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Axially Chiral *N*-Oxide Catalysts for the Allylation and Crotylation of Aromatic Aldehydes: Exploiting Nonlinear Effects

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A new family of IAN-type amine *N*-oxides is presented as catalysts for the allylation and crotylation of aromatic aldehydes with allyltrichlorosilanes. These reaction exhibit a remarkably positive nonlinear effect which enables utilization of the catalysts in subenantiopure form. As enantiopure catalysts are not required under this regime, the synthesis of these *N*-oxides is straightforward through catalytic asymmetric synthesis, avoiding lenghty synthesis from the chiral pool or resolution of diastereoisomers. Studies of the corresponding crotylation with *Z*- and *E*-crotylsilanes suggest that the reaction proceeds through a chair-like transition state.

Introduction

The asymmetric allylation of carbonyl compounds to afford enantioenriched homoallylic alcohols is an essential tool in Organic Chemistry, as these products are crucial building blocks for the synthesis of natural products and biologically active compounds,[1] owing to the orthogonal reactivity of their functional groups and their chiral nature. As such, developing new affordable catalysts that enable precise control of enantio- and diastereoselectivity is essential to obtain these synthetically relevant compounds.

Different methods have been developed based on the type of allylating agents and catalysts.[2] In particular, the addition of allylsilanes to carbonyls can be catalyzed by Lewis acids and bases. However, Lewis base catalysts present a significant advantage in terms of diastereoselectivity. While acid catalysis only promotes *syn* addition, reactions catalyzed by Lewis bases exhibit *syn* or *anti* addition, depending on the geometry of the substituted allylsilane.

The catalytic effect of organic Lewis bases was initially reported in 1993 by Kobayashi and Nishio,[3] who demonstrated that the basic properties of DMF played a crucial role in catalyzing the reaction, as their basic properties enhanced the nucleophile properties of the silane while preserving its Lewis acid character to coordinate the aldehyde and form a closed cyclic transition state. Soon afterward, Denmark and co-workers introduced the first enantioselective version of the reaction using a chiral phosphoramide as a promoter,[4a] but the method was limited by the lack of turnover and low enantioselectivities.

Since then, other families of Lewis base organocatalysts have been developed, including chiral formamides reported by Iseki[5] pyridine-based *N*-oxides **I**–**V** reported by Nakajima,[6] Hayashi[7] and Malkov,[8] and Zhu,[9] among others[10] (Figure 1). While these catalysts are highly effective in the allylation and crotylation of aldehydes, they are limited by their lengthy and complex synthesis, which often involves stoichiometric metal-mediated coupling reactions,[8,9,11] chiral auxiliaries,[7,12] or the resolution of racemates,[8c–d,10b,13] adding additional steps to obtain the final enantiopure catalyst.

In sharp contrast to this approach, in which the enantiopurity of the catalyst is key to ensuring high stereoselectivities, the catalytic synthesis of ligands often leads to the generation of sub-enantiopure catalysts. In principle, these ligands are expected to induce a lower level of enantioselectivity, limited by the maximum enantiopurity of the catalyst, but offer a much more straightforward synthesis using catalytic methods. However, deviations from linearity in the enantioselectivity of reactions are observed in some cases. When this deviation is positive, an amplification of the enantiomeric excess can be obtained with catalysts with lower enantiopurity.[14]

Only two examples of nonlinear effects have been reported for the addition of allyl trichlorosilanes to aldehydes when using organic promoters. In fact, Denmark observed a positive linear effect when using phosphoramide **VI** in his seminal work[4] and

