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Asymmetric synthesis: From transition metals to organocatalysis*

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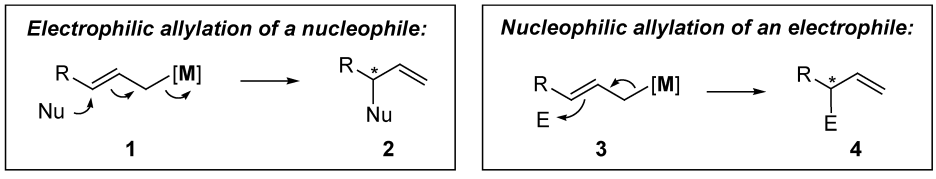
Abstract: Umpolung in the allylation reaction is discussed with examples drawn from transition-metal-catalyzed allylic substitution (with the allylic unit acting as an electrophile) and Lewis base-catalyzed allylation of aldehydes with allyltrichlorosilane (with the allyl acting as a nucleophile). Iridium-catalyzed electrophilic allylation of *O*-nucleophiles has been employed in our new approach to *C*-nucleoside analogs, where the C–O bond (rather than C–C) was constructed stereospecifically. Variation of the absolute configuration in the starting segments allowed the synthesis of all four combinations of D/L-α/β-ribosides. In the nucleophilic allylation of aldehydes, chiral pyridine-type *N*-oxide catalysts are presented, in particular QUINOX and METHOX, and the intriguing behavior of QUINOX is discussed. Here, the π–π interactions between the substrate aldehyde and the catalyst are suggested to rationalize the experimental observations. Good correlation between the calculated energies for the transition states and the experimentally observed enantioselectivities has been obtained.

Keywords: umpolung; allylation; transition-metal-catalyzed; allyltrichlorosilane; Ir-catalyzed; ribosides; QUINOX; METHOX.

INTRODUCTION

Allylation is a synthetic transformation of particular importance since the allylic group thus introduced can be regarded as a relatively benign surrogate of a polyfunctional segment, into which it can be subsequently elaborated without the need for extensive protection/deprotection. Two approaches, characterized by opposite polarity, can be considered as a typical example of umpolung (Scheme 1): one employing the allylic moiety as an electrophile (**1** → **2**) and one as a nucleophile (**3** → **4**).



Scheme 1 Umpolung in the allylation reaction.

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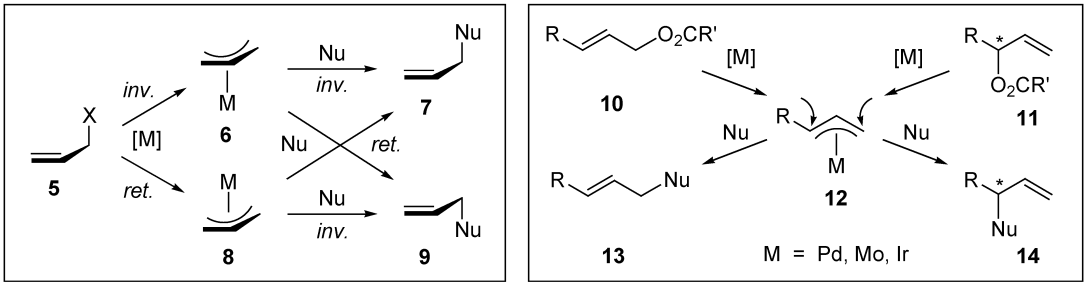
ELECTROPHILIC ALLYLATION CATALYZED BY TRANSITION METALS

The metal-catalyzed electrophilic allylation represents a stereo- and regiocontrolled variant of the classical but rather capricious S_N2/S_N2' substitution [1]. Thus, the Pd(0)-catalyzed version [2] is known to occur via the intermediate η^3-complex **6** (M = Pd), arising from the allylic substrate **5** (X = OAc, OCO_2Me, etc.) via inversion of configuration (Scheme 2) [2]. The subsequent reaction of **6** with the malonate anion and other stabilized *C*-nucleophiles again proceeds with inversion (**6** → **7**) [2], giving an overall retention. By contrast, organometallics and nonstabilized nucleophiles react with retention in the second step (**6** → **9**) owing to the initial coordination of the nucleophile to the metal M, followed by an internal migration [2].



Scheme 2 Stereo- and regiochemistry of the metal-catalyzed electrophilic allylation of a nucleophile.

Although the Pd(0)-catalyzed reaction is dominated by inversion in the first step (**5** → **6**), the retention pathway (**5** → **8**) can be enforced, in some instances, by precoordination of the catalyst either to the leaving group or to another group present in the allylic substrate, as first demonstrated by us [3] and by Kurosawa [4], and later confirmed by other groups [5]. Using the same philosophy, the Ni(0)-catalyzed reaction of an allylic substrate with a Grignard reagent has been shown by us to be altered by a coordinating neighboring group to an overall retention via the *ret-ret* mechanism (**5** → **8** → **7**) [3c].

