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From σ- to π-Electrophilic Lewis Acids. Application to Selective Organic Transformations

Yoshinori Yamamoto

Department of Chemistry, Graduate School of Science, Tohoku University, Sendai 980-8578, Japan

yoshi@mail.tains.tohoku.ac.jp

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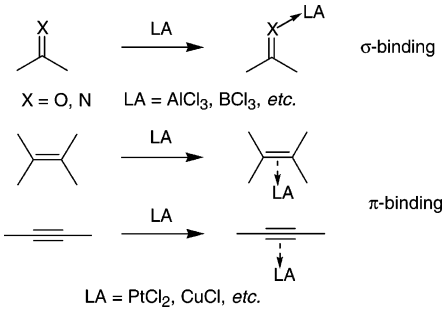

Computed enthalpies of formation for various Lewis acid complexes with representative unsaturated compounds (aldehydes, imines, alkynes, and alkenes) provide a means to evaluate the applicability of a particular catalyst in a catalytic reaction. As expected, main group Lewis acids such as BX_3 show much stronger complexes with heteroatoms than with carbon−carbon multiple bonds (σ-electrophilic Lewis acids). Gold(I) and copper(I) salts with non-nucleophilic anions increase the relative strength of coordination to the carbon−carbon multiple bonds (π-electrophilic Lewis acids). As representative examples for the use of σ-electrophilic Lewis acids in organic synthesis, the Lewis acid mediated allylation reactions of aldehydes and imines with allylic organometallic reagents which give the corresponding homoallyl alcohols and amines, respectively, are mentioned. The allylation method is applied for the synthesis of polycyclic ether marine natural products, such as hemibrevetoxin B, gambierol, and brevetoxin B. As representative examples for the use of π-electrophilic Lewis acids in organic synthesis, the Zr-, Hf-, or Al-catalyzed trans-stereoselective hydro- and carbosilylation/stannylation of alkynes is mentioned. This method is extended to σ−π chelation controlled reduction and allylation of certain alkynylaldehydes. Gold- and copper-catalyzed benzannulation of *ortho*-alkynylaldehydes (and ketones) with alkynes (and alkenes) is discovered, which proceeds through the reverse electron demand Diels−Alder type [4 + 2] cycloaddition catalyzed by the π-electrophilic Lewis acids. This reaction is applied for the short synthesis of (+)-ochromycinone. Palladium and platinum catalysts act as a σ- and/or π-electrophilic catalyst depending on substrates and reaction conditions.

I. Relative Ability of Lewis Acids for Making σ- and π-Complexes

Recent state-of-art research in organic chemistry requires the design of highly selective transformations. In other words, only desired reaction(s) must take place when the substrate is treated with the reagent, even if the structure of the substrate suggests numerous possibilities for reactivity. Organometallic Lewis acids often provide this kind of selectivity, and there is a plenty of known selective transformations catalyzed by various Lewis acids.[1] However, predicting beforehand what direction the particular reaction will take when either this or that catalyst

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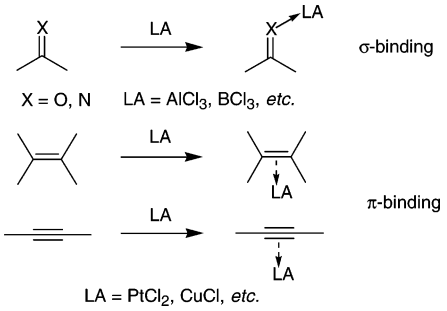
SCHEME 1



will be used remains to be a difficult task, although this knowledge is essential for designing intelligent synthetic strategies on the way to the desired products.[1a] Classic Lewis acids, such as BCl_3, $AlCl_3$, etc., are known to make strong σ-complexes with carbonyl and imine groups[2] that make them versatile catalysts of the Friedel−Crafts,[3] Diels−Alder,[4] and other electrophilic reactions (Scheme 1).

On the other hand, the salts of transition metals can operate as bifunctional Lewis acids activating either (or both) carbon−carbon multiple bonds via π-binding or (and) make the σ-complexes with heteroatoms in the same fashion as the conventional Lewis acids (Scheme 1).[1c,d]

An attempt to classify various Lewis acids by their relative ability for making σ- and π-complexes with appropriate substrates is useful for the deliberate choice of catalysts for the desired transformations, especially in the cases when bi- or polyfunctional substrates are involved. Another stimulating objective of this study was to look for the reasons of the recent growing popularity of gold catalysts used as Lewis acids in various catalytic transformations.[5] Indeed, the reactions catalyzed by auric salts have demonstrated outstanding growth from almost complete neglect before 2000[6] to the extremely hot area in 2006.[7] Table 1 shows the computed heats of formation for the generation of complexes between unsaturated compounds with representative metal chlorides.[8] Additionally, the relative stabilities of the corresponding associates are shown. The lower values of the $\Delta H^{\text{aldehyde(imine)}}/\Delta H^{\text{acetylene(alkene)}}$ indicate the greater trend for binding with the corresponding carbon−carbon multiple bonds.

As could be expected, the main group chlorides show much stronger complexes with heteroatoms than with carbon−carbon multiple bonds. However, if for BCl_3 this trend is clear-cut, $MgCl_2$ and $AlCl_3$ are not completely incapable of the association to acetylenic or olefinic bonds.

Among the investigated chlorides, $PtCl_2$ invariably demonstrates the highest heats of formation as well as the highest preferences for binding with carbon−carbon multiple bonds. This finding corresponds well with a wide range of catalytic applications of platinum catalysts. One should take into account, however, that platinum chloride is a polymer; hence the very similar values demonstrated by AuCl, which is soluble in many organic solvents, might mean that in practice this is a better homogeneous catalyst.

Comparing the ratios of the heats of formation for the Lewis acids containing the same metal in different oxidation state (CuCl and $CuCl_2$, AuCl and $AuCl_3$), one can conclude that the lower oxidation state of the catalyst increases the relative strength of coordination to the carbon−carbon multiple bonds.

The conclusion from comparing the data of Table 1 for the aromatic and aliphatic substrates is that there is no significant difference either in the absolute values or in their ratios. This result allows one to restrict the further analysis for only one set of substrates.

As a next step, the dependence of the heats of formation of the adducts between benzaldehyde **1**, benzimine **2**, and phenylacetylene **3** and different salts of coinage metals (Cu, Ag, Au) and Pt in the lowest oxidation state was investigated (Figure 1).

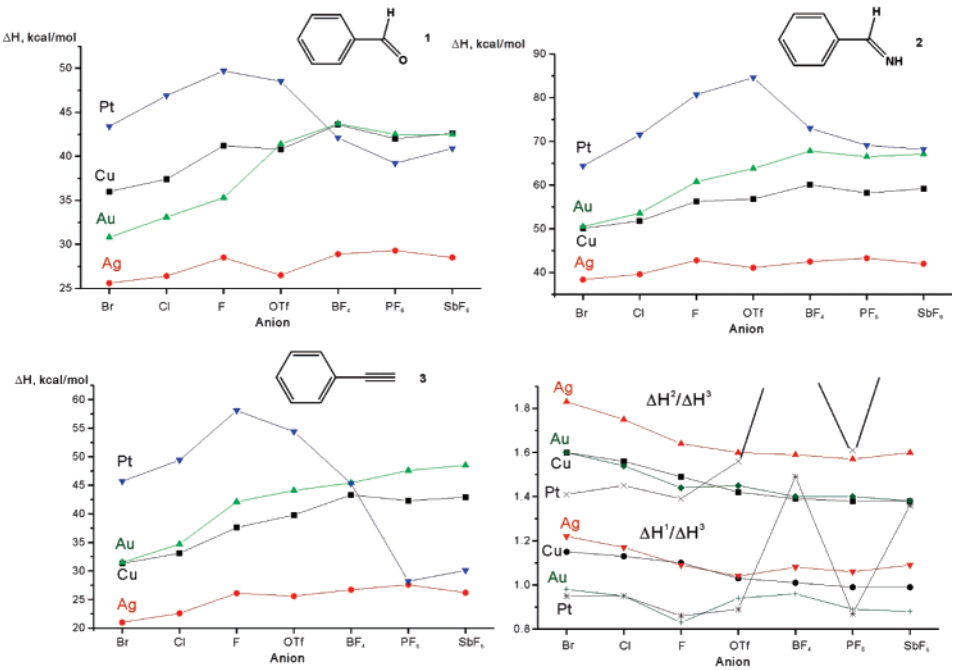
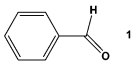
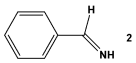
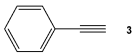
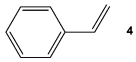
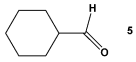
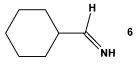
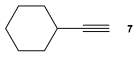
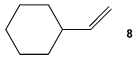


FIGURE 1. Plots displaying the absolute and relative (bottom right) heats of formation for various coinage metals, salts, and representative substrates.