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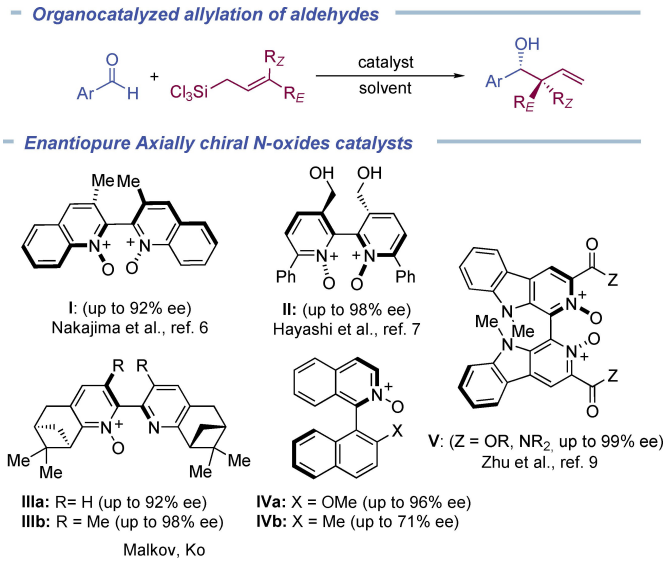


Figure 1. Enantioselective allylation of aromatic aldehydes. Representative *N*-oxide catalysts.

De Sio, Massa and Scettri[15] found a similar behavior with a chiral sulfoxide **VII** (Figure 2). Still, both were used in stoichiometric amounts and only ~60% ee was obtained for the allylation of benzaldehyde. Thus, the effective application of nonlinear effects in the organocatalyzed allylation of aldehydes remains elusive.

In the allylation of aldehydes, the nonlinear effect is attributed to one of the reaction pathways in which silicon is activated by two molecules of the Lewis base catalyst.[4b,15] We speculated that the incorporation of an additional acidic site could promote the formation of inactivated racemic dimers through acid-base interactions.

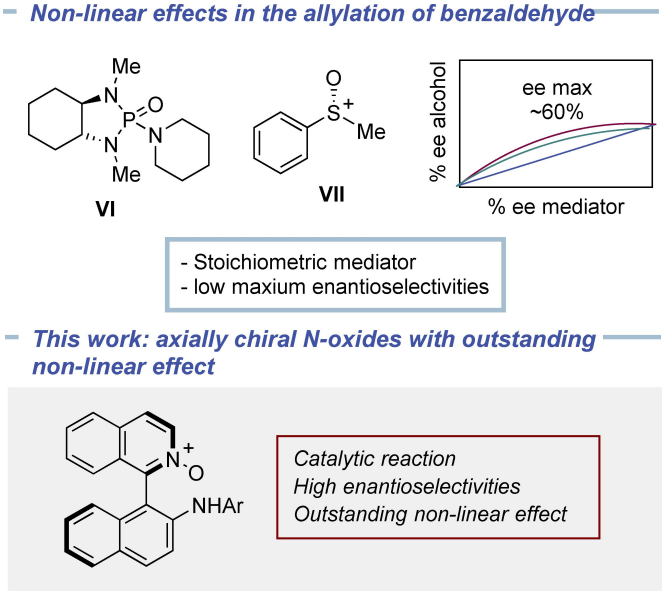


Figure 2. Nonlinear effects in the base-catalyzed allylation of aromatic aldehydes.

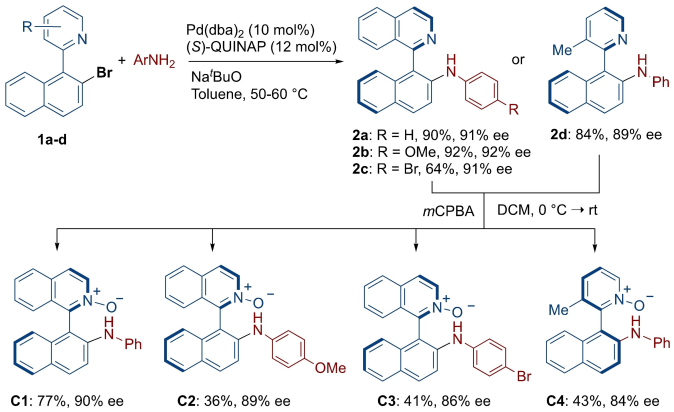
On this basis, we considered axially chiral IAN-type *N*-oxides (IAN = Isoquinoline-Amino Naphthalene) as appealing non-racemic catalyst candidates for the allylation and crotylation of aldehydes for the following reasons: 1) Axially chiral *N*-oxides can be directly related to QUINOX, which is a powerful catalyst in this reaction.[8c,d] 2) The amine group functions as a hydrogen bond donor, facilitating the formation of heterodimers. 3) There is a facile catalytic synthesis for these compounds based on a dynamic kinetic asymmetric Buchwald-Hartwig amination of readily available heterobiaryl electrophiles,[16] avoiding resolution of racemates or long and tedious derivatization sequences from the chiral pool.

