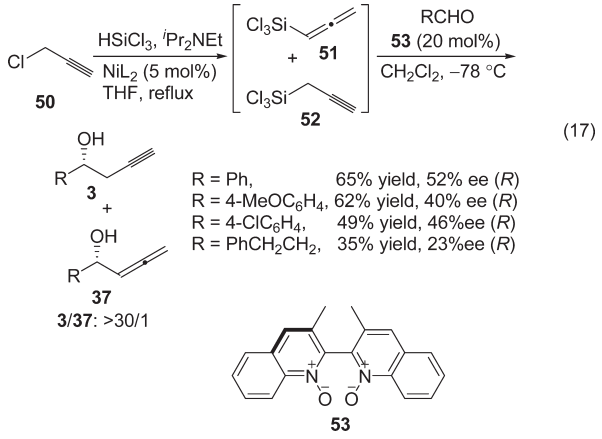
of oligomeric byproducts. On the basis of the X-ray crystallographic study of the bis(oxazolinyl)pyridine−scandium triflate complex, the authors explained the stereochemical course of the addition of allenylsilane to aldehydes. The allenylsilane **47** attacks the *re* face of the aldehydes **46** because the *si* face is effectively shielded by a phenyl group of the bis(oxazolinyl)pyridine ligand.

Although in general chiral Lewis acids are the catalyst of choice in the catalytic asymmetric addition of the propargylic anion to aldehydes, chiral Lewis bases are also effective in some cases. It was found that the chiral *N*-oxide **53** is an efficient catalyst for the reaction of both aromatic and aliphatic aldehydes with mixtures of propargyltrichlorosilane **51** and the allenyltrichlorosilane **52**. The silanes **51** and **52** were prepared in situ from propargyl chloride **50** and afforded the optically active homopropargylic alcohols **3** selectively with excellent regioselectivity, albeit with only moderate enantioselectivity (eq 17).[59] In the silylation of propargyl chloride, the metal appears to dominate the regioselectivity of the reaction as evidenced by the fact that, when CuCl was used instead of nickel bis(acetylacetate), the allenic alcohols **37** were formed as the major isomers.[60]

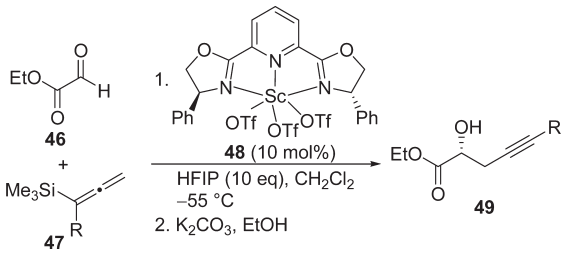


(17)

Although allenyl−metal reagents are the most useful nucleophiles for achieving good regioselectivities in propargylations, propargyl borolane has been used as an alternative in such reactions. Usually, propargyl boranes react rapidly with the aldehydes to furnish the allenylic alcohols.[11c,14d] Chemists at Boehringer Ingelheim achieved an efficient zinc-catalyzed propargylation of aldehydes and ketones using propargyl pinacol boronates and diethanolamine boronates by suppressing the direct reaction of the propargyl boranes with aldehydes. This involved a faster B/Zn exchange.[61−63] However, only a modest enantioselectivity was obtained for the zinc-catalyzed propargylation with chiral amino alcohol ligands. Hence, an enantioselective version of propargylation using propargyl borolane as the nucleophile was developed by using a B/Cu exchange.[64] One possible reaction mechanism could involve an allenyl Cu intermediate **54**,[28d] produced by exposure of the propargyl borolane **34** to Cu−alkoxide. This in turn reacted with the aldehydes and was followed by transmetalation to regenerate the allenyl Cu **54**, thus completing the catalytic cycle (Scheme 5).

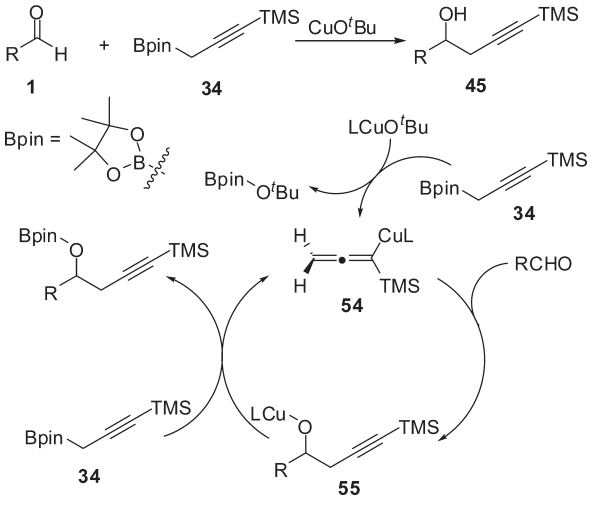
The copper-catalyzed enantioselective propargylation of aromatic, alkenyl, and aliphatic aldehydes **1** with the propargyl borolane reagent **34** was established by utilizing an air-stable bisdihydrobenzooxaphosphole (BIBOP) ligand **56**.[65] This afforded synthetically useful chiral homopropargyl alcohols **45** with excellent ee values (Scheme 6).[66] The protocol

Table 2. Bis(oxazolinyl)pyridine−Scandium Triflate Complex-Catalyzed Enantioselective Addition of Allenylsilanes to Aldehydes

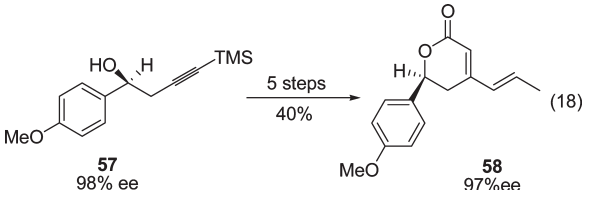


entry	R	yield (%)	ee (%)
1	Me	95	98
2	*n*Bu	90	94
3	Cy	95	90
4	$(CH_2)_3$OTBS	75	93
5	Ph	63	97
6	*i*Pr	96	93

Scheme 5. Proposed Mechanism for Cu−Alkoxide-Catalyzed Reaction of Aldehydes with Propargyl Borolane



showed good tolerance toward several functional groups including −COOR, −CN, and −NHCBz, among others. Surprisingly, substrates bearing heterocycles that were capable of coordinating to the catalyst were also tolerated. One noteworthy application of this method is demonstrated by the five-step conversion of the substrate **57** to yield chiral dihydropyranone **58** in 40% overall yield without racemization (eq 18).



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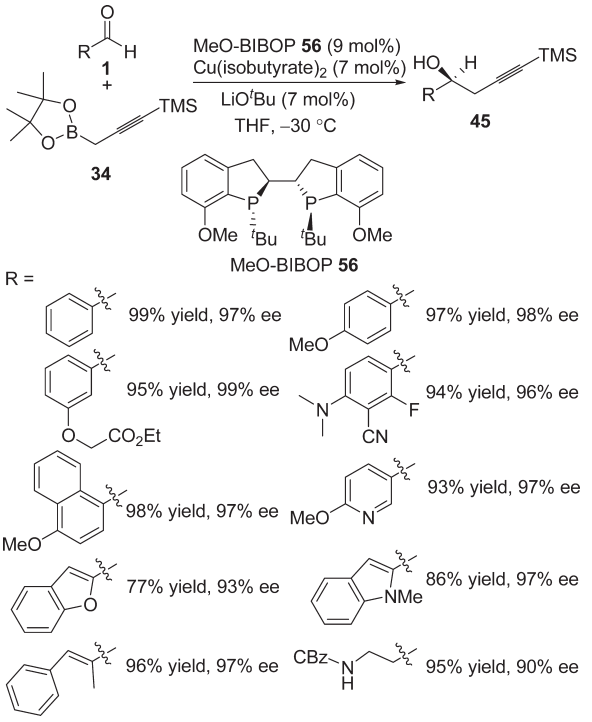
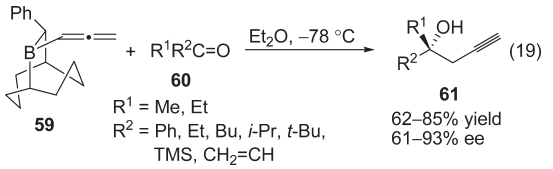
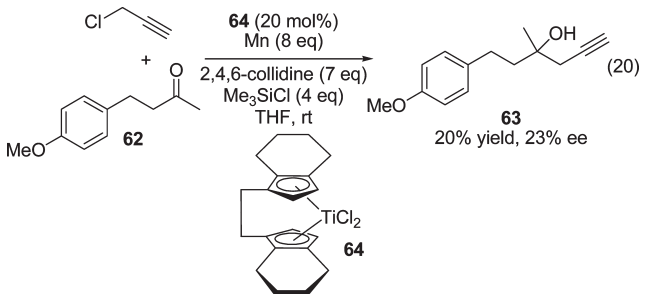
Scheme 6. Cu−Diphosphine-Catalyzed Asymmetric Propargylation of Aldehydes



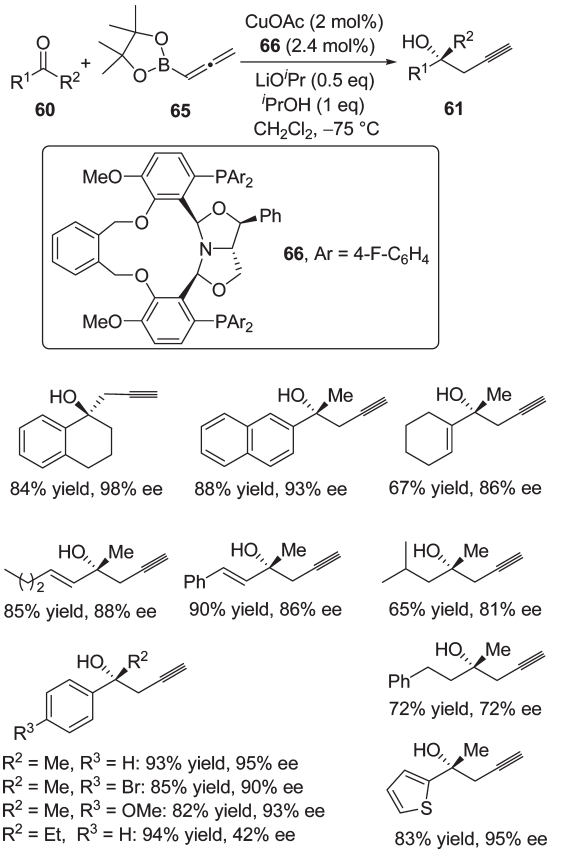
In most cases, aldehydes were the substrates in the catalytic asymmetric propargylation of carbonyl compounds with propargyl reagents. Because it is difficult to differentiate between the two substituents of ketones, reactions involving ketones remained a challenge for a long time. The enantioselective propargylation of ketones **60** using enantiomerically pure 10-phenyl-9-borabicyclo[3.3.2]decane (**59**) as the nucleophile was reported only recently. In general, high enantioselectivities (61−93%) were achieved for the resulting propargylic tertiary products **61** (eq 19).[67]



The commercially available Brintzinger complex **64** was found to catalyze a Barbier-type propargylation of the aliphatic ketone **62** with limited success. This is only one example of such a reaction where both low enantioselectivity (23%) and a low yield (20%) were disclosed (eq 20).[68]



Scheme 7. CuOAc−Diphosphine 66-Catalyzed Asymmetric Propargylation of Ketones



In this context, the great contribution made by Kanai, Shibasaki, and co-workers should be recognized. Their work led to a large step forward in the catalytic enantioselective propargylation of ketones. They demonstrated the excellent catalytic activities of the complex of CuOAc−diphosphine **66** in the enantioselective propargylation of a wide range of aromatic and aliphatic ketones **60** with allenylboronate **65**. Reaction led to the homopropargyl tertiary alcohols **61** with up to 98% enantioselectivity (Scheme 7).[69] Of particular note is the perfect regioselectivity of this reaction. Only γ-addition products were obtained. In all the reactions, there were no detected allenyl alcohol isomers as a result of α-addition. The reaction also showed its tolerance to other functional groups such as bromide, alkene, and heterocycles. This method represents the first practical catalytic asymmetric propargylation synthesis of ketones.