Group 6 complexes have also been shown to catalyze allylic substitution and to give products of an overall retention of configuration (**5** → **7**) [6,7]. We have provided the first evidence that the reaction with malonate nucleophiles, catalyzed by $Mo(CO)_6$, can occur via a double retention (**5** → **8** → **7**) [8,9], in stark contrast to the Pd(0)-catalyzed reaction; this mechanism was later corroborated by Lloyd-Jones and Krska [10]. Rhodium and iridium complexes, also known to catalyze allylic substitution, exhibit retention of configuration, which is believed to originate from double inversion [11–14].

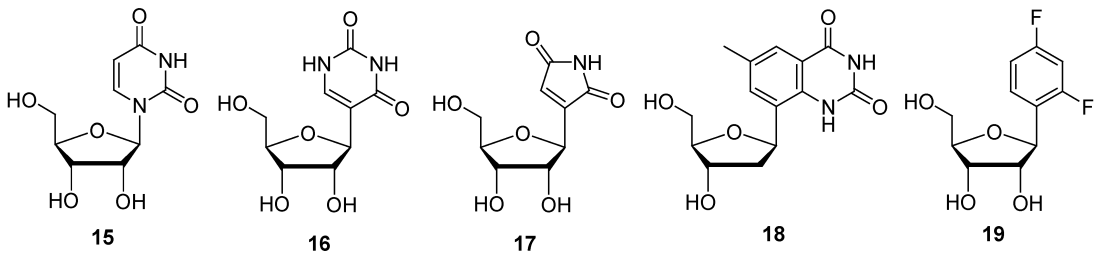
Regiochemistry of the transition-metal-catalyzed allylic substitution represents another intriguing issue. Thus, Pd is known to prefer the attack at the less substituted terminus of the nonsymmetrical η^3-complex **12**, affording the linear product **13**, generally irrespective of whether the terminal or branched allylic substrate **10/11** was used [2,15]. By contrast, Mo, W, Rh, and Ir complexes favor the formation of the branched product **14** [6,7,11–14]. However, the whole picture is further complicated by the "memory effect" that had been extensively studied with Pd [16,17]. Here, if the η^3-complex **12** is generated, its behavior should be, a priori, independent of the starting material, i.e., of whether the linear (**10**) or branched (**11**) allylic substrate was used as the starting material. Nevertheless, this may not always be the case: examples of the preferential conversion of the branched allylic substrate **11** into the branched product **14** have been observed by us and by others [15–17], and the specific conditions, under which the memory effect operates, have been outlined [17].

Enantiocontrol in the transition-metal-catalyzed allylic substitution has been attained by using various chiral ligands. Thus, in the case of symmetrical η^3-complexes, a suitable chiral ligand can control the preferential nucleophilic attack at one of the termini of the allylic system, which in turn results

in the formation of one enantiomer in preference [18]. In the case of Mo(0), where the linear substrate **10** is known to afford mainly the branched (chiral) product **14**, application of chiral ligands has led to high enantioselectivity [19,20]. However, the racemic branched allylic substrate **11** has also been found to produce mainly one enantiomer of **14**, implying that an isomerization of one enantiomer of **11** must occur during the reaction. Using isotopic labeling, we have been able to show that this isomerization occurs via the corresponding η^1-allylic complex **1** [20b].