On the basis of these assumptions, we report herein on the implementation of IAN-derived *N*-oxides as convenient organocatalysts for the asymmetric allylation and crotylation of aldehydes.

Results and Discussion

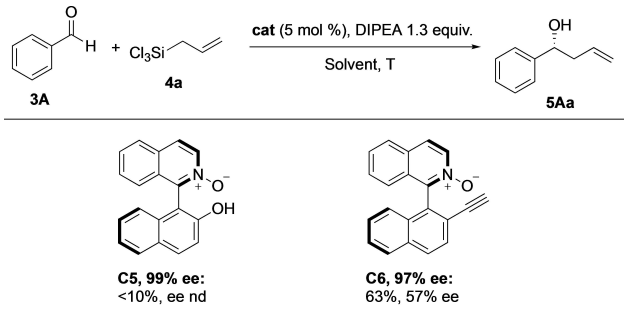
Based on this hypothesis, a family of IAN *N*-oxides **C1**–**C4** was prepared in two steps. First, the corresponding IAN-type amines **2a**–**d** were synthesized from readily available heterobiaryls **1a**–**d** using our previously reported Buchwald-Hartwig amination.[16] The direct oxidation of the isoquinoline moiety with *meta*-chloroperbenzoic acid (*m*CPBA) afforded the corresponding *N*-oxides **C1**–**C4** in moderate to good yields (Scheme 1).

Next, we tested the catalytic activity of these axially chiral *N*-oxides in the model reaction of benzaldehyde **3A** (0.20 mmol) with allyltrichlorosilane **4a** (0.24 mmol) at −40 °C in CH_2Cl_2 using *N,N*-diisopropylethylamine (DIPEA) as an additive[6] and 5 mol% catalyst loading of **C1** as the catalyst. The desired product **5Aa** was obtained in 71% yield and 89% ee (Table 1, entry 1), confirming the catalytic activity and a promising enantioselectivity. Dissapointlying, though, we did not observe any chiral amplification. However, since our design is based on the formation of racemic dimers through hydrogen bond interactions, we thought that this would be highly dependent on factors such as concentration, temperature, and solvent, prompting us to pursue further optimization (Table 1).



Scheme 1. Synthesis of catalysts **C1**–**C4**. [a] Amine **2d** was prepared using (*R*)-QUINAP.

Table 1. Optimization of the reaction conditions.



Entry[a]	Cat.	Solvent	T (°C)	Yield (%)[b]	ee (%)[c]
1	**C1**	CH_2Cl_2	−40	71	89
2	**C1**	CH_2Cl_2	0	50	85
3[d]	**C1**	CH_2Cl_2	−40	71	70
4	**C5**	CH_2Cl_2	−40	<10[e]	nd
5	**C6**	CH_2Cl_2	−40	63[e]	57
6	**C1**	Toluene	−40	>95[e] (88)[b]	97
7	**C2**	Toluene	−40	>95	98
8	**C3**	Toluene	−40	73	96
9	**C4**	Toluene	−40	95	−94
10	**C1**	ACN	−40	58	88
11	**C1**	THF	−40	~20[e]	90
12	**C1**	$CHCl_3$	−40	>95[e]	96

[a] Reactions were performed at −40 °C on a 0.20 mmol scale using anhydrous solvent (1 mL) and DIPEA (0.26 mmol). [b] Isolated yield. [c] Determined by HPLC analysis. [d] 0.5 mL of DCM was used. [e] Estimated yield by ^{1}H NMR.

Surprisingly, changing the temperature from −40 °C to 0 °C (Table 1, entries 1 and 2) resulted in the formation of the homoallylic alcohol **5Aa** in a lower yield. Similarly, we observed lower enantiomeric excesses when the reagent concentration was increased two-fold (Table 1, entries 1 and 3).