TABLE 1. Computed Heats of Formation (B3LYP/SDD, kcal mol^{-1})[a] and Their Selected Ratios (Shown in Bold) of the Substrates 1−8 with Representative Lewis Acids

Lewis Acid	BCl_3	$MgCl_2$	$AlCl_3$	CuCl	$CuCl_2$	AgCl	AuCl	$AuCl_3$	$PtCl_2$
 1	18.9	34.5	40.7	37.4	25.4	26.4	33.1	35.9	46.9
 2	42.1	44.2	55.1	51.8	41.2	39.6	53.6	60.3	71.5
 3	0.9	15.2	19.1	33.1	14.3	22.6	34.7	32.5	49.4
 4	0.4	15.7	19.2	33.6	18.1	24.4	37.5	36.8	53.9
 5	17.2	33.1	38.7	36.6	23.9	26.0	32.7	35.1	38.9
 6	42.6	44.4	55.4	52.2	41.9	40.4	54.3	61.1	72.4
 7	1.3	18.7	18.4	35.3	16.1	25.2	36.2	30.9	49.5
 8	8.8	25.6	26.4	43.6	25.2	34.7	48.1	43.2	68.8
$\Delta H^1/\Delta H^3$	**21.0**	**2.3**	**2.1**	**1.1**	**1.8**	**1.2**	**1.0**	**1.1**	**1.0**
$\Delta H^2/\Delta H^3$	**46.7**	**2.9**	**2.9**	**1.6**	**2.9**	**1.8**	**1.5**	**1.9**	**1.4**
$\Delta H^1/\Delta H^4$	**47.3**	**2.2**	**2.1**	**1.1**	**1.4**	**1.1**	**0.9**	**1.0**	**0.9**
$\Delta H^2/\Delta H^4$	**46.8**	**2.8**	**2.9**	**1.5**	**2.3**	**1.6**	**1.4**	**1.6**	**1.3**
$\Delta H^5/\Delta H^7$	**13.2**	**1.8**	**2.1**	**1.0**	**1.5**	**1.0**	**0.9**	**1.1**	**0.8**
$\Delta H^6/\Delta H^7$	**54.8**	**2.4**	**3.0**	**1.5**	**2.6**	**1.6**	**1.5**	**2.0**	**1.5**
$\Delta H^5/\Delta H^8$	**2.0**	**1.3**	**1.5**	**0.8**	**0.9**	**0.7**	**0.7**	**0.8**	**0.6**
$\Delta H^6/\Delta H^8$	**4.8**	**1.7**	**2.1**	**1.2**	**1.7**	**1.2**	**1.1**	**1.4**	**1.0**

[a] In the gas phase. The heats of formation were calculated by subtraction of the absolute energies of the starting compounds from the absolute energy of the optimized complex between the substrate and the Lewis acid.

The halogenides of all four metals follow the same trend: the heats of formation increase with decreasing nucleophilicity of the anion (from Br to F). Simultaneously, the relative ability of corresponding Lewis acids to bind with phenylacetylene, which is reflected in decreasing values of $\Delta H^1/\Delta H^3$ and $\Delta H^2/\Delta H^3$, increases. For AuCl and CuCl, the same trend prevails when coming to the completely non-nucleophilic anions (BF_4, PF_6, SbF_6): the heats of formation increase together with relative affinity to the triple bond. This effect is almost absent for silver, whereas platinum demonstrates irregular behavior caused by

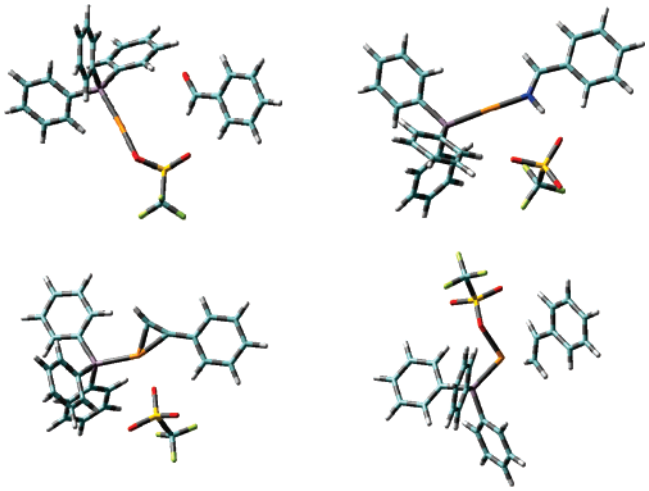


FIGURE 2. Optimized structures (B3LYP/SDD) of the complexes of (Ph_3P)AuOTf with benzaldehyde (upper left), benzimine (upper right), phenylacetylene (lower left), and styrene (lower right). Despite the positive heat of formation, benzaldehyde is not activated by the complex formation. Gold (orange), phosphorus (violet), oxygen (red), nitrogen (blue), fluorine (green), sulfur (yellow).

steric hindrance between two large anions and the coordinating substrate. Thus, the potential importance of the copper and gold salts with non-nucleophilic anions, as important bifunctional catalysts, is indicated. However, only a few of such compounds really exist without stabilizing ligands. Thus, for example, the extremely unstable AuF could be characterized only recently,[9] whereas CuF is a well-known catalyst but is used exclusively in the presence of phosphines.[10] Nevertheless, gold triflates or hexafluoroantimonates are most probably generated in situ when gold chlorides are used in the presence of AgOTf[11] or $AgSbF_6$.[12]

Another possibility to use the most active but unstable catalysts is their stabilization with neutral ligands, most frequently phosphines. The ligation with triphenylphosphine considerably decreases the Lewis acidity of auric salts. Thus, the binding of (Ph_3P)AuCl with phenylacetylene or styrene becomes endothermic ($\Delta H_3 = -4.9$ kcal and $\Delta H_4 = -5.5$ kcal). Nevertheless, the binding is slightly exothermic with (Ph_3P)-AuOTf ($\Delta H_3 = 0.5$ Kcal and $\Delta H_4 = 3.3$ Kcal). Moreover, the complexes of (Ph_3P)AuOTf with **3** and **4** have the expected geometry, appropriate for the multiple carbon−carbon bond activation, whereas the exothermic binding with benzaldehyde **1** is achieved via the hydrogen bonding, and the aldehyde remains nonactivated (see Figure 2). On the other hand, the imine **2** is properly activated by (Ph_3P)AuOTf with considerably large heat of complex formation (Figure 2).

Hence, the oversimplified conclusion from the theoretical study is that the compatibility in coordination strength to carbon−carbon multiple bonds in the presence of aldehyde or imine groups is likely with gold(I) catalysts containing non-nucleophilic anions. If the phosphine ligands are being used for the stabilization of a gold catalyst, the coordination to the multiple carbon−carbon bonds better competes with the coordination to an aldehyde than to an imine. This can be a reason for the gold-catalyzed syntheses of oxygen heterocycles[13] being better known than the synthesis of nitrogen heterocycles.[14,15] Another conclusion is that a very similar performance may be expected from Cu(I) and Au(I) catalysts: all values obtained above are very close for these two cases. Until now, the research on the copper- and gold-catalyzed reactions was carried out more or less independently. Only several studies comparing the performance of gold and copper catalysts were carried out from our laboratories (see section III.2).[16] However, in these examples, the Cu(II) salt ($Cu(OTf)_2$) has been used, whereas the above results indicate that Cu(I) catalysts might be superior.

II. Selective Transformations with *σ*-Electrophilic Lewis Acids

In this section, the allylation reactions using allylic organometallic reagents in the presence or in the absence of *σ*-electrophilic Lewis acids, such as BF_3•OEt_2 and $MgBr_2$, are mentioned. In the first section (1), it is mentioned that the allylation of aldehydes with allylic stannanes in the presence of BF_3•OEt_2 proceeds through an acyclic transition state, affording *syn*-homoallylic alcohols diastereoselectively. In the second section (2), it is stated that the allylation of imines with allylic boranes proceeds through a cyclic transition state, producing very high 1,2-asymmetric induction. In the third section (3), the allylation with allylic stannanes in the presence of Lewis acids is applied to the total synthesis of polycyclic ether marine natural products, such as hemibrevetoxin B, gambierol, and brevetoxin B.

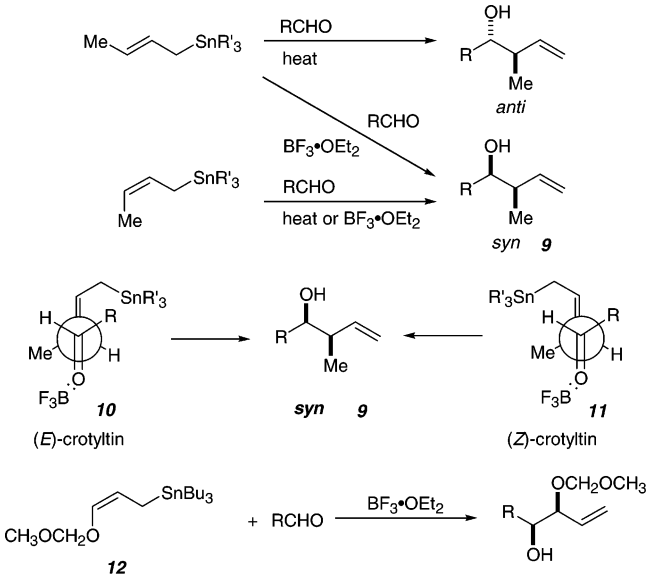
1. Allylic Tin−Lewis Acid Reagents. Reactions of Aldehydes.[17,18] Many years ago, we discovered that the BF_3•OEt_2-mediated reaction of crotyltrialkyltins with aldehydes produced the *syn*-homoallyl alcohol **9** stereoselectively regardless of the geometry of the double bond.[19] This stereochemical outcome was quite unexpected in those days since it had been generally believed that the reaction of allylic organometals with aldehydes must proceed though a chair-like transition state in which the metal cation can interact with the partially negative oxygen and, therefore, the (*E*)-crotylmetals should selectively produce the *anti*-alcohol. To explain this *syn*-selectivity, we proposed the acyclic transition states **10** and **11** in which Lewis acids coordinate to the oxygen atom preventing the coordination of the Sn atom. The crotyltin−aldehyde condensation reaction was then applied to the stereoselective synthesis of the Prelog−Djerassi lactone, verrucarinolactone, invictolide, and statine.[20]

Not only crotyltin but also the *γ*-oxo-substituted allylic tributyltin **12** gave the *syn*-diol stereoselectively upon treatment with aldehyde−Lewis acid complexes. As mentioned later, the *γ*-oxo-substituted allylic tin−aldehyde condensation reaction was applied to the synthesis of *β*-hydroxy cyclic ethers which form the framework of certain marine natural products.