Catalytic enantioselective propargylation reactions of imines are very rare. To date, the only report is from Akiyama's group. The reaction of the α-imino ester **67** with the allenyltins **36** was carried out in the presence of the catalyst, which was derived from $Cu(CH_3CN)_4ClO_4$ and (*R*)-tol-BINAP in Et_2O at −30 °C (eq 21).[70] Although the nature of the substituents on the tin group of the allenyltins has been shown to have a significant influence on both the chemical yield and the regioselectivity, the effect on the enantioselectivity was less pronounced. The introduction of an ester group at the position α to the tin group resulted in a significant decrease in the chemical yields and enantioselectivity. The regioselectivity, on the other hand, remained

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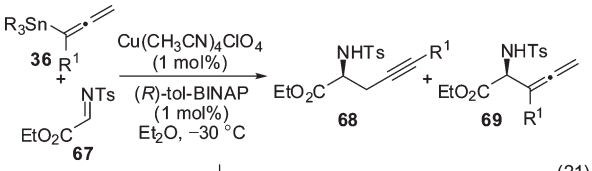
excellent. However, these results are based on data for only one imine.

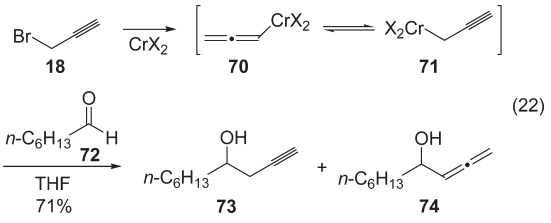


R, R^1	yield (%)	68/69	ee of 69 (%)
n-Bu, H	96	97/3	86
Ph, H	38	89/11	77
n-Bu, CO_2Me	34	>97/<3	11

(21)

3. CHROMIUM-CATALYZED ASYMMETRIC PROPARGYLATION

In addition to the use of organometallic reagents, the use of propargyl halides in the propargylation of carbonyl compounds catalyzed by low-valent metal species has also been developed over recent decades. This is largely due to their excellent compatibility with a range of functional groups, the mild reaction conditions required, the practical experimental condition requirements, and the broad scope of suitable substrates. Chromium salts have proven to be one of the best catalysts for such reactions. This discovery is the direct result of the seminal work of Nozaki, Hiyama, and co-workers in 1977. They found that insertion of Cr(II) into propargyl bromide **18** in anhydrous THF gave rise to mixtures of the reagents allenyl chromium(III) **70** as well as propargylic chromium(III) **71**. These in turn reacted with the aldehyde **72** to afford a mixture of propargylic alcohol **73** and allenyl alcohol **74** in 71% yield (eq 22).[71]

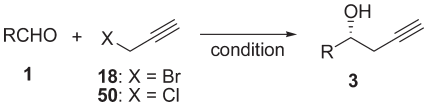


(22)

In the classical chromium-mediated propargylation reaction, a huge excess of a Cr(II) source is usually employed as a one-electron donor to produce the corresponding organochromium reagents. This drawback precludes its application to large-scale syntheses. In 1996, Fürstner and Shi made a great contribution in advancing this field, reporting the first example of an addition of an organic halide to an aldehyde using only a catalytic amount of chromium salts.[72] The key to the success of this approach is that trimethylchlorosilane is used as a scavenger for the chrominum alkoxide arising from the reaction of the organochromium reagents with the aldehyde in the step that releases the Cr(III) moiety. The active Cr(II) species is regenerated by means of a manganese powder as the stoichiometric reductant.

This groundbreaking work of Fürstner and co-workers opened up the practical applications of chromium-catalyzed asymmetric reactions of organic halides to aldehydes. On the basis of Fürstner's findings, Cozzi, Umani-Ronchi, and co-workers developed the first catalytic enantioselective addition of allylic chloride to aldehydes using the chiral complex [Cr(Salen)] as the catalyst.[73] Subsequently, they also found that this same chiral complex can effectively catalyze the asymmetric addition of

Table 3. Asymmetric Catalysis in the Nozaki−Hiyama Propargylation of Aldehydes



entry	condition[a]	R	yield (%)	ee (%)
1	**A**	C_6H_5	50	56
2	**B**	C_6H_5	93	78
3	**C**	C_6H_5	92	73
4	**A**	4-F−C_6H_4	45	56
5	**A**	4-^{t}Bu-C_6H_4	30	45
6	**B**	2-naphthyl	95	74
7	**B**	(*E*)-PhCH=CH	91	73
8	**C**	(*E*)-PhCH=CH	89	70
9	**A**	$C_6H_5CH_2CH_2$	21	15
10	**B**	$C_6H_5CH_2CH_2$	20	−51
11	**D**	$C_6H_5CH_2CH_2$	91	89
12	**B**	$CH_3(CH_2)_4$	55	−58
13	**D**	$CH_3(CH_2)_4$	82	81
14	**B**	cyclohexyl	86	82
15	**B**	^{t}Bu	41	98
16	**D**	^{t}Bu	55	92
17	**D**	TBDPSO$(CH_2)_3$	78	90

[a] Condition **A**: (1) $CrCl_3$/Salen **75** (10 mol %), Mn, TMSCl (2 equiv), CH_3CN. (2) H^+/THF.[74b] Condition **B**: (1) $CrCl_2$/**76c** (10 mol %), Mn (2 equiv), DIPEA (30 mol %), TMSCl (2 equiv), 1,2-dimethoxyethane (DME), room temperature (rt). (2) Tetra-*n*-butylammonium fluoride (TBAF).[77] Condition **C**: $CrBr_3$ (10 mol %), **77a** (11 mol %), LiCl (6.0 equiv) at 0 °C.[78] Condition **D**: $CrBr_3$ (10 mol %), **77b** (11 mol %), LiCl (6.0 equiv) at 0 °C.[78]

propargyl chloride to benzaldehyde.[74] The regioselectivity was within desirable limits, and the homopropargyl alcohol **3** was isolated in 50% yield with 56% ee (entry 1, Table 3). Several other aromatic aldehydes were also found to give the corresponding acetylic alcohols in moderate yields with moderate enantioselectivity (entries 4 and 5, Table 3). However, this catalyst system is not effective for aliphatic aldehydes. A yield of only 21% with an ee of 15% was obtained for 3-phenylpropanal (entry 9, Table 3). The low chemical yield is attributed to undesirable side reactions such as pinacol coupling or reduction of the carbonyl substrate. The regioselectivity of the reaction was explained by the proposed mechanistic model as depicted in Figure 4. The allenyl and propargyl organochromium species are believed to exist in dynamic equilibrium, and their ratio depends on both their structure and the additives used.[75] The fact that the [Cr(Salen)allenyl] complex **A** is more reactive than **B** [Cr(Salen)propargyl] leads to the regiochemistry observed. It should be noted that these catalytic systems involve a range of species and are really quite complicated. For example, some weak Lewis acids (i.e., MnX_2, [Cr(Salen)X]) may also play a subtle role in the catalytic cycle.[76]

The fact that there are still several less-than-ideal aspects to Cozzi and Umani-Ronchi's protocol, for example, low enantioselectivity, low chemical yields, and narrow substrate scope, means that there is an opportunity to develop an even

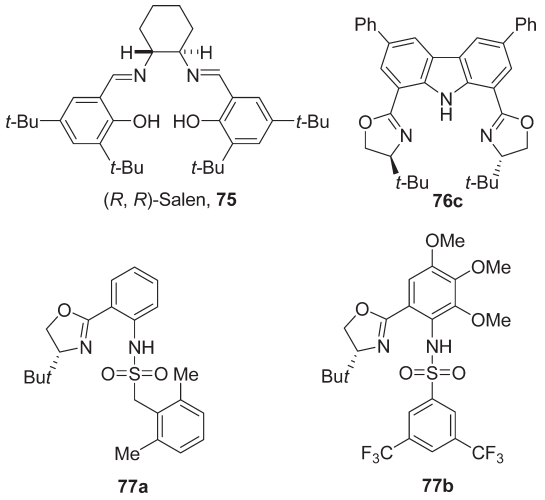


Figure 3. Chiral ligands used in the asymmetric propargylation of aldehydes.

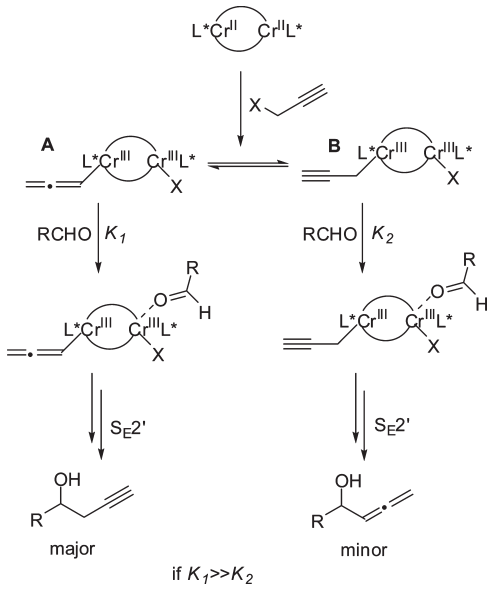


Figure 4. Proposed mechanism for regioselectivity of the [Cr(Salen)]-catalyzed propargylation.

more efficient chiral ligand with a view to achieving better stereocontrol. Chiral tridentate ligands **76** with a carbazole framework were developed by Nakada's group. These proved to be more effective chiral ligands than Salen **75** (Figure 3) in the chromium-catalyzed asymmetric propargylation of aldehydes.[77] The substituent on the ligands **76** plays a key role in the stereocontrol of the reaction (eq 23). The Cr(II) complexes with ligands **76a** and **76b** afforded the (*S*)-product with low ee, whereas that with **76c**, bearing the bulkier *tert*-butyl substituent, yielded the (*R*)-product with a much higher ee. On the downside, a longer reaction time was needed. The Cr(II) complex with the ligand **76c** (Figure 3) was successfully applied to the asymmetric propargylation of various aromatic and aliphatic aldehydes. Optimum enantioselectivities of between 73 and 98% ee were obtained for aromatic and sterically demanding aliphatic aldehydes (entries 2, 6, 7, 14, and 15, Table 3). However, it was found that the yields and ee's were lower for the reactions of linear hydrocinnamaldehyde (20% yield and

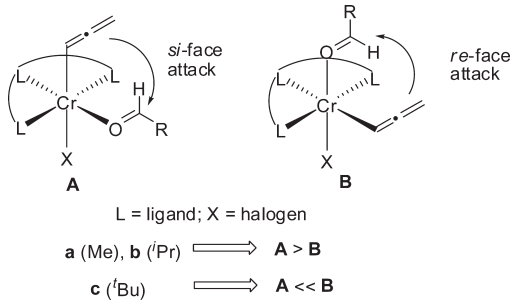
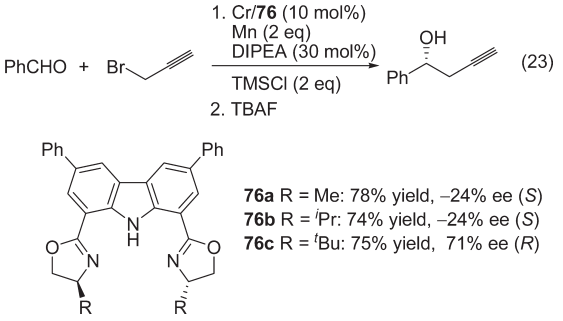


Figure 5. Proposed reaction models A and B for the chromium-catalyzed asymmetric propargylation using ligands **76a**−**c**.