We also tested other *N*-oxide catalysts available from in group under the initial conditions. These catalysts, which had the same naphthyl-isoquinoline skeleton, such as naphthol **C5**[17] and alkyne *N*-oxide **C6**[18] (entries 4 and 5), showed no improvement in either conversion or selectivity. From the results obtained with catalyst **C6**, we can conclude that the naphthyl-isoquinoline *N*-oxide moiety can catalyze the reaction and induce enantioselectivity to some extent. Naphthol **C5** was expected to have a performance similar to that of **C1** because it also contains a hydrogen donor group; however, only traces of the product were found. Hence, it was clear that these catalysts were not suitable for this transformation, suggesting the intervention of beneficial noncovalent substrate-catalyst interactions involving the NHAr moiety in **C1**–**C4**.

Returning to the model catalyst, **C1**, a solvent screening was conducted using acetonitrile (ACN), tetrahydrofuran (THF), toluene, and chloroform. For the polar solvents, the selectivities were maintained, but the reactions afforded lower yields (Table 1, entries 10 and 11). In contrast, nonpolar solvents such as toluene and chloroform showed better conversion and enantioselectivity (Table 1, entries 6 and 12). Moreover, a strong positive nonlinear effect was observed when these solvents were used. Since the stereocontrol was slightly higher when using toluene, we used this solvent to perform the rest of the reactions.

The other IAN-type *N*-oxides were tested for the allylation of benzaldehyde. Every catalyst showed a very good yield for the reaction (≥95%), except for **C3**, which gave a moderate yield (73%). Additionally, the enantioselectivities were excellent (>94% ee in all cases; Table 1), suggesting that the nonlinear effect is general for this family of catalysts. The nonlinear effect was particularly remarkable in the case of **C4**, as alcohol **5Aa** was obtained with 96% ee when the enantiopurity of the catalyst was only 84%.

To further study the nonlinear effect of this family of catalysts and determine the minimum enantiopurity required to obtain over 90% ee of the alcohol, we conducted a series of experiments utilizing **C1** with different enantiopurities. The results of these experiments showed a remarkable positive nonlinear effect, with a selectivity of 95% ee when the optical purity of catalyst **C1** was approximately 75% ee (Figure 3). Although we did not analyze the nonlinear effect of the other ligands of the set, we assume that their behavior is similar due to chemical analogy. In addition, the enantioselectivities obtained with these catalysts **C2**–**C4** match those obtained with **C1**. Because the deviation of the linearity is positive, the minor