The allylic tin, substituted by $SiMe_3$ or SR at the *γ*-position, also exhibited high *syn*-selectivity in the presence of BF_3•OEt_2. These tin reagents were easily obtained by trapping the corresponding heteroatom-substituted allylic carbanions with Bu_3SnCl. It is clear that many allylic organometals, including allylic tin reagents, *behave quite differently in the presence of Lewis acid catalysts*, though the allylic geometry is generally stereodetermining in the absence of Lewis acids.[21,22] We found that allylation of aldehydes with (*E*)-crotyltrialkyltins took place at room temperature under neutral conditions by using a high-pressure technique, giving the *anti*-homoallyl alcohol stereoselectively. This result clearly indicates that a six-membered cyclic transition state is involved under ordinary neutral conditions.

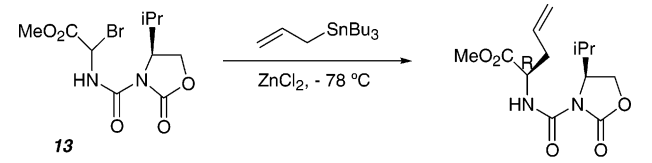
We discovered that Lewis acids are effective not only for *promoting a radical allylation* of certain alkyl bromides but also as chelating agents enhancing stereoselectivity.[23] Nowadays, this concept is accepted widely, but our discovery was made at a very early stage of this chemistry. $ZnCl_2$ accelerated the radical allylation of the α-bromoglycine derivative **13** and also enhanced

SCHEME 2



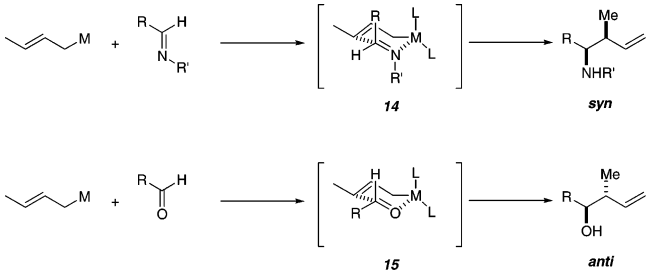
the diastereoselectivity in the free radical allylation. Treatment of **13** (1:1 diastereomeric mixture), bearing the Evans oxazolidinone chiral auxiliary, with allyltributylstannane in the presence of $ZnCl_2$ gave the allylation product with 93:7 diastereoselectivity.

SCHEME 3



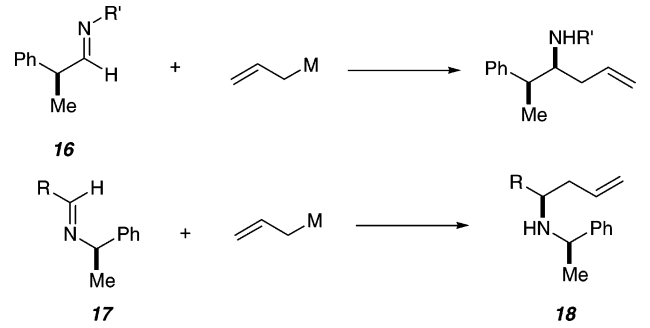
2. Reactions of Imines with Allylic Organometallic Reagents.[17,18,24] The *trans*-geometry of aldimines necessarily forces electrophiles (Lewis acids or metals) to coordinate the nitrogen atom *syn* to the R group. Therefore, the R group must go to the axial position in the chair transition state **14**. Judging from both transition states **14** and **15**, we may obtain the opposite diastereoselectivity in the reactions of imines and aldehydes. In fact, the reactions of *trans*-imines with (*E*)-crotyl-9-BBN produced the *syn*-homoallylamines predominantly,[25] whereas the reaction of aldehydes with (*E*)-crotyl-9-BBN gave the *anti*-homoallyl alcohols predominantly.

SCHEME 4



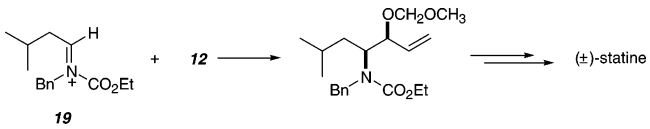
Next, we tested the reaction of allyl-9-BBN with the imines having a chiral center α to the carbon of C═N (**16**) and bearing a chiral center α to the nitrogen of C═N (**17**). Since the α-chiral center of **16** goes to the axial position in the transition state **14**, the selectivity must depend upon both the original steric factor of the chiral center and the steric influence of L (1,2-diaxial interaction). Thus, enhancement of the *syn*-selectivity (Cram selectivity) was expected due to the stereoelectronic effect of the imine group.[26] In fact, the reaction of **16** with allyl-9-BBN showed *syn*-selectivity approaching 100%.[24] The reaction of **17** with allyl-9-BBN gave **18** with very high diastereoselectivity (92:8); a sort of 1,2-axial−equatorial interaction between the R′ group and L in **14** may create high asymmetric induction.[27]

SCHEME 5



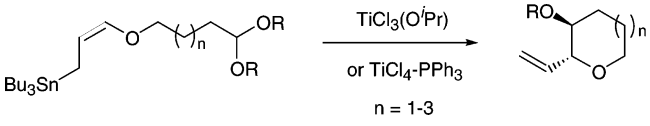
The imine−allylmetal condensation reaction was applied to the synthesis of amino acid derivatives. L-Norvaline butyl ester was prepared from the reaction of the α-imino ester (8-(−)-phenylmenthyl *N*-methoxyiminoacetate), derived from 8-(−)-phenylmenthyl glyoxylate and methoxyamine, with allylic zinc reagent.[28] The reaction of the γ-oxygen-substituted allylic stannane **12** with the acyliminium ion **19**, produced in situ from the corresponding α-ethoxy-*N*-benzyl carbamate and BF_3•OEt_2,[29] gave the *syn*-amino alcohol derivative exclusively in high yield, which was converted to (±)-statine.[30]

SCHEME 6



3. Total Synthesis of Polycyclic Ether Marine Natural Products.[31] **Hemibrevetoxin B.** The highlight of the application of our allylation methodologies is the total synthesis of (+)-hemibrevetoxin B,[32,33] gambierol,[34,35] and brevetoxin B.[36] As mentioned above, we studied the acyclic stereocontrol via allylic organometallic compounds and discovered that the reaction of aldehydes with crotylstannane in the presence of BF_3•OEt_2 gave predominantly the *syn*-homoallylic alcohols regardless of the stereochemistry of the crotyl unit. Similarly, the γ-alkoxy-substituted allylic stannanes produced the *syn*-homoallylic diol derivatives upon treatment with aldehydes (section II.1, **12**). The intramolecular reaction of the γ-alkoxy-substituted allylic stannanes bearing an acetal at the end of the carbon chain gave stereoselectively the corresponding β-alkoxy cyclic ethers in good to high yields.[37] The *trans*-stereochemistry at the α- and β-positions matched well that of the ether framework of polycyclic ethers marine natural products.

SCHEME 7



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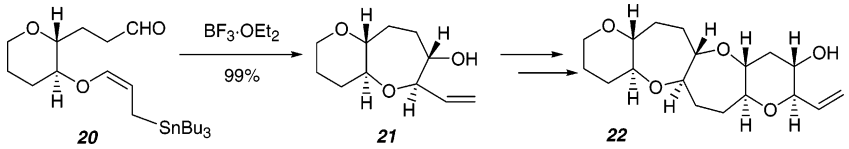

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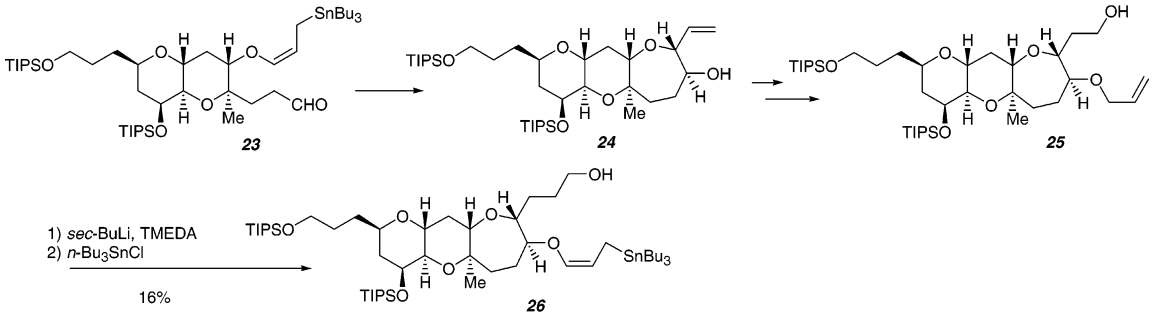
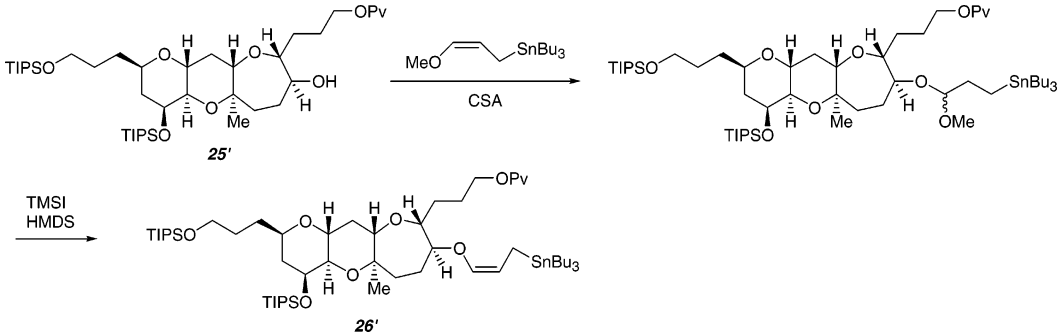


SCHEME 10



Encouraged by the above finding, we investigated the iterative synthesis of polycyclic ethers.[38] The allylic stannane **20** was subjected to the cyclization with BF_3•OEt_2 to give the 6,7-bicyclic ether **21** in quantitative yield with high stereoselectivity. Further manipulation on the hydroxy and vinyl groups of the product, followed by the repeated use of the cyclization method, produced the 6,7,7,6-tetracycle **22**, which is a part of the cyclic ether skeleton of brevetoxin B.[39] This reaction was recognized to be one of the most powerful methods for the synthesis of oxepane derivatives[40] and employed for the synthetic studies of polycyclic ethers.