IRIDIUM-CATALYZED ALLYLATION IN THE SYNTHESIS OF *C*-NUCLEOSIDES

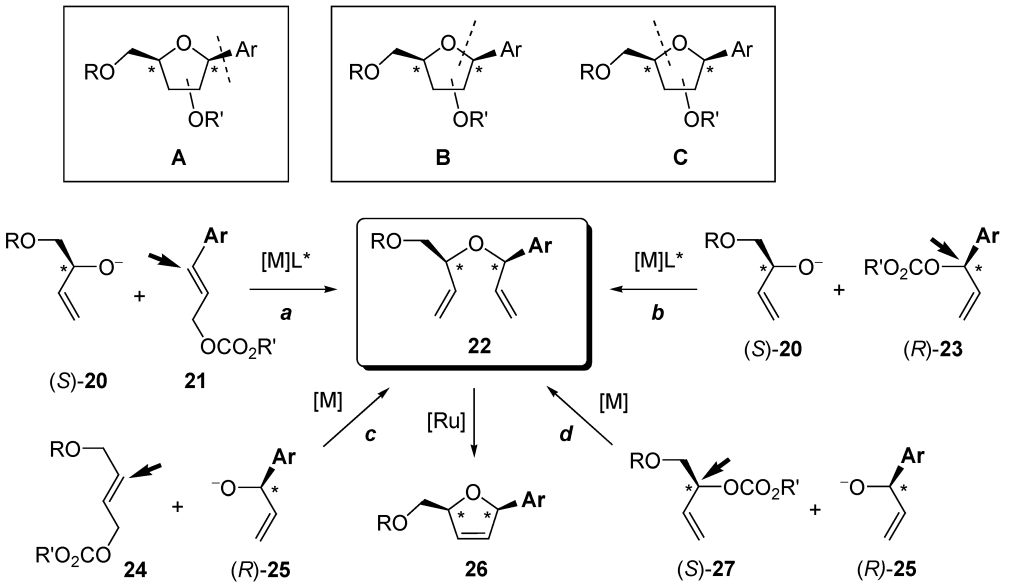
While natural and synthetic *N*-nucleosides (Scheme 3), such as uridine (**15**), are vulnerable to enzymatic attack and acid-catalyzed hydrolysis, their *C*-analogs, such as pseudouridine (**16**) and showdomycin (**17**), are much more stable (compare the acid-sensitive aminal moiety in **15** with the robust ether link in **16** and **17**). Furthermore, unnatural analogs, such as the homologated deoxyuridine **18** or the difluoroderivate **19**, capable of π-stacking, have been intensively studied both as interesting building blocks in chemical biology and as targets in medicinal chemistry [21]. However, in spite of the increased interest in *C*-nucleosides, the methodology for their synthesis is rather limited and requires further development [22]. We believed that transition-metal-catalyzed allylic substitution could be utilized in a novel approach to these important targets and could eliminate some of the existing deficiencies in the synthetic methodology in this area.



Scheme 3 Examples of natural and synthetic nucleosides.

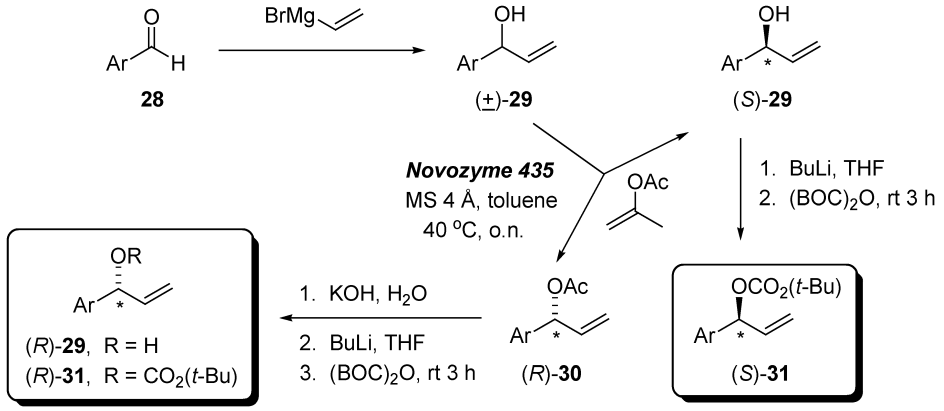
Most of the currently available methods for the synthesis of *C*-nucleosides rely on the construction of the C–C bond between the carbohydrate moiety and the aromatic/heteroaromatic group (**A**; Scheme 4), e.g., by using modified glycosylating reagents or the Heck addition of a suitable arene derivative to a glycal [22]. Since these methods are often characterized by low stereoselectivity or instability of the intermediates, we have embarked on a new strategy that would require a stereoselective construction of the C–O bond (**B** or **C**) from a suitable *O*-nucleophile and an allylic electrophile. Four approaches to the key intermediate **22**, whose cyclization via ring-closing metathesis should give dihydrofuran **26**, can be envisaged: thus, alkoxide **20**, generated from the monoprotected enantiopure 3-butene-1,2-diol, can be expected to react with the allylic substrate **21** or its isomer **23** (pathways ***a*** and ***b***). Alternatively, the enantiopure allylic alkoxide **25** would serve as a nucleophile in the reaction with the allylic substrate **24** or **27** (pathways ***c*** and ***d***). Note that pathways ***a*** and ***c*** would require the use of one enantiopure reactant and a chiral catalyst, whereas pathways ***b*** and ***d*** would make use of two enantiopure reactants each and a nonchiral metal catalyst.

The enantiopure 3-butene-1,2-diol, as a precursor to the monoprotected alkoxide **20**, is commercially available in both enantiomeric forms from butadiene, whereas the nonchiral, protected allylic substrate **24** can be obtained from the commercially available 2-butene-1,4-diol. The nonchiral cinnamyl-type substrate **21** is a textbook synthetic target that can be prepared from the corresponding aldehyde via the Wittig-type methodology.