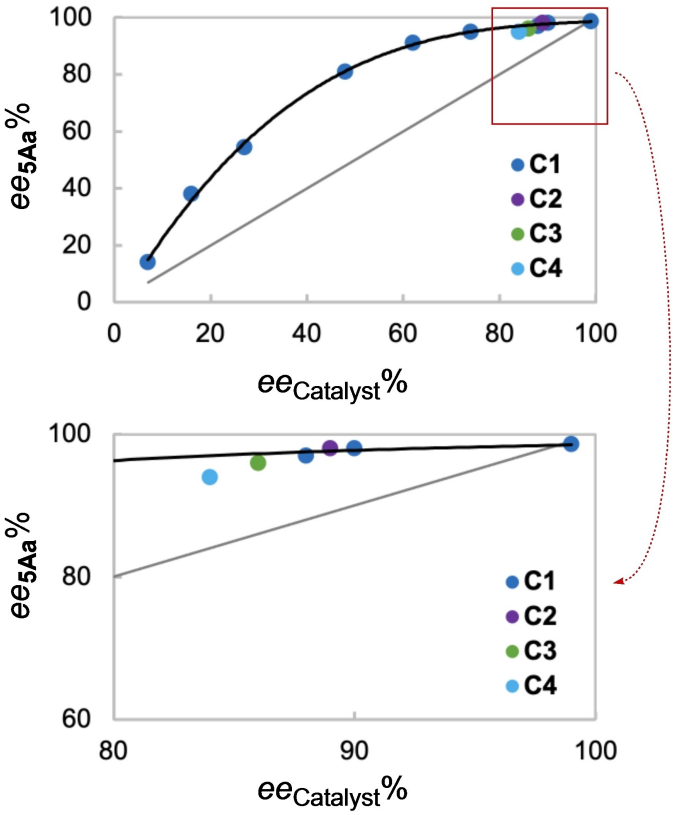


Figure 3. Nonlinear effect of allylation with catalysts **C1**–**C4**. Reactions were performed at −40 °C on a 0.2 mmol scale (**3A**) using anhydrous toluene (1 mL), 1.2 equiv. of **4a** and 1.3 equiv. of DIPEA. Enantiomeric excesses were analyzed by HPLC.

enantiomer of the catalyst must be removed or inactivated during the reaction; otherwise, the maximum enantiomeric excess would be limited to that of the catalyst.

IAN-type *N*-oxides are designed to maximize intermolecular interactions to favor dimerization. In this regard, these catalysts contain both donor and acceptor hydrogen-bonding groups, that is, NH and N–O. To shed light on the origin of this deviation, we attempted to crystallize the catalyst in its enantiopure and in racemic forms, expecting the latter to be more crystalline. Unfortunately, neither of the crystallizations occurred. Thus, we decided to conduct an alternative experiment, in which we recrystallized a non-racemic mixture (72% ee) of catalyst **C1**, affording X-ray quality crystals to our delight. Subsequent SCXRD analysis revealed that the crystals were composed of racemic heterodimers. HPLC analysis of the mother liquor also revealed an increase in the enantiopurity of the catalyst from 72% to 98% ee. Notably, recrystallization was achieved by mimicking the reaction conditions, that is, using the same solvent, toluene, at low temperatures.

X-ray diffraction analysis of the heterodimer revealed the nature of the interaction between the two enantiomers. Based on our hypothesis, we expected an intermolecular hydrogen bond between NH and N–O. However, this interaction occurred in an intramolecular manner (Figure 4). Surprisingly, the dimer was held together via hydrogen bonding between the relatively acidic aromatic C–H at the C3 position of the isoquinoline ring and the N–O.

On the basis of this data and the similarity of **C1** with QUINOX (which showed first-order kinetics[8d]) we initially ascribed the observed NLE to the formation of insoluble heterodimers.[19] However, Denmark and co-workers observed higher-order kinetics in the reaction catalyzed by chiral phosphoramides, thereby supporting that the observed NLE arises from a mechanism involving two molecules of the catalyst bound to the chlorosilane.[4b] Therefore, we decided to perform kinetic experiments to assess this possibility. To evaluate the order of the reaction in the catalyst, we used the Burés method[20] conducting reactions at 2.5 mol%, 5 mol% and 10 mol% of catalyst (see SI for details). Unexpectedly, the kinetic data ruled out first-order kinetics in **C1**, suggesting that the nonlinear effect (NLE) could be attributed to a mechanism involving second-order kinetics in the catalyst. However, the possibility of inactive heterodimer formation contributing to the effect cannot be disregarded.