To demonstrate the usefulness of the allylation methodology, we next examined the total synthesis of hemibrevetoxin B. Cyclization of **23** with BF_3•OEt_2 proceeded smoothly to afford the tricyclic compound **24** as the sole product in 94% yield. Further transformation provided the allylic ether **25**, which was subjected to the usual allylstannane synthesis. However, we encountered a serious problem at this stage. The reaction of **25** with *n*-BuLi/TMEDA/Bu_3SnCl gave the desired allylstannane **26** in only 16% yield. Deprotonation of the sterically bulky allylic ether **25** was very slow, and the decomposition of the resulting allylic anion occurred if a prolonged reaction time was employed.

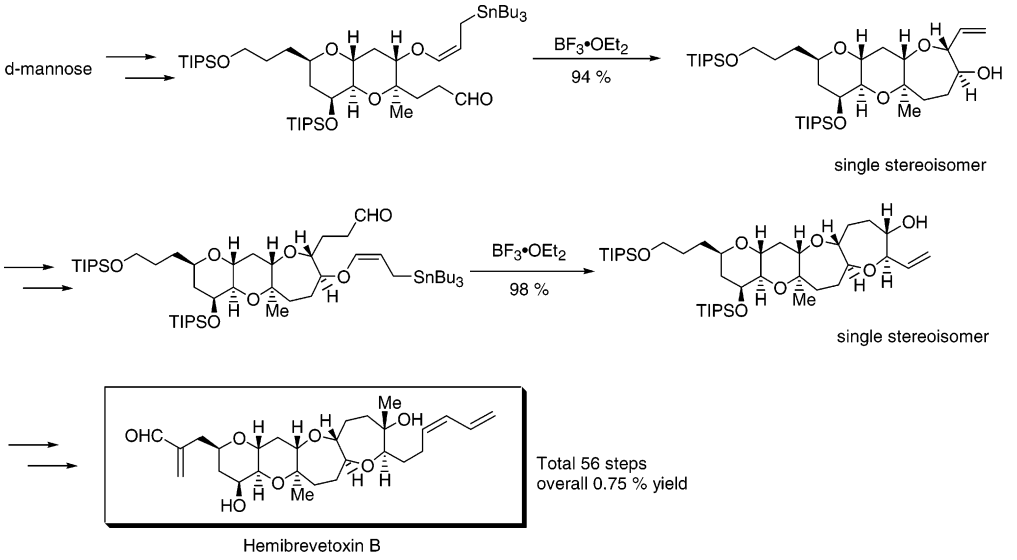
After several unfruitful attempts, we developed a new synthetic route to γ-alkoxyallylstannanes via an acetal cleavage.[41] Treatment of the alcohol **25′** with γ-methoxyallylstannane in the presence of a catalytic amount of CSA proceeded smoothly to give the mixed acetal (γ-methoxy-γ-alkoxypropylstannane) in a high yield, which was treated with TMSI/HMDS, affording the desired γ-alkoxyallylstannane **26′** in 80% yield (two steps from **25′**).

Thus, we completed the total synthesis of hemibrevetoxin B.[32,33] The number of total steps is 56, and the overall yield is 0.75%. Although our strategy was iterative, hemibrevetoxin B was synthesized in a higher yield than Nicolaou's first total synthesis.

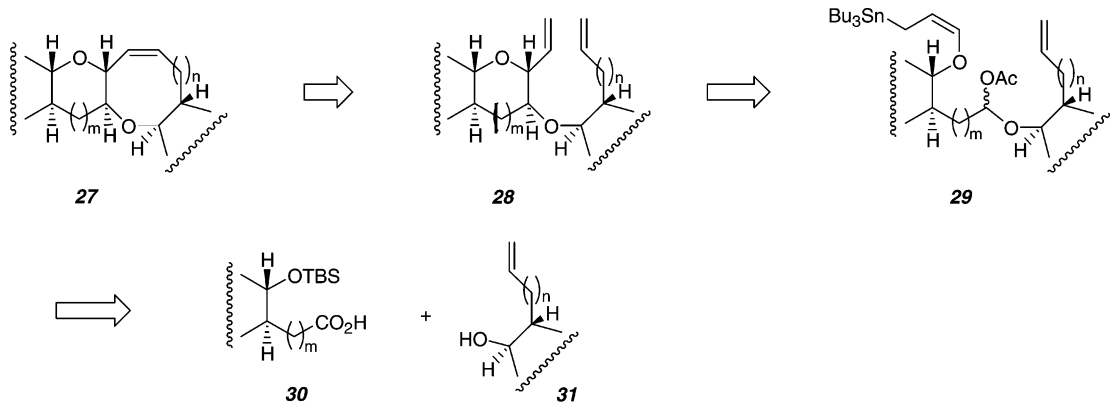
Gambierol and Brevetoxin B. Since most of the marine polycyclic ethers have a large number of continued and fused cyclic ether frameworks, an efficient synthesis of those giant molecules requires a *convergent strategy*, instead of the *linear one* mentioned above. After many unfruitful attempts, we found a convergent and efficient new synthetic strategy.[42,43] The *retro* ring-closing metathesis of **27** leads to the diene **28**. The key point of our strategy is the convergent synthesis of the diene intermediate **28**. We planned to use the α-acetoxy ether **29** as the substrate for the intramolecular allylation. Retrosynthetic disassembly of **29** afforded the carboxylic acid **30** and the alcohol **31**. The ester formation from those two fragments followed by the reductive acetoxylation of the ester would produce **29**. Overall, the allylation−RCM strategy would produce two consecutive cyclic ether rings.

The ABC and FGH ring segments **32** and **33** were converted to the α-acetoxy ether **34** by the DCC coupling in a high yield. Treatment of **34** with $MgBr_2$•OEt_2 afforded a mixture of the desired product **35** and its epimer **36** in 61% yield. Unfortunately, the undesired stereoisomer **36** was obtained as the major component. After several unfruitful attempts, we found that the use of α-chloroacetoxy ether **37**, instead of the α-acetoxyether **34**, gave the desired isomer as the major product (64:34 in 87% combined yield). Most probably, the higher ability of the chloroacetoxy moiety as a leaving group in comparison with that of the acetoxy group would drive the reaction to proceed

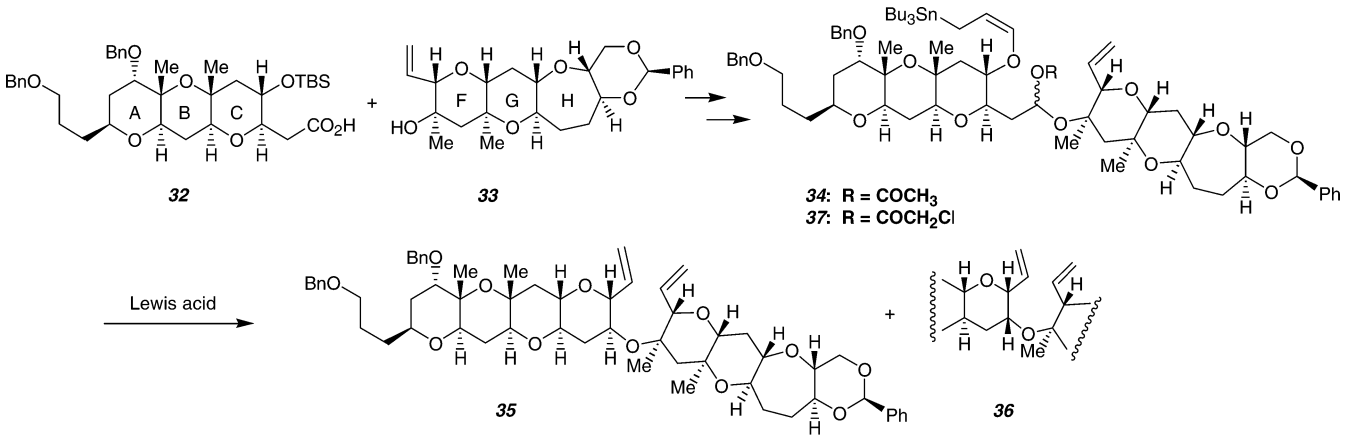
SCHEME 11



SCHEME 12



SCHEME 13

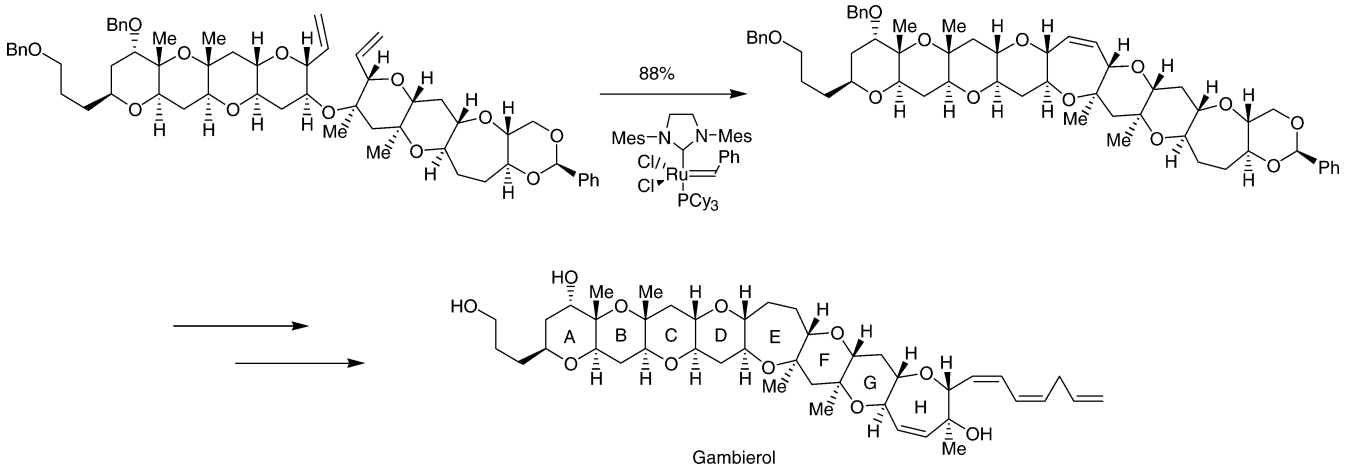


R	Lewis acid	*35* : *36*	yield
acetyl (*34*)	$MgBr_2{\cdot}OEt_2$	36 : 64	61%
chloroacetyl (*37*)	$BF_3{\cdot}OEt_2$	64 : 36	87%