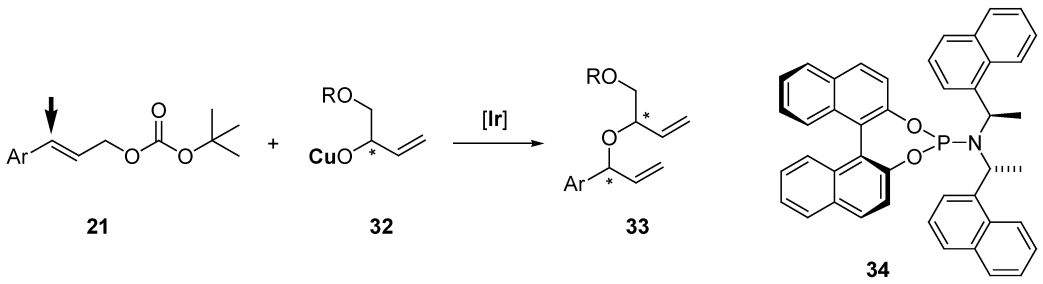
Scheme 4 Retrosynthetic analysis.

The synthesis of the enantiopure *iso*-cinnamyl substrates **23** and **25** requires a reliable methodology for the production of the corresponding alcohols. Addition of CH_2=CHSi(OMe)$_3$ to the corresponding aldehyde **28** (Scheme 5), catalyzed by CuF [23], seemed promising but required an expensive chiral ligand (Segphos) and turned out, in our hands, insufficiently enantioselective in some cases. On the other hand, resolution of racemic *iso*-cinnamyl alcohols (±)-**29** via acetylation with isopropenyl acetate, catalyzed by the solid-supported Novozyme 435, proved very practical in all instances, affording the (*R*)-acetates (*R*)-**30** and unreacted (*S*)-alcohols (*S*)-**29** in ≥99 % ee each, which were readily separated by chromatography. The conversion of the enantiomeric alcohols into the corresponding *t*-butyl carbonates **31** required deprotonation with *n*-BuLi, followed by quenching with BOC-anhydride [24], which minimized the tendency to allylic rearrangement.



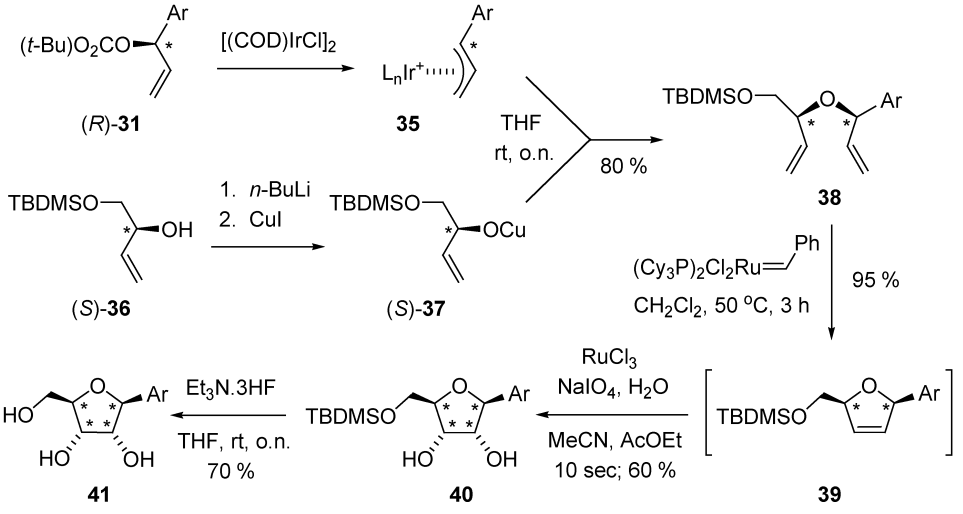
Scheme 5 Synthesis of the enantiopure *iso*-cinnamyl carbonates; for Ar, see Scheme 8.

Transition-metal-catalyzed nucleophilic substitution of the cinnamyl-type carbonates **21** with MeOH, $PhCH_2OH$, and other simple alcohols has been shown by Evans [12], Hartwig [13], and others [14] to require the use of the corresponding Cu(I) alkoxide as the *O*-nucleophile, which in turn can be generated from the alcohol by deprotonation with *n*-BuLi, followed by transmetallation with CuI. In the reactions catalyzed by iridium, various chiral ligands, in particular Feringa–Alexakis phosphorus amidites [25], have been reported to induce high enantioselectivity [13,14b]. When applied to our cinnamyl carbonates **21**, in combination with the chiral Cu(I) alkoxide **32** (following pathway ***a*** in Scheme 5), the Ir-catalyzed reaction proved highly regioselective in favor of the desired branched ether **33** (Scheme 6). However, diastereoselectivity of this reaction was unacceptably low, reaching the maximum of ~40 % de with ligand **34**; other related ligands gave inferior results.