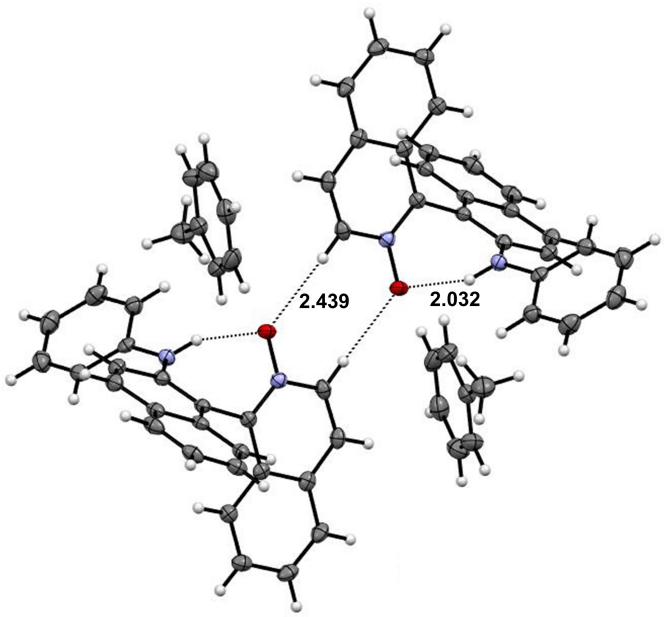
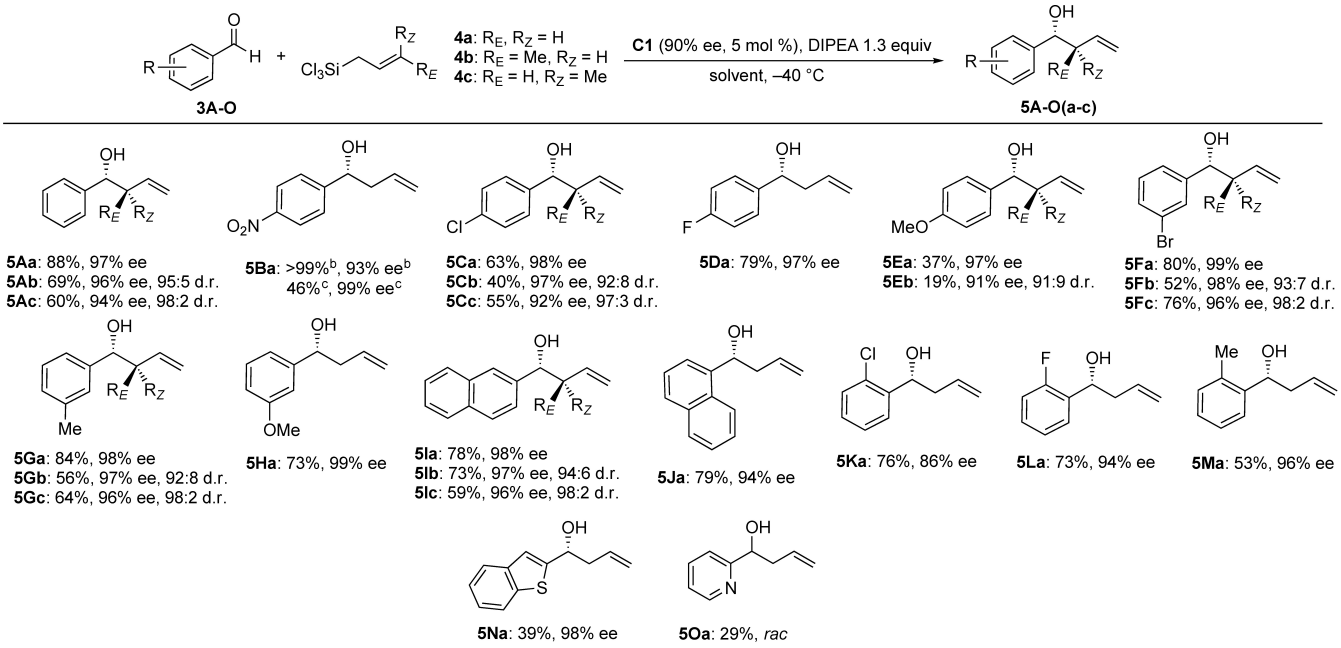


Figure 4. X-Ray structure of **C1** heterochiral dimer.

Because **C1** was obtained in better yields than the other catalysts, and catalyzed the model reaction with the higher enantioselectivity within the series, it was selected as the optimal catalyst to further explore the scope of the reaction.