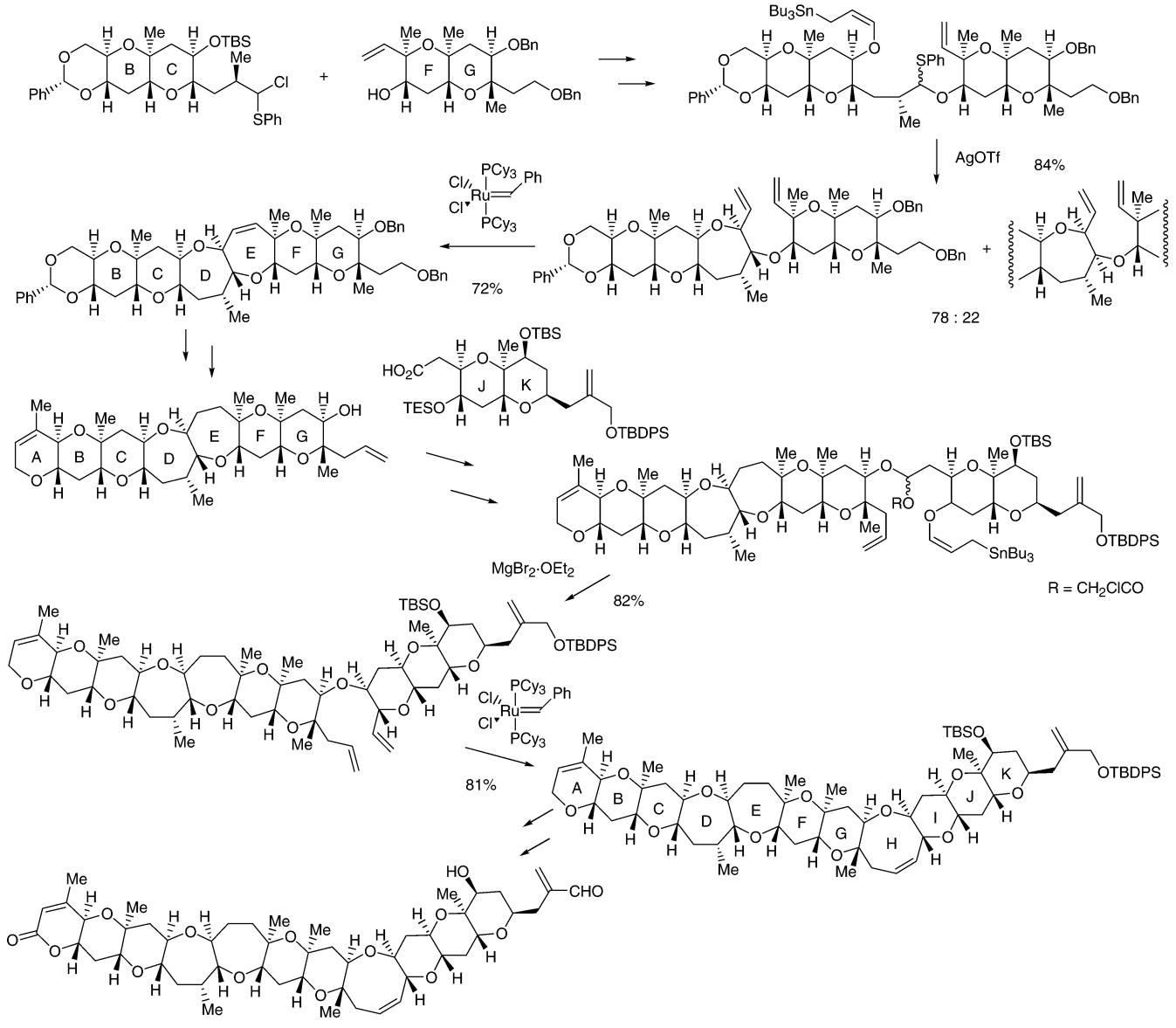
through the S_N1 pathway, giving the desired isomer **35** predominantly.

The diene **35** obtained was then subjected to the ring-closing metathesis using the second-generation Grubbs catalyst, leading to the octacyclic ether in 88% yield. Modification of the H ring and side chain elongation completed the total synthesis of gambierol. The longest linear sequence from the commercially available starting material, 2-deoxy-D-ribose, to gambierol was

SCHEME 14



SCHEME 15



Total 108 steps, longest linear sequences: 63 steps, overall 0.28% yield

66 steps with 1.2% overall yield, and the total number of steps was 102.

Similar transformations starting from the isomer **36** afforded the 16-*epi*-gambierol, which was subjected to mouse toxicity studies.[35] Interestingly, the epimer exhibited no toxicity at the concentration of 14 mg/kg, which is 300 times as much as the LD_{50} value (50 μg/kg) reported for the natural gambierol. This result indicates that the *trans*-fused polycyclic ether framework is essential to the toxicity.

The convergent synthesis of brevetoxin B has been achieved.[36] The *O*,*S*-acetal, prepared from the α-chlorosulfide (BC ring system) and the corresponding alcohol (FG ring system), was converted to the allylic stannane derivative as mentioned above. The intramolecular allylation of the *O*,*S*-acetal was carried out using AgOTf as a Lewis acid to give the ring-closing product, diene derivative, which was subjected to ring-closing metathesis to give the hexacyclic ether, B−G ring fragment. Then the A ring was installed. The A−G ring system was connected with the JK fragment via the ordinary esterification. The resulting A−G and JK combined system was converted to the corresponding allylic stannane, which was subjected to the intramolecular allylation in the presence of $MgBr_2$•OEt_2. Then the resulting diene underwent the RCM, as usual, giving the A−K ring system. The functional group conversion and the installation of the side chain gave brevetoxin B in overall 0.28% yield with 63 steps of the longest linear sequences. Brevetoxin B was synthesized using allylation−RCM methodology in a similar fashion to that described above for gambierol.

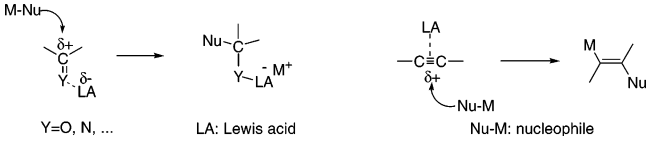
III. Selective Transformations with π-Electrophilic Lewis Acids

The reactions of C−C unsaturated bonds mediated or catalyzed by π-electrophilic Lewis acids, such as copper, gold, and zirconium halides, are mentioned in sections 1 and 2. It is pointed out in section 3 that certain palladium, platinum, and other transition metal complexes act as σ- and/or π-electrophilic Lewis acids. The allylation of aldehydes and imines with bis-π-allylpalladium, in which σ-coordination of Pd(II) to the carbonyl oxygen or imine nitrogen becomes key for the reaction progress and asymmetric induction, is stated in section 4.

1. Hydro- and Carbometalation of Alkynes and $\sigma-\pi$ Chelation. As mentioned above, a typical role of Lewis acid (LA) to enhance the reactivity of a substrate is the formation of a complex with *lone pairs* of C═Y (Y═O, N, ...) multiple bonds, facilitating the nucleophilic attack of Nu^- to the carbon bearing a positive charge. We extended a similar concept to carbon−carbon multiple bonds (π-electrons); it was expected that proper choice of π-electrophilic Lewis acids, including main group elements and transition metals, would make it possible to activate C−C multiple bonds selectively without direct reaction between LA and Nu−M to induce the *trans*-addition of nucleophiles across the multiple bonds (Scheme 16).

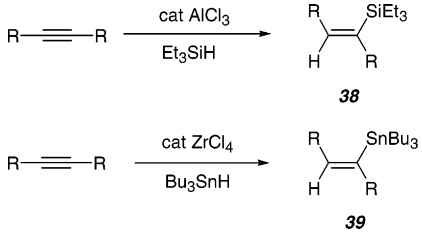
The hydrosilylation of alkynes in the presence of catalytic amounts of $AlCl_3$ gave the corresponding *trans*-hydrosilylation

SCHEME 16. Lewis Acid Coordination to Lone Pairs or to π-Electrons



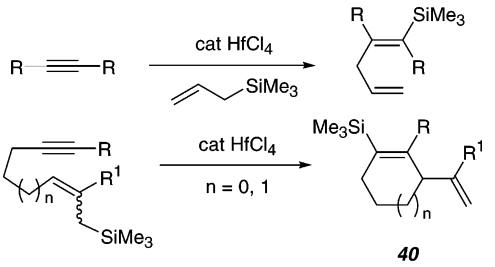
products **38** in high yields,[44] although the transition-metal-catalyzed addition affords the *cis*-hydrosilylation product and the radical-induced addition produces *a mixture of trans- and cis-adducts*. $AlCl_3$ coordinates to an alkyne triple bond, and a hydride from Et_3SiH attacks the electron-deficient triple bond from the side opposite to $AlCl_3$ to produce an alkenylaluminum ate complex, which undergoes coupling between the Et_3Si cation and the alkenyl group with retention of geometry to give **38** stereoselectively together with $AlCl_3$. Very similarly, the $ZrCl_4$-catalyzed hydrostannation of alkynes gave the corresponding *trans*-hydrostannation products **39** in high yields.[45]

SCHEME 17



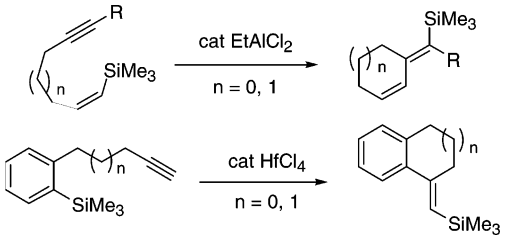
The $HfCl_4$-catalyzed allylsilylation of alkynes proceeded in a *trans*-manner in high yields.[46] The *trans*-allylstannylation also proceeded smoothly with the $ZrCl_4$ catalyst. The intramolecular version of the $HfCl_4$-catalyzed allylsilylation proceeded in the *trans-endo* fashion to give the cyclic alkenylsilanes **40** which are not easily available by other means.[47]

SCHEME 18



Similarly, the intramolecular *trans*-vinylsilylation[48] and arylsilylation[49] of unactivated alkynes proceeded in the presence of Lewis acid catalysts to give the corresponding carbocyclic alkenyl silanes.