51% ee; entry 10, Table 3) and *n*-pentylaldehyde (55% yield and 58% ee; entry 12, Table 3). The Cr(II)−**76c** complex-catalyzed propargylation of aldehydes achieved excellent regioselectivity. There was no allenyl alcohol observed in any of the reactions studied.



The enantioselectivity of this propargylation is rationalized by the model proposed as shown in Figure 5. When the substituent of the ligand **76** is small, an aldehyde attack at the *si*-face of the aldehyde is favored with coordination at the equatorial position preferred (model A, Figure 5). As the ligand substituents in **76** become bulkier, the steric strain increases between the aldehyde and the oxazoline. As a result, the aldehyde coordinates at the apical position, thus favoring the attack at the *re*-face of the aldehyde (model B, Figure 5).

Using another kind of highly efficient chiral ligands, Kishi's group developed the Cr-catalyzed highly enantioselective propargylation of various aliphatic and aromatic aldehydes. They designed and synthesized the sulfonamide series 77 (Figure 3).[78] Using 10 mol % of a catalyst derived from $CrBr_3$ and **77a** or **77b** at 0 °C, they successfully propargylated a range of aldehydes affording products in 55−94% yields with enantioselectivities ranging between 67% and 93% ee (entries 8, 11, 13, 16, 17, Table 3). Kishi's catalyst performs somewhat less well with respect to the enantioselectivity for benzaldehyde and *trans*-cinnamaldehyde than Nakada's catalyst (entries 3 vs 2 and 8 vs 7, Table 3). However, in the case of linear aldehydes, the chiral ligand **77** showed much better asymmetric induction ability than Nakada's ligand **76c** (entries 11 vs 10 and 13 vs 12, Table 3). Although LiCl was found to improve the coupling yield significantly, it also slightly slowed down the coupling rate. A practical route to the homopropargyl alcohol **79** was developed that gave an isolated yield of 78% with 90% ee. This successful reaction utilized a Cr catalyst prepared from Cr(III) bromide and (*R*)-sulfonamide **77b** (entry 17, Table 3). When the reaction was combined with Amano lipase PS-800, it was possible to catalyze the kinetic resolution of compound **79** through esterification. Ultimately, this method

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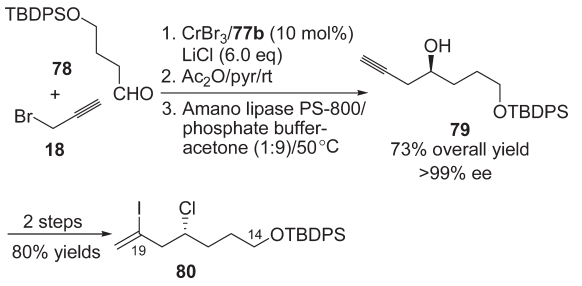
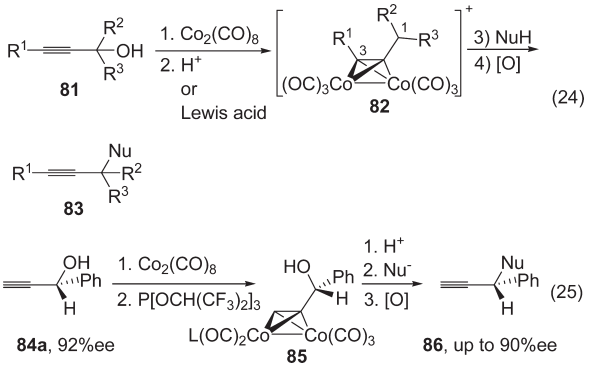
Scheme 8. Synthesis of the C14−C19 Building Block Used for Halichondrins and E7389



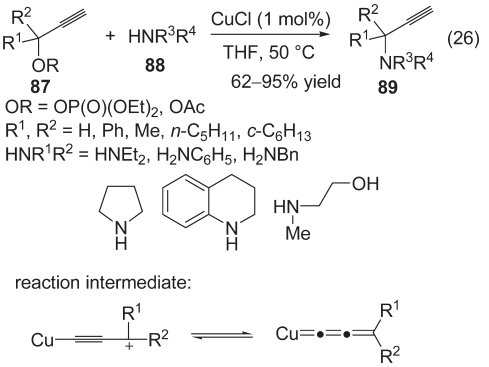
furnished optically pure (*S*)-**79** on a multigram scale. This in turn was transformed into optically pure **80**, which is the C14−C19 building block for halichondrins and E7389 (Scheme 8).[78,79]

4. ASYMMETRIC PROPARGYLIC SUBSTITUTION REACTION

As mentioned in the introduction, the propargylic substitution reaction is another powerful protocol for introducing a propargyl group into a range of substrates. The Nicholas reaction is one good example. This was discovered in 1977 when Lockwood and Nicholas were studying the reaction of electron-rich aromatic compounds with (propargyl)$Co_2(CO)_6^+$ complexes to producing C-propargylated aromatic derivatives. After demetalation, good to excellent yields of the desired products were obtained.[80] This reaction features the facile introduction and removal of the cobalt carbonyl moiety. This approaches overcomes the poor regioselectivity associated with the coupling reactions of more conventional propargyl synthons.[81] The reaction can proceed either by an inter- or intramolecular pathway. A variety of nucleophiles including carbon, oxygen, hydrogen, sulfur, fluoride, and nitrogen attack the parent (propargyl)$Co_2(CO)_6^+$ complex exclusively at the C1 of the propargyl moiety. The resulting propargylation products **83** were obtained after treatment of the intermediate by mild oxidative demetalation (eq 24).[82] It should be noted that this reaction provides a very versatile range of products. In 1993, the first successful stereoselective Nicholas reaction was realized using a chiral cobalt cluster with moderate to good enantioselectivity. The key to its success was by virtue of the configurational stability of the chiral −(C≡CR)$Co_2(CO)_5$L cluster fragment as well as the diastereoselective nature of its formation and its subsequent reactions (eq 25).[83]



In spite of the great success of the Nicholas reaction, there are, however, several drawbacks: stoichiometric amounts of the metal complexes are needed to stabilize the propargylic cations, and additional experimental steps are needed both to incorporate and to remove the metal complex before and after propargylation to access the propargylic products. Ideally, from both a practicability and sustainability viewpoint in organic synthesis, catalytic and single-step propargylation reactions are more appealing. With this in mind, great achievements were made by Murahashi and co-workers. In 1994, they reported a copper(I) chloride-catalyzed propargylic amination using propargyl phosphates and acetates **87** in THF. This reaction afforded the corresponding propargyl amines **89** in 62−95% yield (eq 26).[84] A copper−alkynyl complex with a cationic γ-carbon atom and its resonance structure, the copper−allenylidene complex, were proposed as the key intermediates. These reactions provide not only the catalytic version of the propargylic substitution reaction but also good regioselectivity control of the reaction.

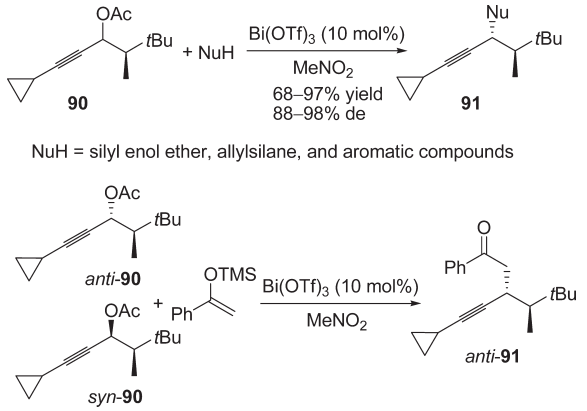


Since then, many transition metal compounds, including Ti, Fe, Ni, Cu, Ru, Ph, Pd, Re, Ir, Pt, and Au, have all been successfully used as catalysts in direct propargylic substitutions using propargylic alcohols as well as their derivatives.[1b,d−1f,85] These metal-catalyzed propargylic substitution reactions have several unique characteristics: (1) the great range of efficient catalysts that are available; (2) high regioselectivities; (3) the variety of functional groups that are tolerated; and (4) the wide array of suitable nucleophiles such as carbon, oxygen, sulfur, and nitrogen

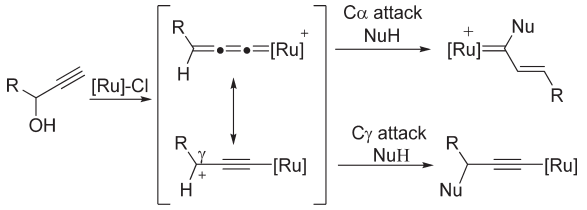
Propargylic alcohols and their derivatives containing a terminal acetylenic group are the most frequently used substrates for propargylation. Some procedures have been developed recently using terminal substituted propargyl alcohols in the propargylations. It was found that the air- and moisture-tolerant rhenium derivative [(dppm)$ReOCl_3$] can be a powerful catalyst for highly regioselective propargylations using terminally substituted propargyl alcohols with a wide variety of nucleophiles such as alcohols, sulfonamides, carbamates, allylsilanes, and aromatic compounds.[86] The iridium complex, [Ir(cod)$(POPh_3)_2$]OTf,[87a] as well as the trimethylphosphite-modified Wilkinson catalyst[87b] also proved useful in the propargylic substitution reaction of 3-substituted propargylic esters with enoxysilanes and the aliphatic-substituted propargylic esters with toluenesulfonamide derivatives, respectively. Some other transition metals, such as Pt[88] and Au,[89] Lewis acids, such as Sc$(OTf)_3$,[90] $TiCl_4$,[91] $BF_3\cdot OEt_2$,[92] and Bi$(OTf)_3$,[93] and Brønsted acids[94] are also efficient catalysts for the propargylic substitution reactions of propargylic alcohols and their derivatives. Recently, a series of Bi$(OTf)_3$-catalyzed diastereoselective propargylic substitution reactions using carbon nucleophiles such as silyl enol ethers, allylsilane, and aromatic compounds was developed. The diastereoselectivities ranged from 88% to 98% diastereomeric

dx.doi.org/10.1021/cr100284m |*Chem. Rev.* 2011, 111, 1914–1937

Scheme 9. Bi(OTf)$_3$-Catalyzed Diastereoselective Propargylic Substitution with Chiral Propargylic Acetate 90



Scheme 10. Reactivity of the Ruthenium−Allenylidene Complex

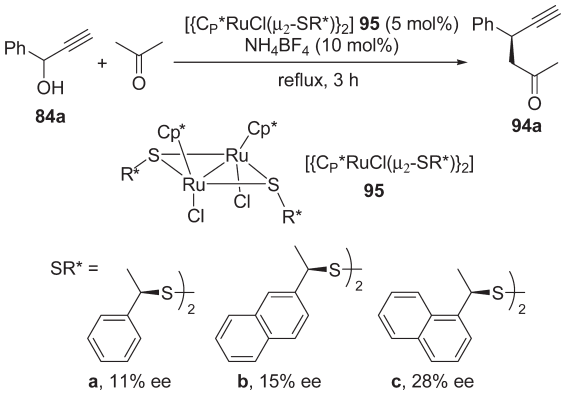


excess (de) (Scheme 9).[95] Both the *anti*-**90** and *syn*-**90** diastereoisomers reacted with silyl enol ether to preferentially afford the *anti*-**91**. A S_N1-type process for the reaction was proposed.