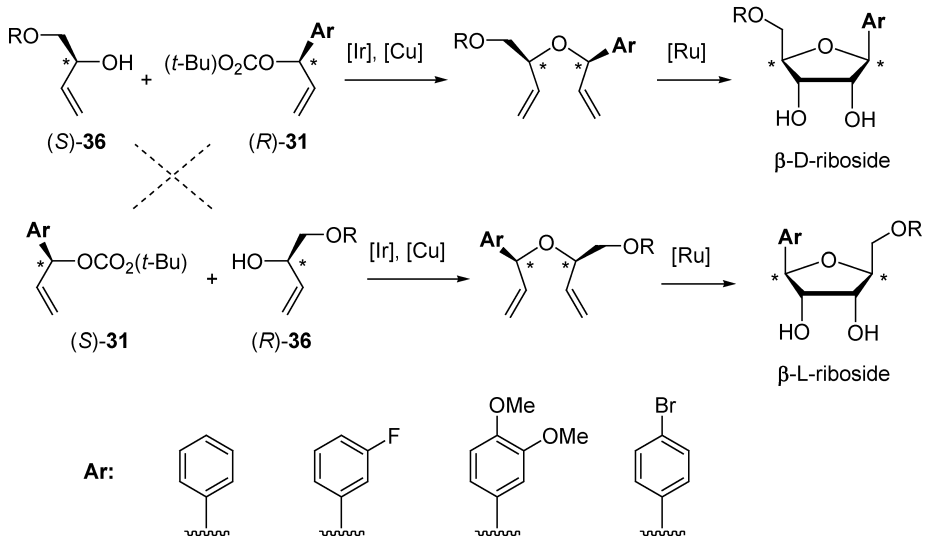
Scheme 6 Iridium-catalyzed allylic sybstitution (R = Piv, Trt, TBDPS, TBDMS); for Ar, see Scheme 8.

Since the cinnamyl carbonates exhibited mediocre stereoselectivity, we turned to their enantiopure *iso*-cinnamyl isomers **23** (pathway ***b*** in Scheme 5). Optimization of the catalyst led to the simple phosphine-free, commercially available $[(COD)IrCl]_2$. This complex exhibited excellent regio- and diastereoselectivity, affording practically pure *iso*-cinnamyl ethers **38** from carbonates (*R*)-**31** and the Cu(I) alkoxide, generated from the enantiopure mono-protected diol (*S*)-**36** (Scheme 7) [26]. Ruthenium-catalyzed ring-closing metathesis of **38** afforded the enantiopure *cis*-derivatives **39** [27], whose dihydroxylation, catalyzed by ruthenium with $NaIO_4$ as the stoichiometric oxidant [28], gave rise to diols **40**. Deprotection of the latter derivatives afforded D-ribosides **41**.



Scheme 7 Synthesis of *C*-ribosides; for Ar, see Scheme 8.

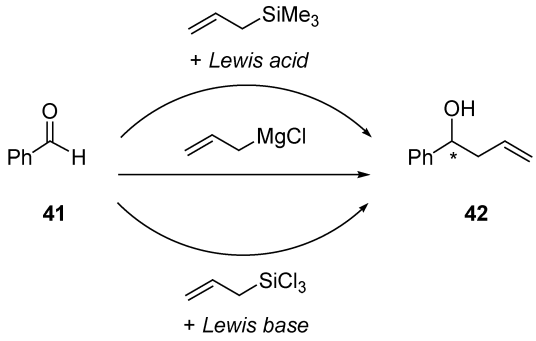
By further combination we were able to generate a small library of D- and L-β-ribosides (Scheme 8), generally in good overall yields and with excellent stereoselectivity, which demonstrates the versatility of this approach. In analogy, (*R*)-**31** afforded the corresponding D- and L-α-ribosides.



Scheme 8 Synthesis of D- and L-ribosides (R = TBDMS).