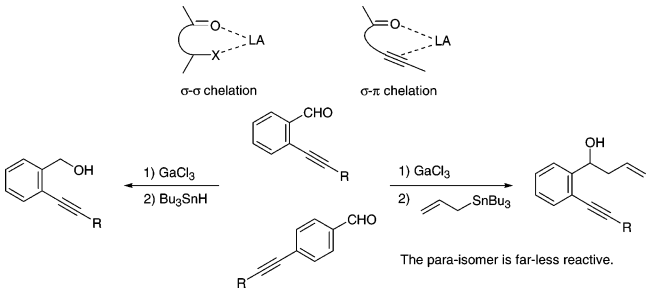
SCHEME 19



It is well accepted that the σ-chelation controlled reaction proceeds through the coordination of a Lewis acid to *a lone pair* of heteroatoms ($\sigma-\sigma$ chelation). It occurred to us that regio-, chemo-, and stereoselectivities must be controlled through $\sigma-\pi$ chelation, as well, using π- and σ-electrophilic Lewis acids ($\sigma-\pi$ chelation). We discovered that the $\sigma-\pi$ chelation controlled regio- and chemoselective reaction of certain alkynylaldehydes with Bu_3SnH or allylstannane takes

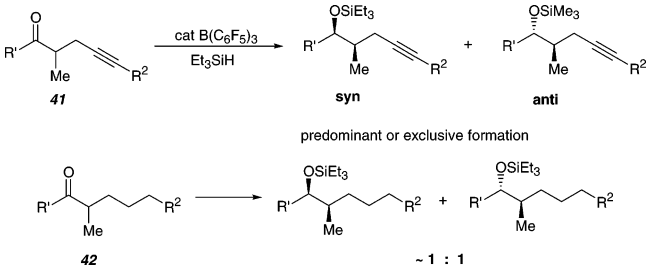
place in the presence of $GaCl_3$.[50] The reaction of a 1:1 mixture of *ortho*- and *para*-alkynylaldehydes with Bu_3SnH (1 equiv) or allyltributylstannane (1 equiv) in the presence of $GaCl_3$ (1 equiv) gave the corresponding products from the *ortho* substrates, and the *para* starting materials were recovered.

SCHEME 20



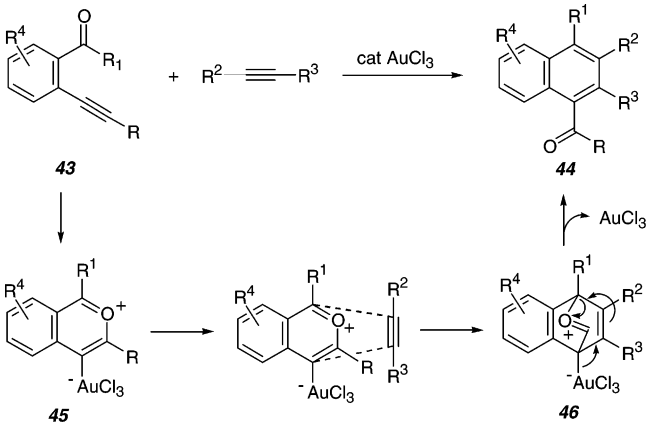
Although $\sigma-\sigma$ chelation of carbonyl derivatives bearing heteroatom-containing functionalities is well-known, the control of the stereoselective addition of nucleophiles to carbonyl compounds through $\sigma-\pi$ chelation is novel. The $B(C_6F_5)_3$-catalyzed reduction of the ketones **41** with Et_3SiH gave the *syn*-product either predominantly or exclusively (R^1 = Ph, R^2 = H; *syn*:*anti* = 7:1, R^1 = *t*-Bu, R^2 = H; *syn*:*anti* = >30:1) (1,2-asymmetric induction through $\sigma-\pi$ chelation), whereas the reduction of the corresponding saturated ketones **42** afforded approximately a 1:1 mixture of the *syn*- and *anti*-products.[51] The asymmetric induction via the $\sigma-\pi$ chelation control can be extended to the 1,3-systems; the hydrosilylation of 3-methyl-1-phenyl-5-trimethylsilyl-4-pentyn-1-one with Ph_2MeSiH in the presence of $B(C_6F_5)_3$ catalyst gave the *anti*-product stereoselectively, whereas no selectivity was observed in the reaction of the saturated analogue (3-methyl-1-phenyl-5-trimethylsilylpentan-1-one).

SCHEME 21

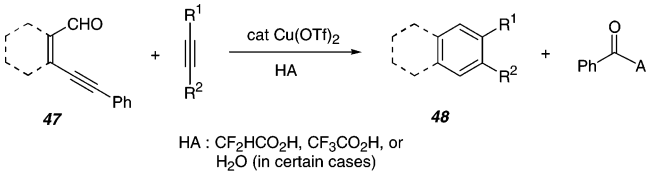


2. Benzannulation Catalyzed by π-Electrophilic Au and Cu Catalysts. While a large number of research has focused on the Lewis acid catalyzed [4 + 2] Diels−Alder reaction, during our work investigating π-coordination, we discovered Lewis acid catalyzed [4 + 2] benzannulation. Researching the π-coordination of Lewis acids, we discovered that the $AuCl_3$-catalyzed formal [4 + 2] benzannulation between the *ortho*-alkynylbenzaldehydes (and ketones) **43** and alkynes produced the naphthyl ketones **44** in good to high yields.[52] The reaction proceeds, most probably, through the formation of the auric ate complex **45**, the cycloaddition between **45** and alkynes, and the subsequent rearrangement of the resulting pyrilium ion intermediate **46**. On the other hand, the reaction of *ortho*-alkynylbenzaldehydes (or enynals) **47** with alkynes in the presence of a catalytic amount of $Cu(OTf)_2$ and *a stoichiometric amount* of *HA* (a Brønsted acid) produced the debenzoylated naphthalenes (or benzenes, respectively) **48** in good to high yields.[53]

SCHEME 23

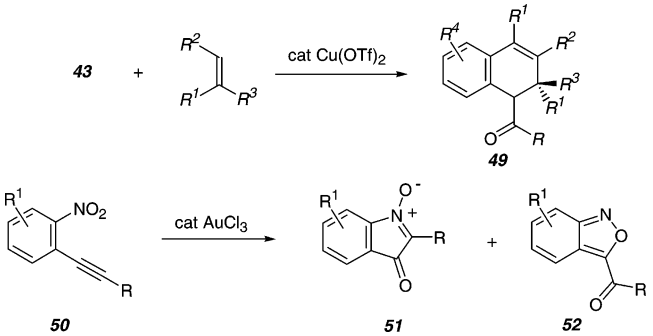


SCHEME 24



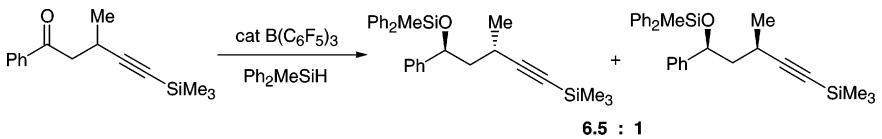
Functionalized 1,2-dihydronaphthalenes **49** were synthesized in good to high yields from the $Cu(OTf)_2$-catalyzed [4 + 2] cycloaddition of *ortho*-alkynylbenzaldehydes (and ketones) with alkenes.[54] The $AuBr_3$-catalyzed cyclization of the *ortho*-(alkynyl)nitrobenzenes **50** gave the isatogens **51** in good yields, while the anthranils **52** were obtained in the case of *ortho*-(alkylalkynyl)nitrobenzenes (R = alkyl).[55]

SCHEME 25



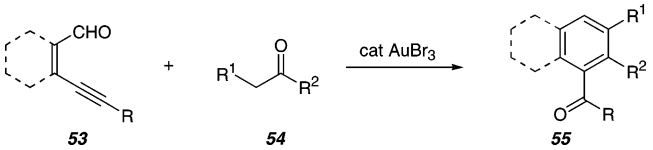
The $AuBr_3$-catalyzed reaction of the enynal unit **53** with the carbonyl compounds **54**, instead of alkynes, gave the benzan-

SCHEME 22



nulation products **55** in good to high yields.[56] The carbonyl compounds **54** undergo enolization under the reaction conditions, and the resulting enols react with **53**, giving the [4 + 2] benzannulation products.