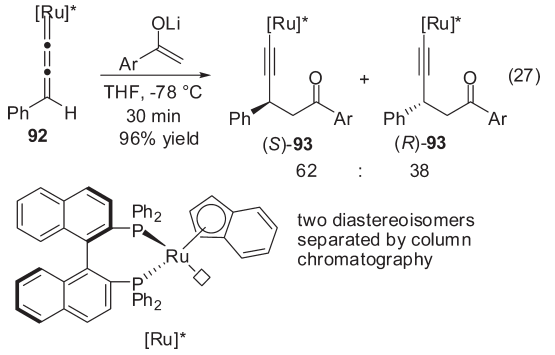
Among the transition metals used as catalysts in propargylations, ruthenium derivatives, especially thiolate-bridged diruthenium complexes, have been widely studied. Some unique properties have been demonstrated. The ruthenium-catalyzed reactions work well with a wide array of propargylic alcohols including tertiary alcohols and a variety of nucleophiles, such as alcohols, amines, thiols, phosphine oxide, ketones, and electron-rich aromatic compounds. These form new bonds with regioselective control.[1f,85] The reactive cationic ruthenium allenylidene complexes are usually formed via dehydration of the propargylic alcohols, which are stable due to the substantial contribution of the ruthenium−alkynyl resonance form (Scheme 10).[96] It has been well established, both experimentally and theoretically, that the Cα or Cγ positions of the allenylidene moiety are electrophilic. However, nucleophilic substitution occurs regioselectively at the Cγ position using the electron-rich nucleophiles.[85b,97]

As a result of studies by Nishibayashi and Uemura, the Ru-catalyzed propargylation reaction using thiolate-bridged diruthenium complexes was made practicable. These catalysts effect the nucleophilic substitution of propargylic alcohols containing terminal and internal triple bonds with a wide range of heteroatom- and carbon-centered nucleophiles. Resulting reactions afford the corresponding functionalized propargylic compounds in high yields with complete regioselectivity.[1f,85] Importantly, enantioselective propargylic substitutions have been achieved when stoichiometric amounts of chiral ruthenium allenylidene complexes **92**, derived from achiral propargylic alcohols, reacted

Scheme 11. Ruthenium-Catalyzed Asymmetric Propargylic Alkylation with Propargylic Alcohol 84a



with lithium enolates. The resulting two diastereoisomers of the σ-alkynyl complexes **93** bear completely opposite configurations with almost 100% ee. They were separated readily using column chromatography (eq 27).[98] This procedure provides a synthetically useful approach to propargylic substitution products with high ee. However, one drawback is that the reaction needs stoichiometric amounts of the chiral metal complex.



4.1. Catalytic Asymmetric Propargylic Substitution Using Carbon Nucleophiles

Intense research over many years by several groups has been expended in an effort to make the asymmetric propargylic substitution reaction catalytic. Nishibayashi and Uemura's group are recognized as having made the most significant contribution. In 2003, Hidai, Uemura, and co-workers reported the first example of a catalytic asymmetric propargylic substitution reaction.[99] They found that when the propargylic alcohol **84a** was reacted using the diruthenium complex **95**, bearing a chiral thiolate bridging ligand as catalyst, the corresponding alkylated product **94a** was formed in good yields, with up to 35% ee (Scheme 11). In this reaction, the catalyst **95** was generated in situ from the reaction of $[Cp^*RuCl(\mu_2\text{-}Cl)]_2$ with optically active thiols, which in turn created a chiral environment around the diruthenium site. This was a unique breakthrough in metal-catalyzed asymmetric propargylic substitution reactions. It not only provided the first example of a transition metal-catalyzed asymmetric version of propargylic substitution reactions but also opened the door for applications using chiral polymetallic clusters in asymmetric synthesis.

To improve the enantioselectivity of the reaction, an additional phenyl ring was introduced into the chiral thiol ligand moiety. This made it possible for it to interact with a phenyl ring of the

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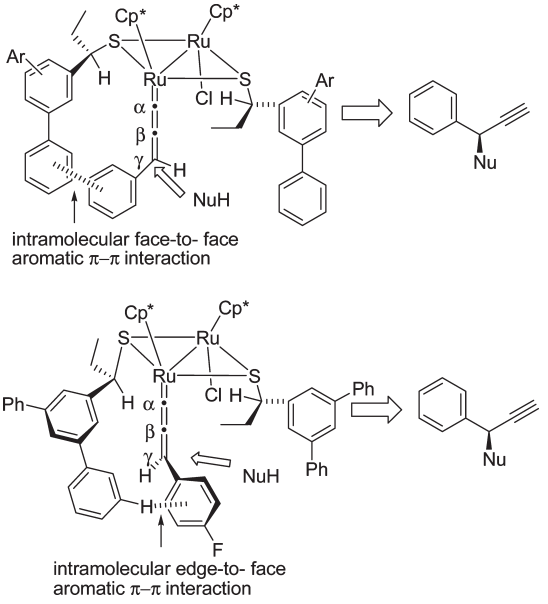
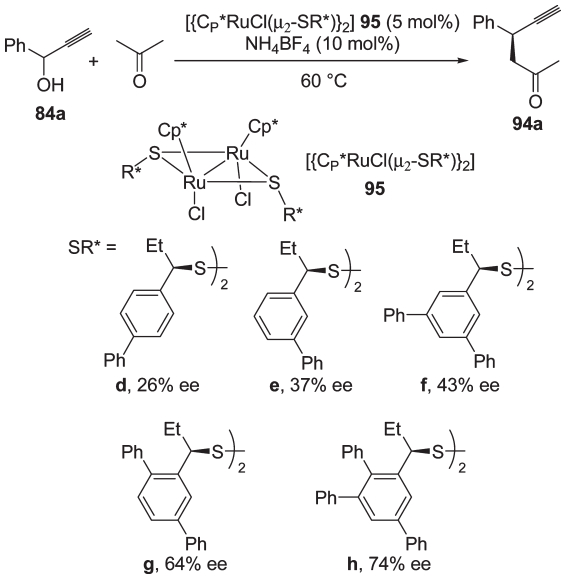
Scheme 12. Model of the Transition State of Nucleophilic Attack on the Cγ Atom of the Allenylidene Complex



Scheme 13. Ruthenium-Catalyzed Asymmetric Propargylic Alkylation with the Propargylic Alcohol 84a

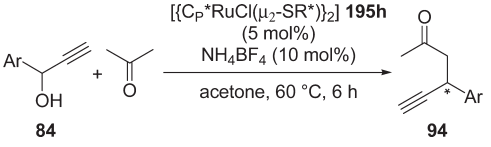


ruthenium−allenylidene complexe through face-to-face aromatic $\pi-\pi$ interactions. The nucleophiles are believed to attack the Cγ atom of the allenylidene−ligand complex from the side that is not blocked by the chiral ligand (Scheme 12). However, an X-ray study of the allenylidene complexes indicates the existence of an intramolecular edge-to-face aromatic $\pi-\pi$ interaction[100] between a specific allenylidene and the chiral ligand in the solid state (Scheme 12).[101] The corresponding molecular structure was further supported by ^{1}H NMR data. The high stereoselectivity in the ruthenium-catalyzed asymmetric propargylic substitutions of propargylic alcohols with nucleophiles may contribute to this intramolecular edge-to-face aromatic $\pi-\pi$ interaction.

The enantioselectivity of the reaction increased greatly when catalytic amounts of modified chiral thiolate-bridged diruthenium complexes **95d−h** were used in the propargylic alkylation with the propargylic alcohol **84a**. The best result (74% ee) was obtained in the presence of **95h**, which was prepared in situ from a tetranuclear ruthenium(II) complex and the corresponding chiral disulfide (Scheme 13).[102] The presence of NH_4BF_4 or NH_4PF_6 as additives proved to be crucial for a successful reaction. This catalyst system is applicable to a wide variety of propargylic alcohols **84** (Table 4). The reaction is fully regioselective and tolerates substituents such as methyl, methoxy, and chloro on the phenyl ring of the propargylic alcohols. The best enantioselectivity (82% ee) was obtained for the propargylic alcohol with two phenyl groups in the meta-positions of the benzene ring (entry 8, Table 4). The absolute configuration of the alkylated product **94a** was determined as *R* (entry 1, Table 4). This is consistent with the proposed transition state as shown in Scheme 12. This reaction represents the first synthetically useful asymmetric propargylic substitution.

Epoxides, carbonyl compounds, activated alkenes, and their analogues as well as propargylic alcohols have all been used as electrophiles in the transition metal-catalyzed Friedel−Crafts alkylation of aromatic compounds.[103] Because water is the only byproduct, this reaction provides a general and a synthetically green access to a variety of propargylated aromatic compounds. A transition metal-catalyzed asymmetric version of Friedel−Crafts-type propargylation has been developed by using chiral thiolate-bridge diruthenium complexes. With the ruthenium complex **95h** still as the catalyst, various propargylic alcohols **84** proved to be viable substrates for the asymmetric version of a Friedel−Crafts-type propargylation. An example is the reaction of 2-methylfuran in $ClCH_2CH_2Cl$ at 60 °C (eq 28).[104] In some cases, optically pure propargylated aromatic compounds **96** were obtained after a single recrystallization. Also using a Friedel−Crafts reaction, when methylthiophene was the substrate, a similar product **97** was obtained using the chiral diruthenium complex **95h**.

Table 4. Ruthenium-Catalyzed Asymmetric Propargylic Alkylation with Propargylic Alcohols 84



entry	Ar	yield	ee
1	Ph	56	74 (*R*)
2	*o*-MeC_6H_4	61	72
3	*p*-$MeOC_6H_4$	14	68
4	*p*-ClC_6H_4	57	68
5	1-naphthyl	42	70
6	2-naphthyl	50	70
7	*p*-PhC_6H_4	50	70
8	3,5-$Ph_2C_6H_3$	58	82

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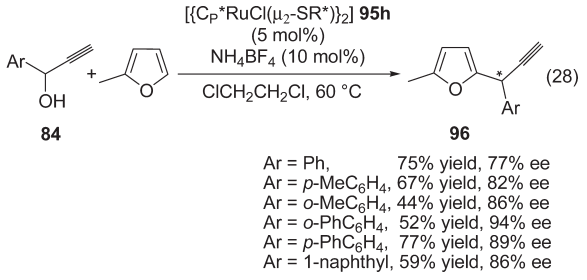
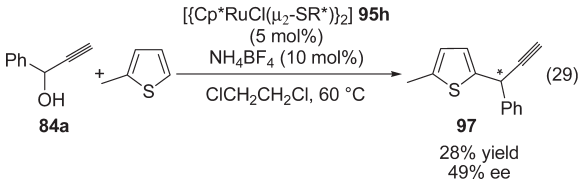
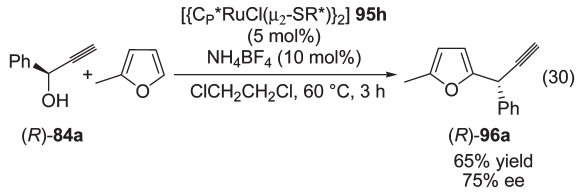
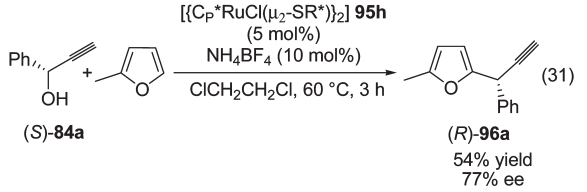
However, the enantioselectivity and the yield were lower (eq 29).[105]

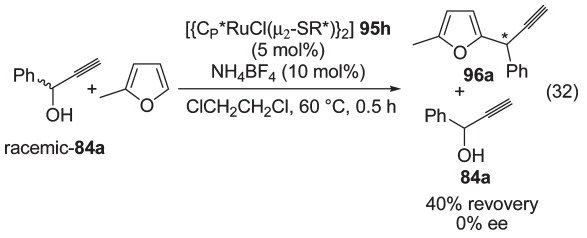




With a view to elucidating the reaction mechanism, the authors reacted the optically active propargylic alcohols (*R*)- and (*S*)-**84a** with 2-methylfuran using **95h** as the catalyst. The resulting propargylated product **96a** with the *R* configuration and similar enantioselectivities was found in both cases (eqs 30 and 31). It suggests that the chiral allenylidene intermediates readily racemized before the attack of the 2-methylfuran. No optical activity was observed for **84a**, the recovered reactant from the reaction under the conditions shown in eq 32. This indicates that (*R*)-**84a** and (*S*)-**84a** have similar reactivities.