ORGANOCATALYZED ALLYLATION OF ALDEHYDES WITH ALLYL TRICHLOROSILANES

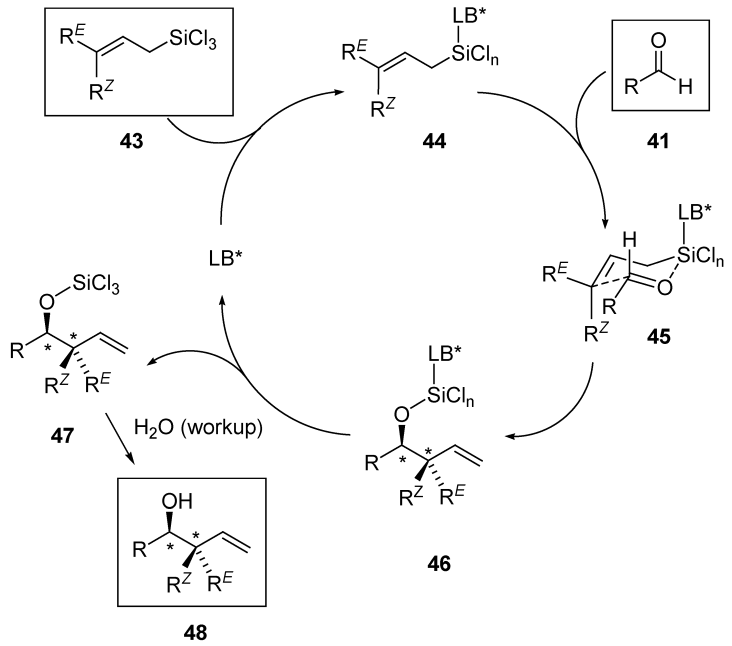
Allylation of aldehydes, such as **41**, with the corresponding Grignard reagent (Scheme 9) is a textbook example that would be rather difficult to run in an enantioselective, catalytic fashion [29]. On the other hand, allylation can also be attained with $AllylSiMe_3$ and its congeners in the presence of a Lewis acid, which coordinates to the carbonyl group [30]. Since the coordinated species is much more reactive than the free aldehyde, only a catalytic amount of the Lewis acid is required. Naturally, if the Lewis acid is chiral, an enantioselective reaction can be expected [30]. Alternatively, addition of a Lewis base should enhance the reactivity of the nucleophilic silane, which in turn should also lead to allylation. However,



Scheme 9 Nucleophilic allylation of aldehydes.

Lewis bases, such as DMF [31,32], DMSO [31,33], and HMPA [33,34] are typically inert to $AllylSiMe_3$ and require $AllylSiCl_3$ [35], whose silicon atom is more Lewis acidic [30–36].

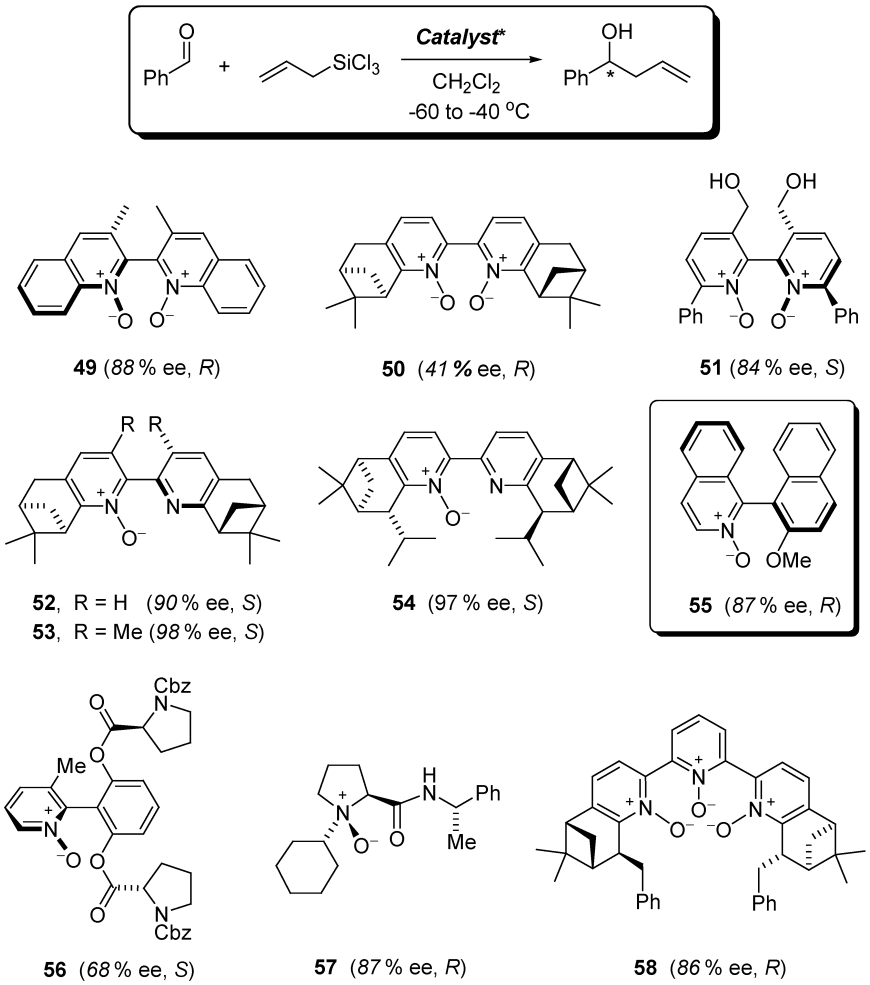
If the latter reaction proceeds through a closed transition state (**45** in Scheme 10), good diastereocontrol can be expected in the case of *trans*- and *cis*-$CrotylSiCl_3$ (**43**) [37,38]: Here, the *anti*-diastereoisomer of **48** should be obtained from *trans*-crotyl derivative, whereas the *syn*-isomer of **48** should result from the reaction of the *cis*-isomer of **43**. Furthermore, the chiral information can be expected to be conveyed from the Lewis base to the product, so that one enantiomer should be obtained in preference. Provided the Lewis base dissociates from the intermediate **46** with sufficient rate, it can act as a catalyst (rather than a stoichiometric reagent).