SCHEME 26

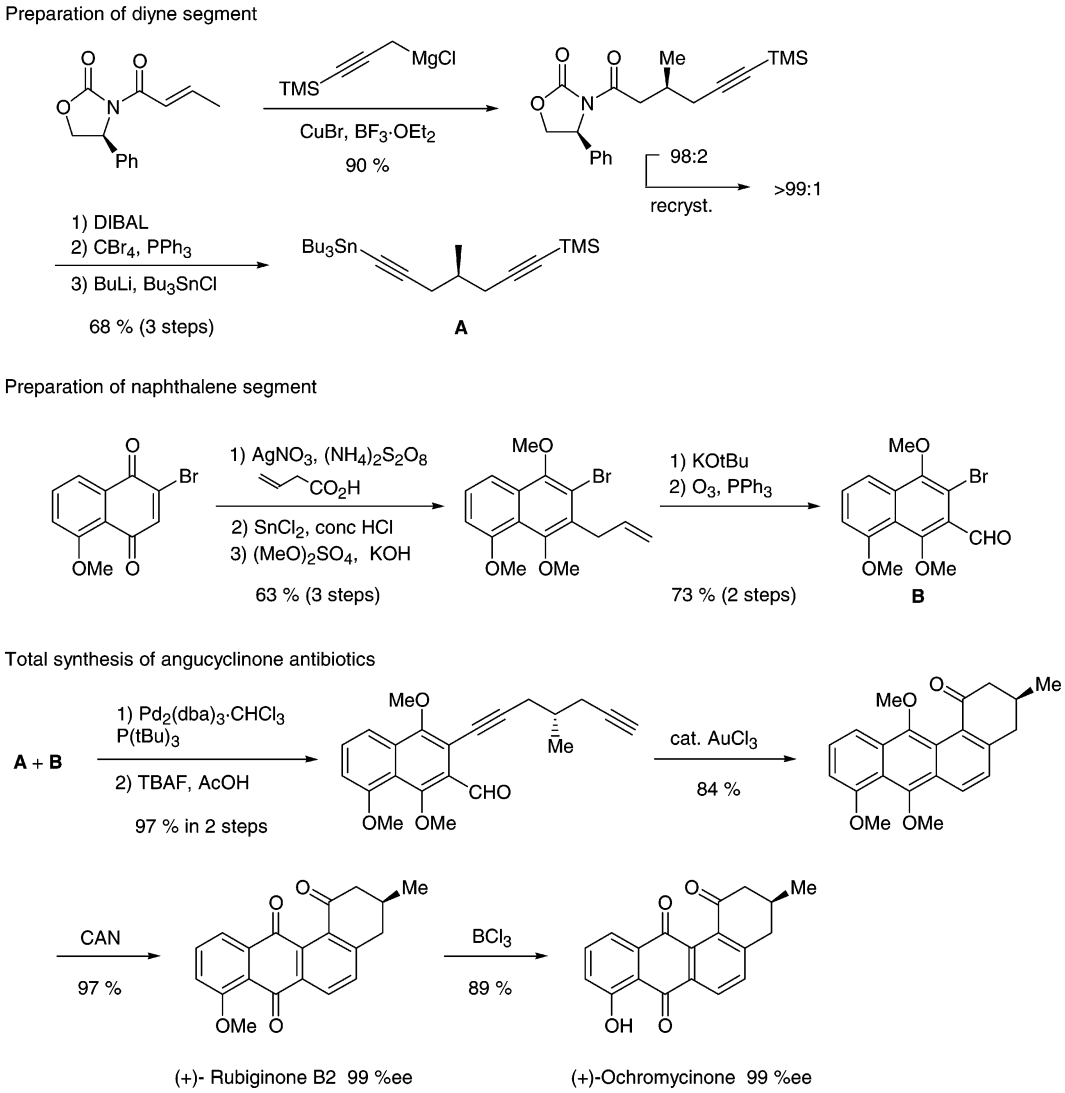


An efficient synthesis of angucyclinone antibiotics, (+)-ochromycinone and (+)-rubiginone B_2, was achieved using this chemistry.[57] The diyne **A** was synthesized through the Michael addition of the propargylic copper reagent to the crotyl amide derivative, followed by removal of the chiral auxiliary and subsequent alkynylation of the resulting aldehyde, and the naphthalene segment **B** was prepared by the conventional methods. The Sonogashira coupling between **A** and **B** gave the corresponding alkynyl naphthalene derivative in high yields. The key step involves the facile formation of a 2,3-dihydrophenanthren-4(1*H*)-one skeleton, an important framework of angucyclinone, via the intramolecular [4 + 2] benzannulation catalyzed by $AuBr_3$ or $AuCl_3$.[57] Actually, the benzannulation proceeded in a high yield, and the targeted compounds were obtained with very high enantiomeric excesses and in high chemical yields.

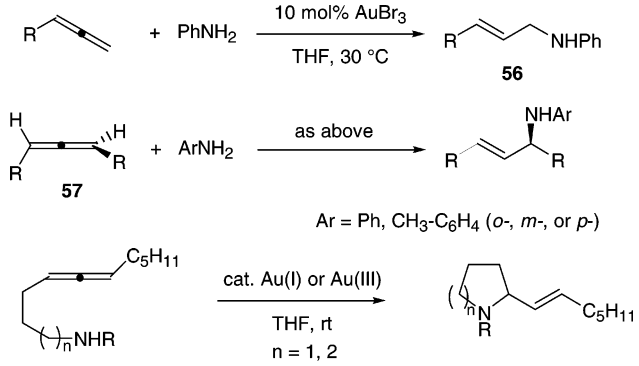
Intermolecular $AuBr_3$-catalyzed addition of anilines to the chiral allenes **57** went along with a high axial to central chirality transfer and a high regioselectivity.[58] The reaction seems to proceed regioselectively through the coordination of the terminal C−C double bond to gold(III), followed by the addition of the nitrogen nucleophile from the plane opposite to that coordinated by gold, and subsequent formation of the allylamines **56** via a vinyl gold intermediate; no allyl gold species is formed. The intramolecular hydroamination of aminoallenes was catalyzed by gold(I) and gold(III) to give the corresponding 2-vinyl pyrrolidines and piperidines in high yields.[59]

3. The *σ*- and/or *π*-Electrophilic Pd and Pt Catalysts. One of the representative roles of transition metal catalysts, $M'X_n$, such as $Pd(II)X_2$, is the formation of a complex with *π*-electrons of alkene or alkyne multiple bonds, which makes feasible the attack of Nu^- to an electron-deficient carbon to give an organopalladium intermediate having a C−Nu bond (*π*-electrophilic LA; Scheme 16). We found that a Pd(II) catalyst in fact exhibits a *dual role*; $Pd(OAc)_2$ catalyzed the reaction of

SCHEME 27

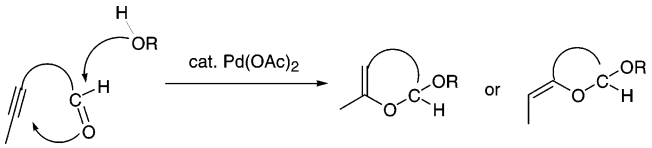


SCHEME 28



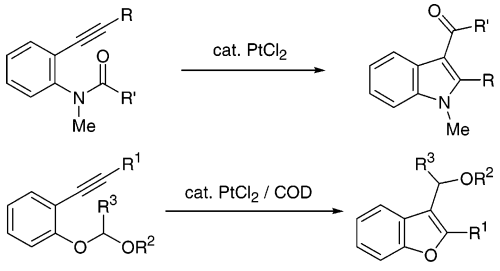
alkynylaldehydes with ROH to give the alkenyl cyclic ethers in good to high yields.[60] Here, the attack of ROH to aldehyde is catalyzed by Lewis acidic $Pd(OAc)_2$, and the nucleophilic oxygen of the resulting hemiacetal reacts with alkyne complexed by Pd(II), giving the alkenyl ethers. The preferential coordination of Pd(II) to the carbonyl oxygen rather than the π-electron of the alkyne was confirmed by ^{13}C NMR analysis of a 1:1 mixture of the alkynylaldehyde and $Pd(OAc)_2$ in THF-d_8.

SCHEME 29



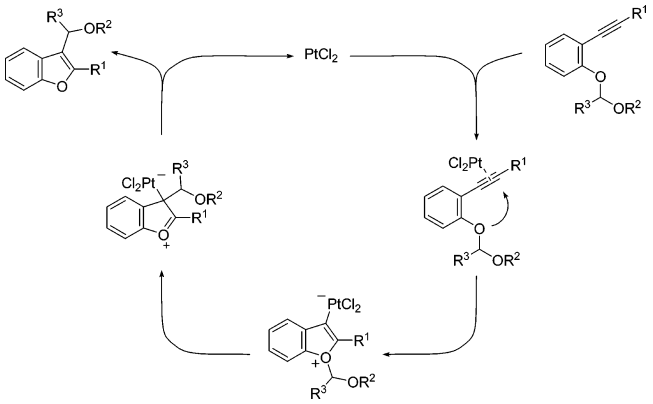
Recently, we found that Pt(II)-catalyzed reaction of *ortho*-alkynylamides in anisole produced the corresponding 2,3-disubstituted indoles in high yields.[61] The $PtCl_2$-catalyzed reaction of *ortho*-alkynylphenyl acetates in the presence of COD produced 3-(α-alkoxyalkyl)benzofuranes in good to high yields.[62] Most probably, the coordination of alkyne to the π-electrophilic Pt(II) and subsequent C−N (or C−O) bond formation, followed by 1,3-migration of acyl carbocation (or α-alkoxy carbocation), takes place in these reactions. The proposed mechanism for the benzofuranes from *ortho*-alkynylphenyl acetates is shown below. COD probably works as an activating agent to disconnect Pt−Cl bonds of polymeric platinum chloride and to generate a reactive platinum catalyst (the role of an aromatic solvent, anisole, in the case of the indole synthesis is perhaps similar).