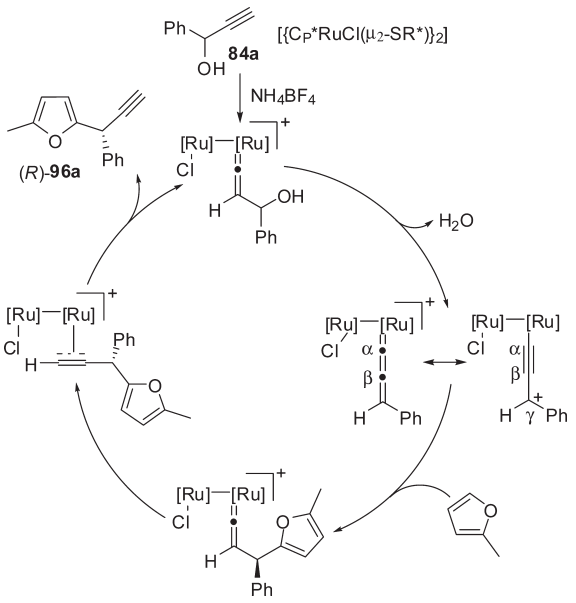




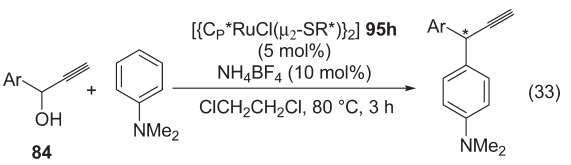


On the basis of the above experimental results, a possible reaction mechanism for this enantioselective Friedel—Crafts-type propargylation was proposed (Scheme 14). The ruthenium—allenylidene, derived from the reaction of a chiral diruthenium complex with **84a**, and its ruthenium—alkynyl isomer are the key proposed intermediates. 2-Methylfuran attacks the Cγ atom of the ruthenium—allenylidene to give the vinylidene complex, which in turn is converted into a η^2-coordinated alkyne complex. The subsequent reaction with another propargylic alcohol **84a** leads to the propargylated furan **96a** and is accompanied by regeneration of the starting complex. The synergistic effect of the diruthenium complex is critical for the catalytic reaction.[106]

Scheme 14. Proposed Reaction Mechanism for the Ruthenium-Catalyzed Enantioselective Propargylation of 2-Methylfuran with Propargylic Alcohols



In addition to methylfuran and methylthiophene, *N*,*N*-dimethylaniline is also a suitable nucleophile for this type of propargylic substitution reaction, although its reactivity is lower than that of 2-alkylfuran. Thus, harsher reaction conditions (80 °C) and a large excess of *N*,*N*-dimethylaniline (10 equiv) proved to be necessary for the reaction to occur. Once more, the diruthenium complex **95h** was the optimal catalyst. High enantioselectivities were achieved, but the yields were only moderate. This reaction warrants further investigation. The propargylated product **98a** was shown to have the *R* absolute configuration (eq 33). It has been proposed that the reaction of *N*,*N*-dimethylaniline with propargylic alcohols **84** occurs via a transition state as shown in Scheme 12.



Ar = Ph (**a**), 49% yield, 83% ee (*R*)
Ar = *p*-ClC$_6$H$_4$, 46% yield, 83% ee
Ar = *p*-MeC$_6$H$_4$, 53% yield, 85% ee
Ar = *o*-MeC$_6$H$_4$, 36% yield, 94% ee
Ar = *p*-PhC$_6$H$_4$, 38% yield, 89% ee
Ar = 1-naphthyl, 43% yield, 92% ee

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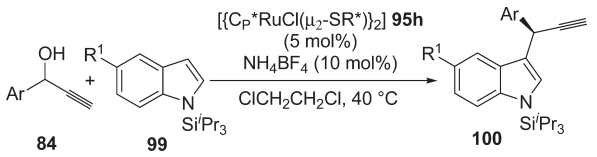
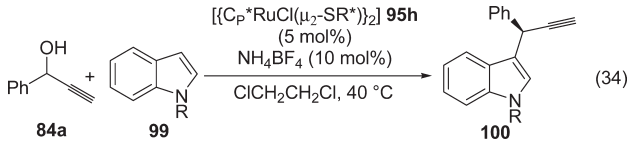
Table 5. Ruthenium-Catalyzed Enantioselective Propargylation of *N*-(Triisopropyl)indole with Propargylic Alcohols



entry	R	Ar	yield (%)	ee (%)
1	H	Ph	77	78
2	H	4-ClC_6H_4	72	79
3	H	4-PhC_6H_4	76	90
4	H	1-naphthyl	81	92
5	Me	1-naphthyl	82	95
6	Cl	1-naphthyl	78	91
7	OMe	1-naphthyl	71	87

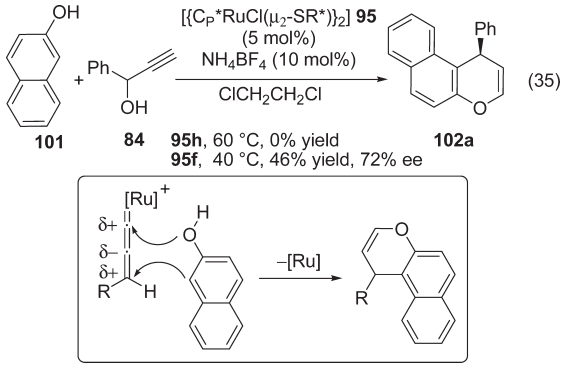
Nishibayashi's group extended asymmetric propargylations using Friedel−Crafts alkylation to include indoles by using the chiral diruthenium complex **95h**.[107] The substituent on the nitrogen of the indoles greatly influences the enantioselectivity of the reaction. Indoles bearing a bulky group such as *tert*-butyldimethylsilyl or triisopropylsilyl group give better enantioselectivities (eq 34). Excellent enantioselectivity was realized for the reaction of various propargylic alcohols **84** with *N*-(triisopropylsilyl)-5-substituted indoles **99** using 5 mol % of the diruthenium complex **95h** (Table 5). The absolute configuration of the product **100** (entry 4 in Table 5) was determined to be *R*. This result is in good agreement with the previously proposed model shown in Scheme 12.



(34)

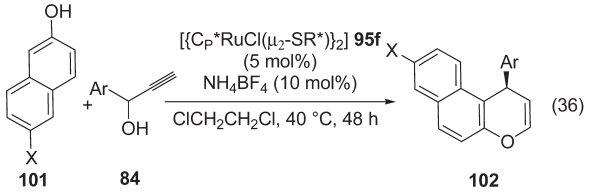
R = H, 71% yield, 35% ee
R = Me, 77% yield, 61% ee
R = $SiMe_3$, -- yield, 37% ee
R = $SiMe_2{}^tBu$, 63% yield, 73% ee
R = Si^iPr_3, 70% yield, 82% ee

The scope of asymmetric Friedel−Crafts alkylations using propargylic alcohols as electrophiles has been extended even further to 2-naphthols. Nishibayashi and co-workers reported a ruthenium-catalyzed enantioselective [3 + 3]-cycloaddition of propargylic alcohols with 2-naphthols to afford the corresponding naphthopyran derivatives. The reaction is based on a tandem attack of the nucleophile to the electrophilic γ-carbon and α-carbon of the ruthenium−allenylidene intermediate (eq 35).[108b] This catalytic reaction provides a simple and efficient one-pot synthesis for naphthopyrans, which is an important subunit found in a number of biologically active compounds used as anticoagulants and as spasmolytic, diuretic, anticancer, and antianaphylactic agents.[109]



(35)

Surprisingly, although the diruthenium complex **95h** proved to be an excellent catalyst for the enantioselective propargylation of a variety of aromatic compounds as discussed above, it showed no catalytic activity in cycloadditions. The diruthenium complex **95f**, on the other hand, which has less phenyl substituents compared to **95h**, afforded 1-phenyl-1*H*-naphtho[2,1-*b*]pyran (**102a**) in 46% isolated yield with 72% ee (eq 35).[108b] The enantioselective [3 + 3]-cycloaddition catalyzed by the chiral diruthenium complex **95f** has been applied to several 2-naphthols **101** as well as various propargylic alcohols **84** (eq 36).



(36)

a: X = H, Ar = Ph, 46% yield, 72% ee
b: X = H, Ar = 4-MeC_6H_4, 49% yield, 64% ee
c: X = H, Ar = 3,5-$Ph_2C_6H_3$, 43% yield, 96% ee
d: X = H, Ar = 2-naphthyl, 42% yield, 81% ee
e: X = Br, Ar = Ph, 28% yield, 83% ee
f: X = Br, Ar = 3,5-$Ph_2C_6H_3$, 53% yield, 99% ee

As described in eq 36, the cycloaddition suffers from only moderate yields in all cases because of the formation of propargylated naphthols as side products. For example, in addition to the cycloaddition product **102f**, the propargylated naphthol **103f** was also isolated in 26% yield when the propargylic alcohol **84f** was reacted with 6-bromo-2-naphthol (eq 37). The products **102f** and **103f** have opposite absolute configurations. These results reflect to some extent the occurrence of a kinetic resolution process. This was shown to be, in fact, the case by using the chiral complex **95f** to transform racemic **103f** to the cycloaddition product (*R*)-**102f** (53% ee, 55% yield) together with the (*S*)-**103f** (99% ee, 33% yield) (eq 38). Additionally, (*S*)-**103f** with 99% ee was converted to (*S*)-**102f** with 99% ee in 52% isolated yield. This particular reaction was mediated by a racemic diruthenium complex (eq 39), which suggests that the cycloaddition may proceed via an initial propargylation of 2-naphthol followed by cyclization, which takes place without any loss of optical purity at the propargylic position (eq 40).