Scheme 10 Lewis base-catalyzed nucleophilic allylation of aldehydes.

Denmark has developed a series of chiral Lewis-basic phosphoramides, exhibiting good to high enantioselectivity in the allylation reaction [33,39–41]. However, these catalysts essentially represent chiral analogs of HMPA, which may affect their large-scale application in view of their potential toxicity.

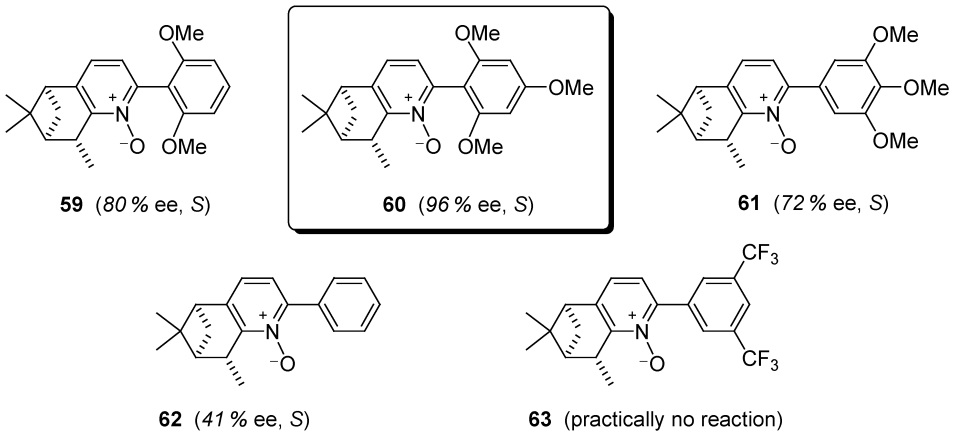
Pyridine-type *N*-oxides (Scheme 11) represent another class of chiral Lewis-basic catalysts for the allylation reaction. Thus, Nakajima first demonstrated that the axially chiral biquinoline *N*,*N*′-dioxide **49** can catalyze the allylation with high yields and enantioselectivity (71–92 % ee at –78 °C) [42]; in comparison, our terpene-derived *N*,*N*′-dioxide **50** exhibited rather modest asymmetric induction [43]. These efforts were later followed by Hayashi, who reported good asymmetric induction attained with the bipyridine analog **51** and its congeners (with 56–98 % ee) [44]. Catalyst **51** is remarkably reactive, so that its loading can be reduced to 0.1 mol % level, and moderate activity is retained even at 0.01 mol % loading [44], which renders **51** one of the most reactive organocatalyst reported to date. A chelation model, where both *N*-oxide groups of the catalyst coordinate Si of the reagent, have been proposed to account for the reactivity [42–44].



Scheme 11 *N*-Oxide organocatalysts for allylation of benzaldehyde with allyltrichlorosilane. The configuration of the resulting alcohol is shown in parentheses for each catalyst.

Prior to Hayashi's report [44], we [43] had introduced the terpene-derived bipyridine *N*-monooxides **52–54** (PINDOX, Me_2PINDOX, and *iso*-PINDOX) as even more enantioselective catalysts than the bisoxide **49**, although the reactions were slower, especially with the severely hindered *iso*-PINDOX (**54**). The most successful derivative of this series, Me_2PINDOX (**53**), combines the effects of both central and axial chirality. However, the barrier to the rotation about the chiral axis is rather low, and as a result, **53** isomerizes within several days (in solution) to a 1:2 mixture of **53** and its atropoisomer, which attenuates the asymmetric induction [43b]. PINDOX (**52**) and *iso*-PINDOX (**54**) lack the restriction of the rotation, so that a suitable configuration is apparently established on coordination to the silicon atom of the allylating reagent [43]. In analogy to the *O*,*O*-chelation model proposed for dioxides **49–51**, *O*,*N*-chelation of Si in $AllylSiCl_3$ by the *N*-oxide group and the nitrogen of the second pyridine nucleus was considered for **52–54** [43]. Nevertheless, there was no direct evidence for the coordination to the nitrogen. Other *N*-oxides, namely, our QUINOX (**55**) [45] and derivatives **56–58** [46–48] have also been shown to catalyze the allylation reaction [49,50].