SCHEME 30

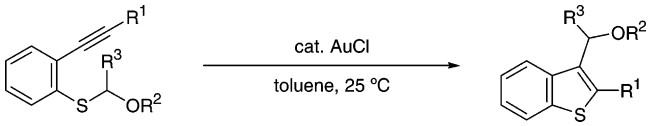


It occurred to us that a similar migration may take place in (*ortho*-alkynyl phenyl)sulfides by judicious choice of catalyst. The gold(I)-catalyzed cyclization of (α-alkoxyalkyl)(*ortho*-alkynyl phenyl)sulfides, under mild conditions, gave 2,3-disubstituted benzothiophenes in excellent yields.[63]

SCHEME 31

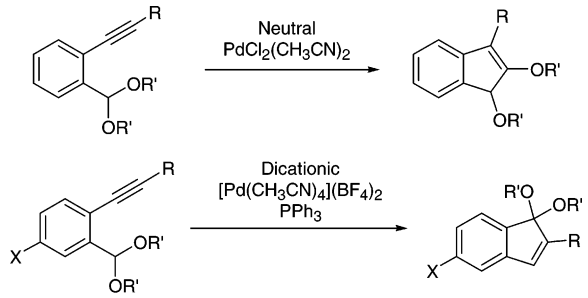


SCHEME 32



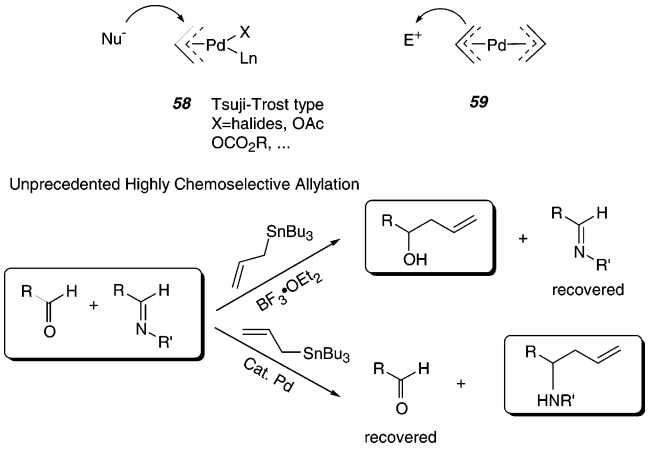
A new catalytic cyclization of *ortho*-alkynylbenzaldehyde acetals to the functional indenes was found to be strictly controlled by the catalytic species of Pd (or Pt); the neutral Pd(II) (or more preferably $PtCl_2$/β-pinene catalyst) gave the 1,2-di(OR′)-indenes,[64] whereas the dicationic Pd/1 equiv of PPh_3 afforded the 1,1-di(OR′)-indenes in good yields.[65] In the former case, the $\sigma-\pi$ coordination of Pd(II) or Pt(II) to OR′ and alkyne is a starting point of the migration reaction, and in the latter case, π-coordination of the Pd dicationic complex to the benzene ring is a key step controlled by the number of vacant coordination sites.

SCHEME 33



4. Nucleophilic Reactivity of Bis-π-allylpalladium. σ-Coordination to Aldehydes and Imines. It is widely accepted that π-allylpalladium complexes **58**, which are key intermediates for the Tsuji−Trost reaction, have an electrophilic character and react with nucleophiles to afford the corresponding allylation products. Recently, we found that bis-π-allylpalladium complex **59** reacts with electrophiles, such as aldehydes and imines, to produce the carbon−carbon bond in a manner different from the reaction via **58**.[66] The reaction of allylstannane with aldehydes or with imines in the presence of Pd(II) catalysts gave the corresponding homoallylic alcohols or imines in high yields. Allyltributylstannane reacts with $PdCl_2(PPh_3)_2$ to form π-allylPdCl(PPh_3), PPh_3, and Bu_3SnCl, and the further reaction of π-allylPdCl(PPh_3) with allylSnBu_3 gives **59**, Bu_3SnCl, and PPh_3. The bis-π-allylpalladium **59** reacts with aldehydes to afford a π-allyl(homoallylalkoxy)palladium intermediate, which under-

SCHEME 34



goes transmetalation with allylSnBu$_3$ to give the corresponding homoallylOSnBu$_3$, and **59** is regenerated. The resulting homoallylOSnBu$_3$ undergoes protonolysis to give the final product, homoallyl alcohol.[66] Very interestingly, the chemoselective allylation of imines in the presence of aldehydes was accomplished in this catalytic process, whereas the ordinary chemoselectivity (selective allylation of aldehydes in the presence of imines) was observed in the Lewis acid mediated allylation.[66] The mechanism and chemoselectivity of the Pd(II)-catalyzed aldehyde allylation reaction via bis-π-allylpalladium complex has been computationally investigated using state-of-the-art density functional theory (DFT) calculations (Figure 3).[67] The transfer of formaldehyde to the π-allyl group of bis-π-allylpalladium complex is a thermodynamically favored process ($\Delta G = -1.4$ kcal/mol), and the Gibbs free energy of activation ($\Delta G^{\ddagger}$) corresponds to 23.0 kcal/mol. Further support for the proposed reaction mechanism, which proceeds through the σ-coordination (via the O atom) of aldehyde to the Pd(II) center, comes from correctly predicting the chemoselectivity of the reaction when it is conducted with mixed bis-π-allylpalladium complexes containing crotyl, methallyl, and 2-methoxyallyl groups; the reactivity order toward benzaldehyde was 2-methoxyallyl > methallyl > allyl > crotyl.[66]

The catalytic asymmetric allylation of imines with allyltributylstannane proceeded in the presence of the chiral π-allylpalladium complex **60** to give the corresponding homoallylamines in high yields with a range of 91−60% ee.[68] It was revealed that the use of 1 equiv of water is important to obtain high enantioselectivities and reproducible results.[69] The important homoallylamine intermediate leading to DMP 777 was synthesized in 91% ee through the palladium-catalyzed allylation method. Replacement of allylstannanes by allylsilanes was accomplished using 0.5 equiv of TBAF (tetrabutylammonium fluoride), and similar level of ee was achieved with the chiral palladium catalyst **60**.[70] Here also, the use of protic additives, such as MeOH, enhanced both chemical yield and ee of the products in the reaction of imines with tetraallylsilane.[71]

IV. Summary

Organometallic Lewis acids (R*MX$_n$) having a chiral group (R*) and Lewis acids (MX$_n$L*) having a chiral ligand (L*) are becoming more and more important as a catalyst for selective and asymmetric organic transformation. Those Lewis acids have inevitably highly sophisticated and designed structure, and in

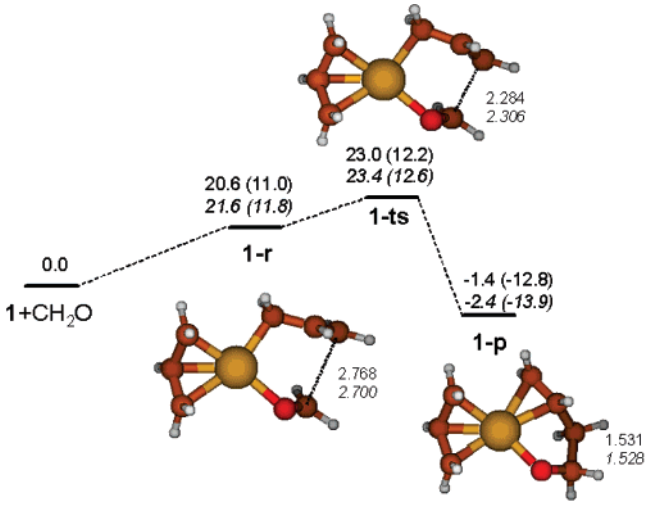
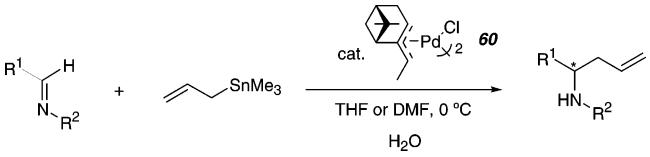
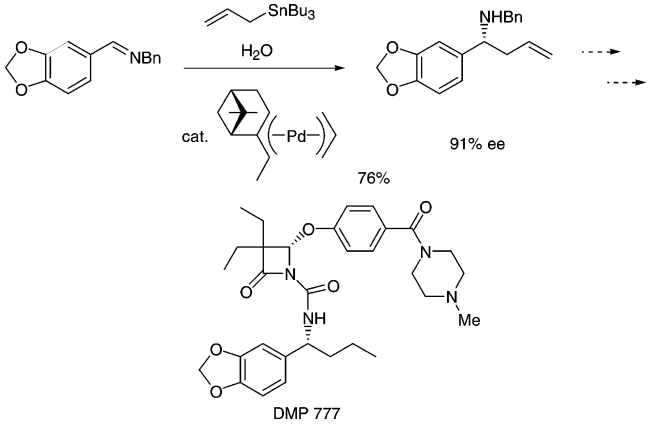


FIGURE 3. Aldehyde allylation via bis-π-allylpalladium **59**. The relative Gibbs free energies and ZPE-corrected electronic energies (in parentheses) are given in kcal/mol. The values in italics correspond to results obtained using the SDD basis set for Pd only. Distances are given in angstroms.

SCHEME 35



SCHEME 36



general, the reactivity or activity as an acid catalyst decreases in comparison with simple Lewis acids (MX$_n$). Accordingly, rather activated and reactive substrates are used for the reactions using such designed Lewis acids. Often, it is antinomy to obtain a wide applicability and wide scope of reagents/catalysts/reactions and to obtain high selectivity and high specificity of them. Here, the reactivity and selectivity of rather simple Lewis acids MX$_n$ toward simple organic molecules (except polycyclic ethers) have been surveyed, and the result of Table 1 may be useful as a rule of thumb for organic chemists in order to figure out the balance between σ- and π-electrophilic nature of Lewis acids. It is noteworthy that the Lewis acid mediated allylation can be applied to huge organic compounds, such as the precursors of gambierol and brevetoxin B, having a molecular length of about 3 nm. The emerging research area is the development of new reactions using π-electrophilic Lewis acids,

such as Au, Pt, and Cu, and especially the development of catalytic asymmetric reactions using the designed π-electrophilic Lewis acids will become increasingly important.

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Supporting Information Available: Tables containing the computed energies and the DFT-optimized geometries (Cartesian coordinates) of the Lewis acid complexes with representative unsaturated compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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