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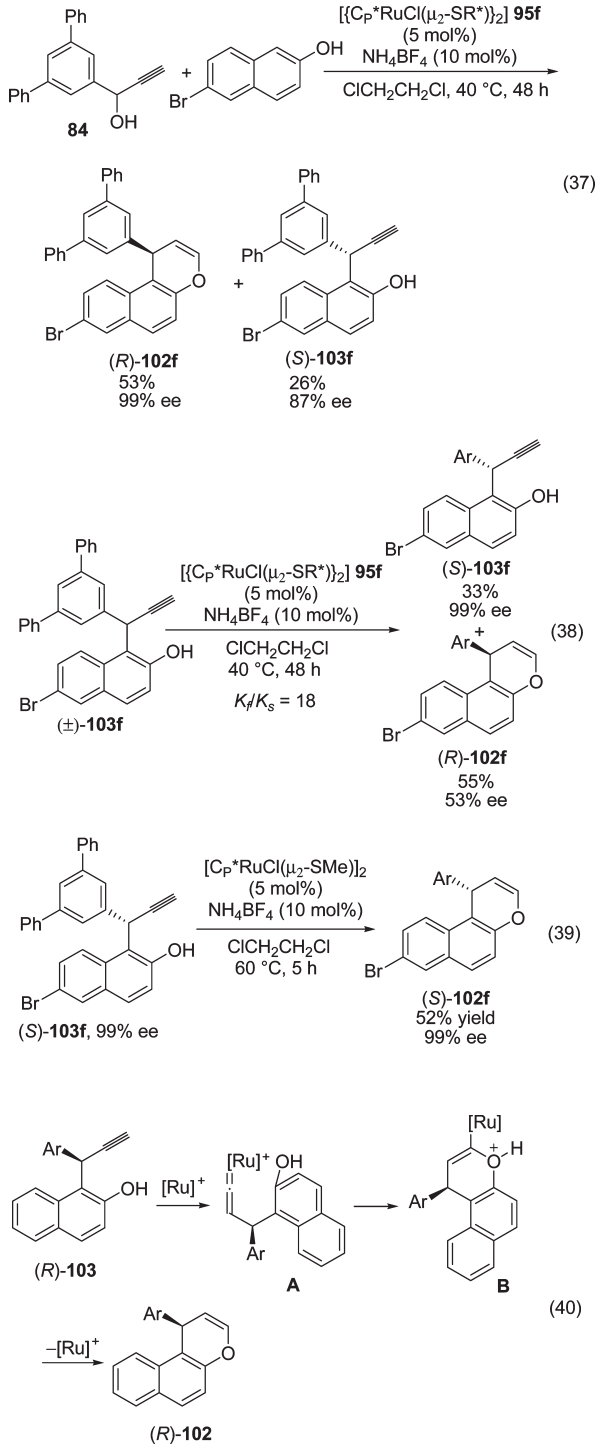
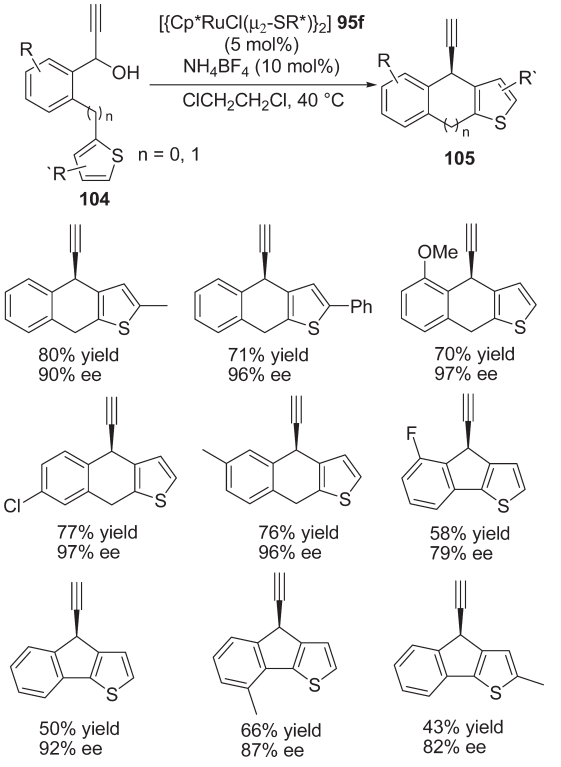
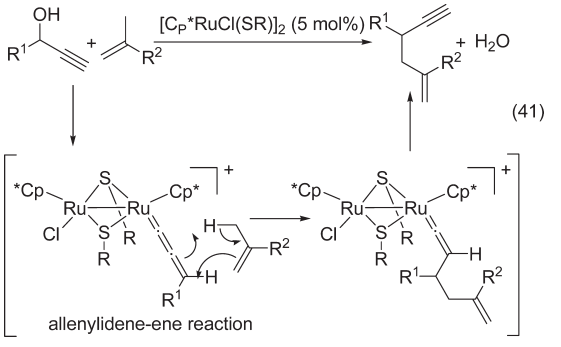


An intramolecular version of transition metal-catalyzed asymmetric propargylic substitution reactions of aromatic compounds has also been developed. Using propargylic alcohols bearing a thiophene moiety as substrates, intramolecular cyclization proceeded smoothly with high enantioselectivity in the presence of catalytic amounts of the chiral ruthenium complex **95f** (Scheme 15).[105] The product **105** had a *R*-configuration at the propargylic position. This suggests that the reaction may take place with the same transition state as that shown in Scheme 12.

Scheme 15. Ruthenium-Catalyzed Enantioselective Intramolecular Propargylation of Thiophenes Using Propargylic Alcohols





Using a ruthenium catalyst, an allenylidene−ene type reaction between propargylic alcohols and alkenes can give the propargylic substitution products through either an inter- or intramolecular mechanism (eq 41).[110] An intramolecular enantioselective propargylation of propargylic alcohols bearing an alkene moiety has also been developed. It makes it possible to access optically active chromanes, benzochromanes, thiochromanes, and 1,2,3,4-tetrahydroquinolines,[111] all of which can be found in many natural and biologically active compounds (Table 6).[112] Once again, the diruthenium complex **95f** displayed its super capability of stereoselective control using the current protocol. The geometry of the alkene moiety of the substrates **106** was found to have an effect on the reaction activity, the chemical yield, the diastereoselectivity, and the enantioselectivity (entry 4 vs 1, Table 6). The nature of the

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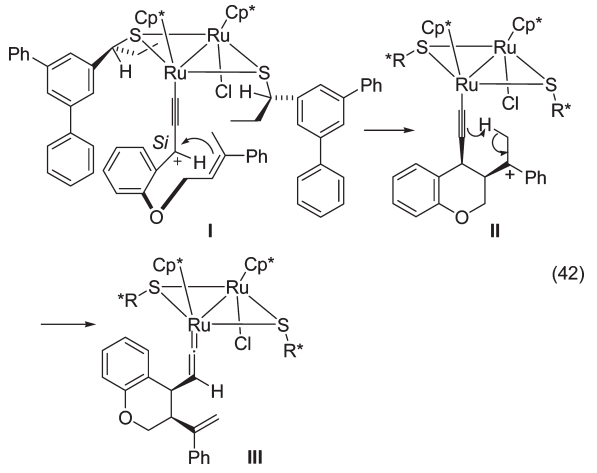
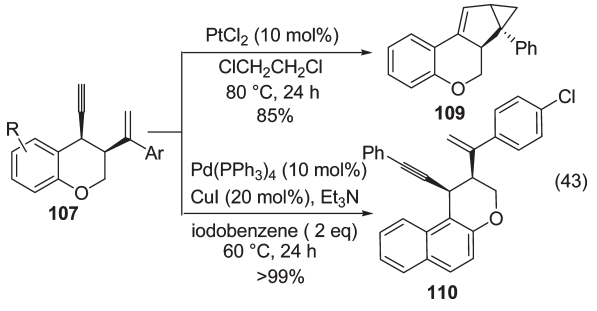
substituent on the alkene moiety of the substrates **106** was also found to play a decisive role on the enantioselectivity (entries 1−3, Table 6). This methodology was also found to work well for the synthesis of other S- and N-containing heterocycles (entries 5 and 6, Table 6).

A stepwise process has been suggested to explain the reaction mechanism. This involves an intramolecular attack of an alkene on the cationic γ-carbon in **I** from the *si*-face to provide the alkynyl complex **II**, followed by proton transfer to the alkynyl moiety to give the corresponding vinylidene complex **III** (eq 42).



(42)

Further conversion of the resulting chiral chromane **107** to its derivatives **109** and **110**, with retention of optical purity, illustrates the potential of this method for the synthesis of more complicated molecules (eq 43).

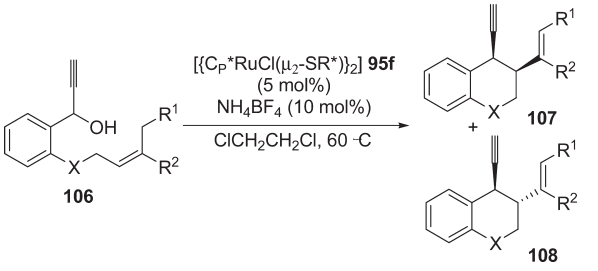


(43)

Density functional theory (DFT) calculations show that ruthenium−allenylidene complexes are common reactive intermediates for these Ru-catalyzed carbon−carbon bond-forming reactions between propargylic alcohols and alkenes or ketones. The reaction starts with the nucleophilic attack of the π-electrons on propene or vinyl alcohol to form a ruthenium−alkynyl complex, which is a resonance structure of the ruthenium−allenylidene complex (Scheme 16).[113] However, it can then proceed through different pathways because of the difference in the acidity of the hydrogen atom that is transferred to the C_β atom. A stepwise process is involved for the carbon−carbon bond-forming reaction with propene, whereas for vinyl alcohol it occurs via a concerted pathway.

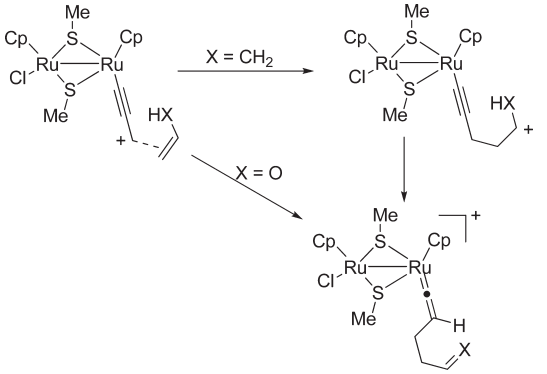
As reported by Nishibayashi and co-workers, aldehydes are also viable nucleophiles for catalytic asymmetric propargylic substitution with propargylic alcohols.[114] On the basis of the well-known chemistry of secondary amine-catalyzed reactions of aldehydes, a cooperative catalytic reaction was designed to realize

Table 6. Ruthenium-Catalyzed Enantioselective Intramolecular Reactions of Propargylic Alcohols and Alkenes



entry	X, R^1, R^2	yield (%)	*syn*/*anti*	ee of *syn* (%)
1	O, H, Ph	85	17/1	93
2	O, H, ^{t}Bu	87	>99/1	76
3	O, H, Me	85	10/1	33
4	O, Ph, Me	65	1/2.5	33
5	S, H, Ph	91	>99/1	89
6	NPh, H, Ph	65	14/1	98

Scheme 16. Different Reaction Pathways for the Nucleophilic Attack of Propene or Vinyl Alcohol on a Ruthenium−Alkynyl Complex



the propargylation of aldehydes with propargyl alcohols using both a transition metal catalyst and an organocatalyst. A ruthenium complex activates the propargyl alcohol to form a ruthenium−allenylidene complex as the electrophile, which is in turn attacked by the enamine generated in situ from the aldehyde and the secondary amine. The products afforded are propargylic alkylated products (Scheme 17).

When the 1-aryl−propargylic alcohols **84** reacted with a variety of aldehydes **111** in the presence of catalytic amounts of (*S*)-α,α,-bis[3,5-bis(trifluoromethyl)phenyl]-2-pyrrolidinemethanol trimethylsilyl ether (**113**), the methanethiolate-bridged diruthenium complex [{Cp*RuCl(μ_2-SMe)}$_2$] (Cp* = η^5-C_5Me_5), and NH_4BF_4 in toluene at room temperature, the corresponding propargylic alkylated products **112** were obtained in excellent yields as a mixture of two diastereoisomers, each with high enantioselectivity. However, the diastereoselectivity was only 1.7−3.3:1, which could be further improved (Table 7). This catalytic propargylation is noteworthy as it represents a new

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Scheme 17. Cooperative Catalytic Propargylation with Aldehydes As Nucleophiles Using Both Transition Metal and Organocatalysts

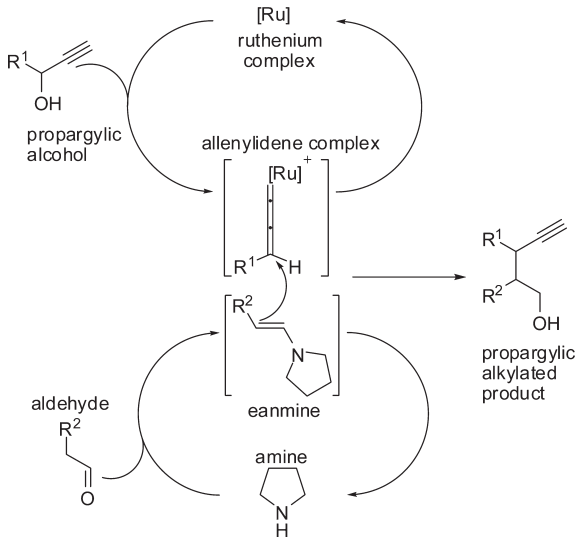
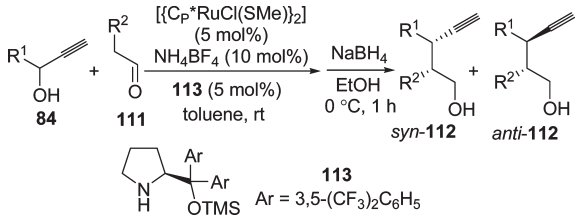


Table 7. Enantioselective Propargylic Alkylation of Aldehydes 111 with Propargylic Alcohols 84

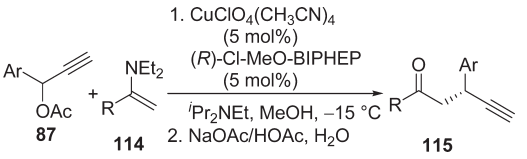


entry	R^1	R^2	yield (%)	*syn*/*anti*	ee (%) *syn*/*anti*
1	Ph	Bn	89	2.2/1	96/89
2	*p*-MeC_6H_4	Bn	90	2.5/1	97/86
3	*p*-FC_6H_4	Bn	88	2.1/1	95/87
4	*o*-$MeOC_6H_4$	Bn	93	3.3/1	99/93
5	Ph	*p*-$ClC_6H_4CH_2$	90	2.2/1	96/87
6	Ph	$Me(CH_2)_4$	91	1.7/1	92/85
7	*o*-$MeOC_6H_4$	$CyCH_2$	86	2.1/1	98/92

type of intermolecular alkylation of aldehydes.[115] The catalyst system is cooperative and quite efficient due to the fact that it suppresses the rather facile self-aldol condensation of the aldehydes, which can occur because excess aldehyde was used.