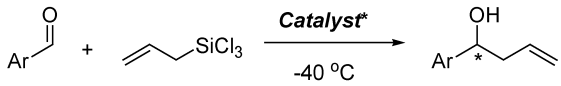
To address the issue of *N*,*O*-chelation, we have synthesized monodentate *N*-oxides **59–63** lacking the second pyridine nucleus (Scheme 12). The dimethoxy derivative **59** turned out to catalyze the reaction effectively and exhibited 80 % ee in the allylation of benzaldehyde [51,52]. METHOX (**60**) proved to be even more reactive and enantioselective (96 % ee at 1–5 mol % loading, –40 °C in MeCN) [51,52], while its isomer **61** behaved in a similar way as **59**. All these results suggest that coordination to nitrogen in **52–54** may either be absent or play a minor role. The comparison of **59**, **60**, and **61** shows that the steric bulk of the MeO groups in 2,6-positions (as in **59** and **60**) cannot be solely responsible for the enantioselectivity, otherwise **61** (with the MeO groups in 3,4,5-positions) should exhibit much lower enantioselectivity than **59/60**, while **60** would not be expected to be superior to **59** (owing to the same substitution pattern in the vicinity of the reaction center). Interestingly, the phenyl derivative **62**, lacking the MeO groups, also turned out to catalyze the allylation, though with lower enantioselectivity (41 % ee) [51]. By contrast, the electron-poor di-trifluoromethyl derivative **63** proved practically inert, demonstrating that an electron-rich aromatic moiety in the catalyst (as in **60**) is beneficial to the reaction, whereas an electron-poor unit renders the molecule catalytically inactive.



Scheme 12 Electronic effects of the *N*-oxide monodentate catalysts on the enantioselectivity of allylation of benzaldehyde. The configuration of the resulting alcohol is shown in parentheses for each catalyst.

The latter behavior suggests that arene–arene interactions between the catalyst and the substrate play an important role. For the *N*,*N*'-dioxide catalyst **51**, Hayashi reported a variation of enantioselectivity as a function of the electronic properties of substituted benzaldehydes **64** in the range of 56–94 % ee, with the electron-rich *p*-methoxy benzaldehyde (**64c**) giving the highest selectivity (Scheme 13) [44]. By contrast, little variation was observed for our electron-rich METHOX **60** (Scheme 13) [52]. On the other hand, our QUINOX (**55**) exhibited a strong dependence of selectivity on the Ar group (within the range of 16–96 % ee!) but in the opposite direction than Hayashi's **51**, giving the best results with the electron-poor **64b** [45].

The intriguing behavior of QUINOX (**55**) was further elucidated with the aid of kinetic and computational methods and isotopic labeling. This approach has allowed the formulation of an associative mechanism with the difference in the transition-state (TS) barriers $\Delta\Delta G^{\neq}$ = 2.0 kcal mol^{-1} in favor of the (*R*) reaction channel [45b,53]. This figure predicts the formation of (*R*)-**65a** in 98 % ee, which is in a good agreement with the experimental value of 87 % ee. The dissociative route was found to be higher in energy, and would favor the formation of the opposite, i.e., (*S*)-enantiomer. In the case of *p*-methoxybenzaldehyde (**64c**), the associative mechanism is also favored but with only 0.8 kcal mol^{-1} difference in the TS barriers for the formation of the individual enantiomers. This energy gap predicts the formation of (*R*)-**65c** in 62 % ee (45 % ee observed experimentally at 273 K [45]). The calculations further



64a–c **65a–c**

64	51 % / ee	55 % / ee	60 % / ee
a, Ar = Ph	95 / 84	60 / 87	95 / 96
b, Ar = 4-CF_3-Ph	83 / 56	85 / 96	86 / 93
c, Ar =4-MeO-Ph	96 / 94	70 / 12	95 / 96

Scheme 13 Electronic effect in the aldehyde on the allylation catalyzed by selected *N*-oxides (**51**, **55**, and **60**).

showed that the methoxynaphthalene unit of QUINOX (**55**) and benzaldehyde (PhCHO) in the TS are arranged in a parallel orientation, allowing π–π interactions [45b].

CONCLUSIONS

Two approaches to allylation, with the opposite polarity of the allylic unit, were discussed. Our contribution to the stereo- and enantiocontrol in the transition-metal-catalyzed allylic substitution has been summarized (Pd, Mo, and Ni). Ir-catalyzed substitution (as an example, where the allylic unit acts as an electrophile) has now been employed in our new approach to *C*-nucleoside analogs, where the C–O (rather than C–C) was constructed stereospecifically. Variation of the absolute configuration in the starting segments allowed the synthesis of all combination of D/L-α/β-ribosides. The opposite polarity in the allylation, where allylsilanes act as nucleophiles, has been discussed in the second part and new chiral, Lewis-basic catalysts revealed. The intriguing mode of action of QUINOX (**55**) has been studied and a likely mechanism formulated, which involves the π–π interaction between the substrate aldehyde and the catalyst. Good correlation between the calculated energies for the TSs and the experimentally observed enantioselectivities have been obtained.

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