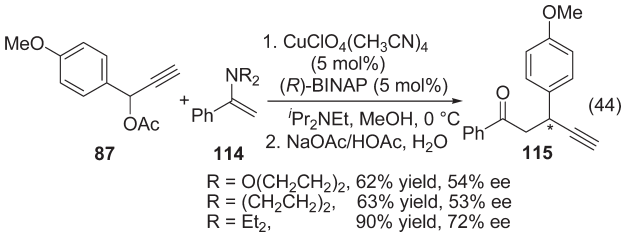
Enamines can act as useful equivalents of the α-carbanions of ketones and consequently have proved useful in organic synthesis. One advantage is that their use avoids the need for a strong base. There are some relevant examples from the literature describing application using enamines as a variation of "hard" carbanions in transition metal-catalyzed allylic alkylation reactions.[116] For example, Fang and Hou were the first to report the use of enamines as carbon nucleophiles in asymmetric propargylic substitution reactions using $CuClO_4$/(*R*)-Cl−MeO−BIPHEP as the catalyst.[117] They thus extended the scope of

Table 8. Enantioselective Cu-Catalyzed Propargylic Substitution of Enamines with Propargylic Acetates

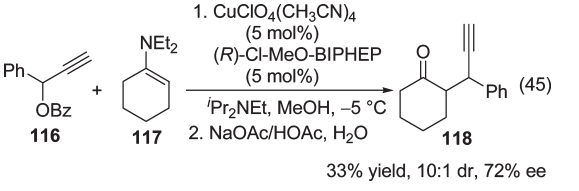


entry	R	Ar	yield (%)	ee (%)
1	Ph	4-$MeOC_6H_4$	88	81
2	Ph	Ph	77	85
3	Ph	3-MeC_6H_4	83	84
4	Ph	4-ClC_6H_4	73	85
5	Ph	1-naphthyl	95	73
6	Ph	2-furyl	80	67
7	4-$NO_2C_6H_4$	Ph	61	91
8	3-pyridyl	Ph	40	84
9	4-MeC_6H_4	Ph	72	80

useful nucleophiles from acetone to other ketones because this catalyst had previously been used by Nishibayashi in the Cu-catalyzed asymmetric propargylic amination with propargylic acetates (vide infra).[118] The substituent on the nitrogen of the enamines **114** affects not only the enantioselectivity but also the reactivity of the reaction (eq 44). A unique solvent effect for the reaction was also found in that MeOH was the only solvent that worked. Only very poor yields or in some cases no reaction was observed in other common solvents such as THF, toluene, and CH_2Cl_2. The catalyst, prepared from $CuClO_4$ and (*R*)-Cl−MeO−BIPHEP, was found to efficiently catalyze the reaction of a wide range of enamines **114** and propargyl acetates **87**. The propargylic-substituted products **115** were formed in good to high yields with 67−91% ee (Table 8). Electron-withdrawing or electron-donating groups on both the enamine and the propargyl acetates proved to be suitable substrates for the reaction.



It is worth noting that the enamine **117** derived from the aliphatic cyclohexanone could also be used as a substrate for reaction with the propargylic acetate **116**. OBz was the leaving group, and the product **118** was formed with 72% ee and 10:1 dr, albeit the yield was lower (eq 45).



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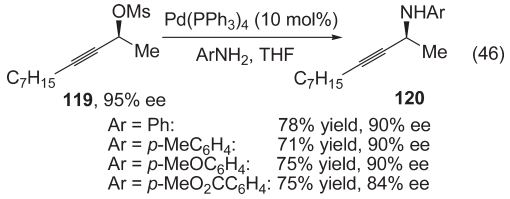
4.2. Catalytic Asymmetric Propargylic Substitution Using Heteroatom Nucleophiles

In addition to carbon-based nucleophiles, heteroatom-centered nucleophiles, such as alcohols,[86a,119] amines,[87b,93b,120] thiols,[93a,121] and diphenylphosphine oxide,[122] have also been used in propargylic substitution reactions with propargylic alcohols or their derivatives using a transition metal or Lewis acid as catalyst. When the nonracemic propargylic mesylate **119** reacted with arylamines in the presence of $Pd(PPh_3)_4$, the optically active propargylic amines **120** were afforded exclusively with retention of both enantioselectivity and configuration (eq 46).[123] A possible pathway for this conversion was proposed as involving an *anti*-S_N2'-type oxidative addition of Pd(0) to the mesylate and subsequent *anti*-S_N2' attack by the amine on the allenyl Pd intermediate.[124]



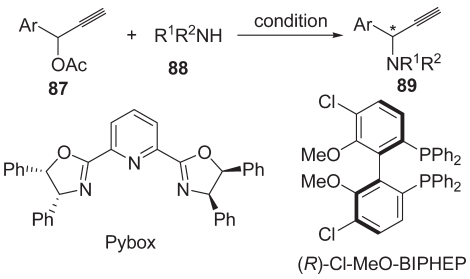
However, it took more than 10 years for the catalytic asymmetric version to be independently developed by the research groups of van Maarseveen and Nishibayashi. Both groups adopted copper as the catalyst with 2,6-bis(oxazolinyl)pyridines (pybox) used as the chiral ligand by van Maarseveen and co-workers.[125] Nishibayashi and co-workers, on the other hand, utilized a chiral diphosphine[118] such as BINAP or BIPHEP as the ligand. In both cases, high enantioselectivities were achieved for aromatic propargylic acetates **87**. Selectivity was found to be low for the corresponding aliphatic compounds (Table 9). By widely screening the range of nucleophiles, Nishibayashi's group found that the enantiomeric excess of the resulting propargyl amines **89** increased to >90% when *N*-methyl-4-(trifluoromethyl)aniline as nucleophile was used (entries 9, 10, 13, and 14, Table 9). This is compared to <90% ee for the other anilines tried (entries 8 and 11, Table 9). The same chiral catalyst was used in all cases.[126]

The propargylic amine was converted to an optically active ClickPhine ligand **122**[127] in two steps. The high efficiency of this reaction demonstrates the useful application of this methodology in organic synthesis (Scheme 18).

A catalytic cycle for the copper-catalyzed propargylic amination with propargylic acetates was proposed by van Maarseveen and co-workers (Scheme 19).[125] The same copper−alkynyl complex and its resonance structure, the copper−allenylidene complex, which were proposed earlier by Murahashi and co-workers,[84] are the suggested reactive intermediates. The nucleophilic attack of the amine onto the copper−allenylidene complex (step D) and subsequent proteolysis (step E) releases the propargylic amine, which completes the catalytic cycle. The authors suggested that the efficient shielding of one side of the cationic intermediate by the copper−pybox complex determines both the regio- and enantioselectivity of the reaction during step D. This mechanism explains why the reaction requires the use of propargyl substrates with terminal acetylene. However, van Maarseveen's proposed reaction mechanism would benefit from the support of further experimental evidence.

More recently, Nishibayashi and co-workers proposed a reaction pathway for the copper-catalyzed propargylic amination with propargylic acetates similar to van Maarseveen's.[126] The

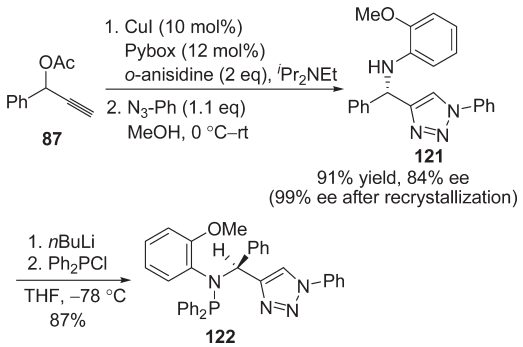
Table 9. Propargylic Amination with Various Propargylic Acetates and Amines



entry	condition[a]	Ar	R^1, R^2	yield (%)	ee (%)
1	**A**	Ph	2-$MeOC_6H_4$, H	97	85
2	**A**	4-$MeOC_6H_4$	2-$MeOC_6H_4$, H	97	83
3	**A**	4-$CF_3C_6H_4$	2-$MeOC_6H_4$, H	84	80
4	**A**	2-pyridyl	2-$MeOC_6H_4$, H	80	74
5	**A**	2-naphthyl	2-$MeOC_6H_4$, H	96	86
6	**A**	^{i}Pr	2-$MeOC_6H_4$, H	27	40
7	**A**	Ph	Ph, H	94	87
8	**B**	Ph	Ph, Me	96	85
9	**B**	3-thienyl	4-$CF_3C_6H_4$, Me	87	92
10	**B**	3-furyl	4-$CF_3C_6H_4$, Me	85	90
11	**B**	Ph	4-ClC_6H_4, Me	96	89
12	**B**	Ph	$-(CH_2)_5-$	64	80
13	**B**	Ph	4-$CF_3C_6H_4$, Me	72	93
14	**B**	1-naphthyl	4-$CF_3C_6H_4$, Me	93	98

[a] Condition **A**: CuI (10 mol %)/pybox (12 mol %), ^{i}Pr_2NEt, MeOH, −20 °C.[130] Condition **B**: CuOTf·0.5(C_6H_6) (5 mol %)/(*R*)-Cl−MeO−BIPHEP (10 mol %), ^{i}Pr_2NEt, MeOH, 0 °C.[123,131]

Scheme 18. Synthesis of the Chiral ClickPhine Ligand



experimental results revealed that the copper−allenylidene complex is the key intermediate. This conclusion was also supported by density functional theory calculations for the model reaction. Here the attack of the amines to the γ-carbon atom of the allenylidene ligand is a key step in determining the stereoselectivity. It was proposed that a transition state of the copper−allenylidene complex with the chiral ligand BIPHEP accounts for the high enantioselectivity of the (*S*)-propargylic amine (**89**) as shown in Scheme 20. The *re*-face of the γ-carbon of the copper−allenylidene complex is open to attack by the

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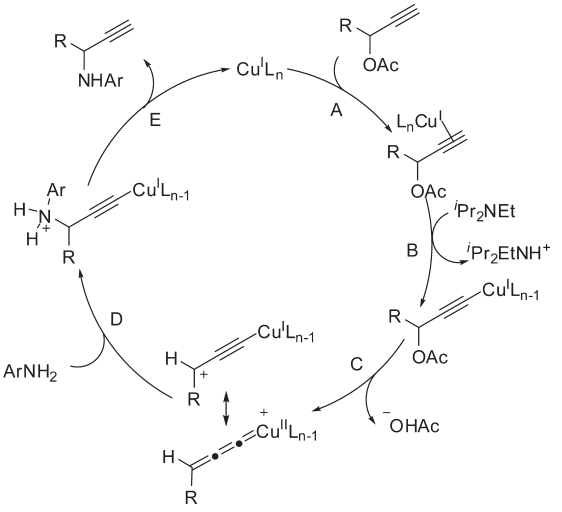
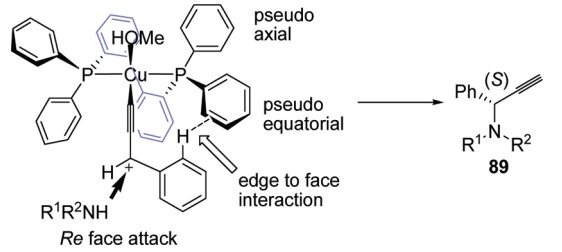
Scheme 19. Proposed Catalytic Cycle for the Copper-Catalyzed Propargylic Amination with Propargylic Acetates



Scheme 20. Model of the Transition State of the Copper−Allenylidene Complex Bearing (*R*)-BIPHEP



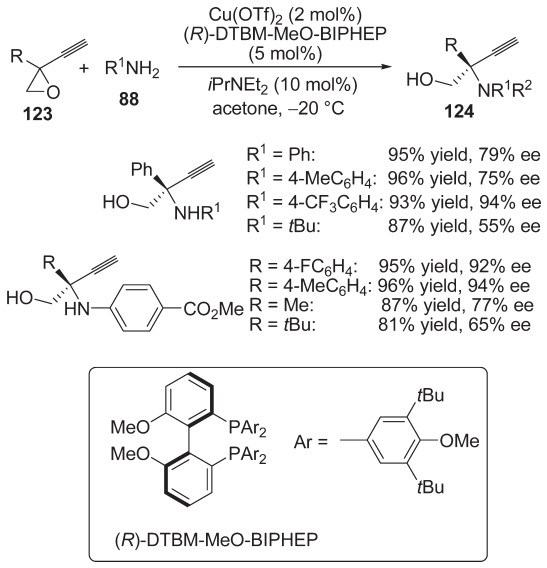
N-methylaniline. The edge-to-face aromatic interaction between the phenyl group of the chiral ligand BIPHEP and the allenylidene ligand is considered as an essential factor in achieving the high enantioselectivity.

Ethynyl epoxides are also good electrophiles in catalytic asymmetric propargylic substitution reactions. The ability of the complex between $Cu(OTf)_2$ and (*R*)-DTBM−MeO−BIPHEP in asymmetric propargylic aminations was established in the enantioselective ring-opening reaction of the racemic ethynyl epoxides **123** with amines. The reaction gave the corresponding optically active β-amino alcohols **124**. This valuable moiety is found widely in natural products, biologically active compounds, and chiral ligands (Scheme 21).[128] Copper−allenylidene complexes have been suggested as the key intermediates. It is worth noting that the chiral quaternary carbon center is present throughout the reaction.

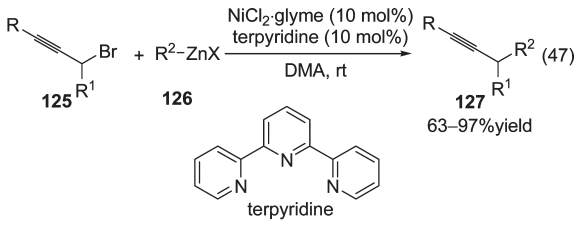
5. COUPLING REACTIONS OF METAL REAGENTS WITH PROPARGYLIC HALIDES

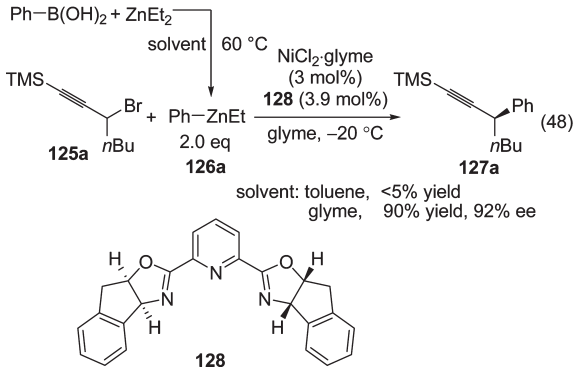
Smith and Fu developed a Ni-catalyzed Negishi cross-coupling reaction under mild, base-free conditions for propargylic chlorides and bromides **125** with organozinc **126** using terpyridine as the ligand.[129] The corresponding cross-coupling products **127** were obtained in high yields. The catalytic system

Scheme 21. Enantioselective Copper-Catalyzed Ring-Opening Reactions of Racemic Ethynyl Epoxides with Amines



is tolerant to several functional groups such as chloride, ether, and ester (eq 47).





Subsequently, Smith and Fu extended this reaction to asymmetric coupling using the chiral Ni/pybox complex as the catalyst. A wide array of racemic propargylic halides **125** and arylzincs **127** can undergo this highly selective asymmetric Negishi reaction (Table 10).[130] The arylzinc reagents are prepared from the readily available arylboronic acids, which are treated with diethylzinc. The solvent used has a significant effect on the reaction as shown in eq 48. Glyme proved to be the most suitable solvent. Different propargylic bromides **125** with TMS, Me_2PhSi, and triisopropylsilyl (TIPS) as protecting groups and a range of functional groups such as acetals, ether, ester, and olefins all proved to be suitable electrophiles for the reaction (Table 10).

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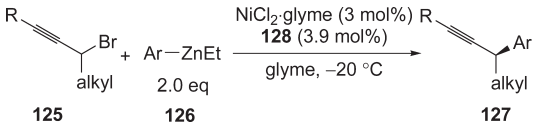
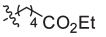
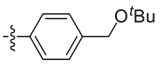
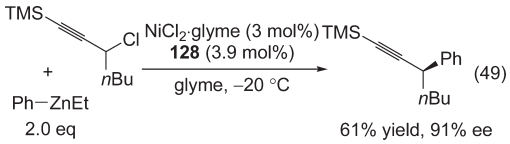
Table 10. Asymmetric Cross-Couplings of Propargylic Bromides with Arylzinc



entry	R	Alkyl	Ar	yield (%)	ee (%)
1	Me_2PhSi	*n*Bu	4-FC_6H_4	88	88
2	TIPS	Et	2-^{t}BuC_6H_4	81	93
3	TMS	*n*Bu	2-naphthyl	70	93
4	TMS			76	94
5	TMS		3-$MeOC_6H_4$	79	94
6	Et	Me	4-$MeOC_6H_4$	76	91
7	cyclohexyl	Et	4-$MeOC_6H_4$	63	89
8	Ph	Et	Ph	83	89

Propargylic chloride has been shown to also undergo cross-coupling smoothly with high enantioselectivity (91%) (eq 49) under established conditions.



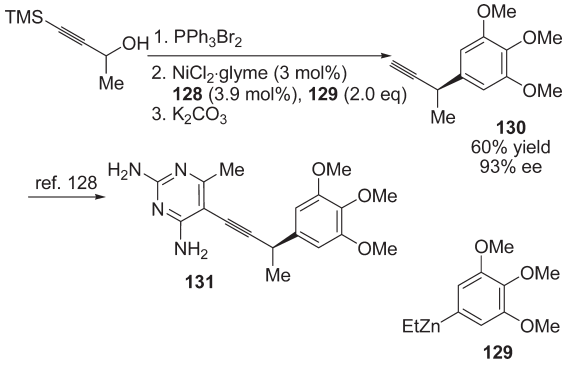
The high efficiency of this asymmetric coupling reaction makes it a highly suitable methodology in organic synthesis. On a gram-scale, the propargylic bromide was coupled with arylzinc reagent **129** in the presence of Ni/pybox **128** to furnish the propargylated product **130** in 93% ee. This is the key intermediate for the synthesis of dihydrofolate reductase inhibitors **131**[131] (Scheme 22).

This particular reaction exhibits a high efficiency over a wide range of substrates and can be carried out under mild reaction conditions, and the starting material is also easily available. Although currently examples of the asymmetric cross-coupling reaction of propargylic halides with metal reagents are still somewhat limited, this class of reactions clearly represents a new strategy and direction for metal-catalyzed asymmetric propargylation reactions.

6. SUMMARY AND PERSPECTIVE

Catalytic asymmetric propargylations have been shown to be highly efficient and selective reactions. Using them, various highly useful organic chiral building blocks, such as homopropargyl alcohol and propargylic amines, can be made with excellent enantioselectivities from readily available starting materials. In this review, some elegant applications of asymmetric propargylations in organic synthesis have been discussed. Many novel catalysts such as thiolate-bridged diruthenium complexes and new chiral ligands such as diphosphine, which have been custom designed and synthesized to realize asymmetric propargylations with high efficiency, are reported. Although great progress has been achieved, catalytic asymmetric propargylation reactions are still in the early stages of development compared to what has been achieved in asymmetric catalysis. At present, only a limited number of metals and ligands have been used and only a few catalyst systems have been optimized regarding catalytic activity and selectivity. The scope of the substrates is still somewhat narrow; the range of suitable electrophiles and nucleophiles is still quite limited. Last, but not least, the number of useful protocols already adopted for catalytic asymmetric propargylation reactions remains insufficient. All of these are challenges that remain to be explored. It is to be expected, however, that with a greater understanding of these reactions, new catalysts as well as new strategies will be developed, the scope of the substrates will be expanded, and eventually these reactions will be more widely applied.

Scheme 22. Catalytic Asymmetric Synthesis of a Potent Dihydrofolate Reductase Inhibitor



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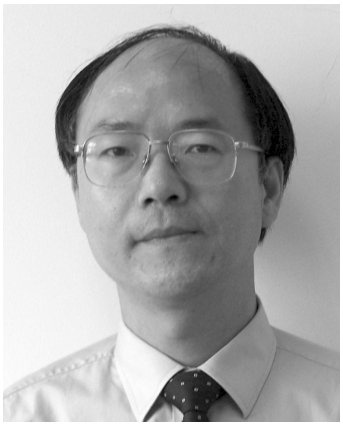
Chang-Hua Ding received his Ph.D. degree under the guidance of Prof. Xue-Long Hou in 2005 at the Shanghai Institute of Organic Chemistry (SIOC), Chinese Academy of Sciences. During 2005−2007, he was a postdoctoral fellow in the group of Prof. Junzo Otera at Okayama University of Science. He moved to Prof. Keiji Maruoka's group at Kyoto University as a research associate from 2007 to 2009. He has been an associate professor in the group of Prof. Xue-Long Hou at SIOC since 2009. His research interests focus on the development of asymmetric catalytic transformations and their application in organic synthesis.



Xue-Long Hou graduated from the Shanghai First Medical College in 1978. After working there for two years, he entered the Shanghai Institute of Organic Chemistry (SIOC), Chinese Academy of Sciences and obtained his Ph.D. in 1986 under the mentorship of Professors Wei Yuan Huang of SIOC and Henry N. C. Wong of the Chinese University of Hong Kong. He was awarded an Alexander von Humboldt research fellowship and completed two years of postdoctoral research with Professor Emanuel Vogel at Cologne University, Germany. He returned to SIOC in 1989 and was promoted to full professor in 1997. He was awarded the Second Class Award of Natural Science of China twice in 1997 and 2002, a First Class Award for Advancement of Science and Technology of Shanghai in 2001, the Eli Lilly Scientific Excellence Award in China in 2005, Leadership of Shanghai in 2007, and a Yao Zeng Huang Organometallic Chemistry Award from the Chinese Chemical Society in 2010. He also obtained the National Outstanding Youth Fund (2000−2003). He works in the fields of organometallic chemistry directed towards organic synthesis and organocatalysis, especially the design of chiral ligands and their applications in asymmetric catalysis.

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