We performed the allylation reaction using different aromatic aldehydes **3 A**–**N** with diverse electronic properties and substitution patterns (Scheme 2). In general, the reaction proceeded with excellent enantioselectivity (>90% ee in most cases and up to 99% ee). Comparing the optical purity of the *p*-substituted series **A**–**E**, it is worth noting that this method is highly tolerant to the electronic properties of the substrate. In fact, the enantioselectivity difference between the products of *p*-nitrobenzaldehyde, **5Ba**, and *p*-anisaldehyde, **5Ea**, was only 4%, albeit the latter was obtained in lower yield.[20] This represents a significant improvement over the most competitive analog, QUINOX, which fails to achieve high levels of enantioselectivity in reactions with electron-rich aldehydes.[8c,d] Additionally, this small range of enantiomeric excess might indicate that there must be an efficient, unique and common transition state for the stereodetermining step, irrespective of the electronic properties of the substrate. Regarding the reaction yields, aldehydes with electron-withdrawing groups behaved better than those with electron-donating groups, regardless of the substitution pattern. As previously mentioned, extreme cases were represented by the products obtained from *p*-nitrobenzaldehyde (**5Ba**, >99%) and *p*-anisaldehyde (**5Ea**, 37%). It should be noted that, in the former case, chloroform was used as the solvent because the aldehyde was poorly soluble in toluene. At any rate, the *p*-substituted series **3A**–**E** is the most reactive as a whole, while the *o*-substituted series **3J**–**M** is the least reactive one, presumably due to the steric hindrance they cause next to the electrophilic center. In addition, catalyst **C1** has a better performance with electron-withdrawing aldehydes; just opposite to most *N*-oxide catalysts and in line with QUINOX.[8c,d] In addition, the allylation of heterocyclic derivatives such as thiophene and pyridine aldehydes **3N** and **3O** were also explored with divergent results. While the pyridine product **5Oa** was isolated in poor yield and in racemic form, the thiophene derivative **5Na** was obtained with an excellent 98% ee, albeit in moderate yield. We also attempted the allylation of more challenging substrates such as cinnamaldehyde or dihydrocinnamaldehyde. Unfortunately, the corresponding homoallylic alcohol was obtained in low yield and selectivity in the former case, while no reaction takes place in the latter.[20]

To extend the scope and shed light on the reaction mechanism, we performed the reaction with the corresponding



[a] Reaction conditions: 0.2 mmol scale in toluene (1 mL), 1.2 equiv of **4a**, **4b** (*E*/*Z* = 95:5) or **4c** (*Z*/*E* = 96:4), 1.3 equiv of DIPEA. Reaction times: 20 h, 48 h and 72 h for **4a,** (*E*)-**4b** and (*Z*)-**4c**, respectively. [b] The reaction was carried out in $CHCl_3$. [c] The reaction was carried out at a 0.4 mmol scale using a catalyst loading of 2 mol% in toluene.

Scheme 2. Allylation and crotylation of aldehydes catalyzed by **C1**: Scope.[a]

(*E*)−**4b** and (*Z*)−**4c** crotyltrichlorosilanes. In these cases, we found that the reaction was slower, requiring 48 h and 72 h for (*E*)−**4b** and (*Z*)−**4c** silanes, respectively. Interestingly, contrary to the reaction catalyzed by QUINOX, (*E*)-crotylsilane reacted faster than the (*Z*)-isomer when **C1** was used.[8d] After performing the reaction with several aldehydes **3**, diastereoselectivities were as high as expected for Lewis base-catalyzed crotylations, being higher for the (*Z*)-isomer, even though the reaction was slower. In any case, the observed diastereoselectivity is in agreement with a chair-like transition state[3,8c,d,21] because it explains the *syn*- or *anti*- addition depending on the stereoisomerism of the crotylsilane (Scheme 2). Interestingly, the strong positive nonlinear effect was observed not only for the allylation reactions but also for the (*E*)- and (*Z*)-crotylations.

Conclusions

In conclusion, axially chiral IAN-type *N*-oxides have been shown to be excellent catalysts for the enantioselective allylation and crotylation of aromatic aldehydes with a remarkable positive nonlinear effect, unprecedented in this type of reaction. In contrast to other chiral *N*-oxide derivatives, these catalysts were prepared in a straightforward manner, avoiding lengthy synthetic routes from the chiral pool or resolution of diastereomers, which are common procedures for this type of catalysts. The origin of this nonlinear effect can be explained by the observed second-order kinetics in the catalyst, although the formation of off-cycle heterodimers stabilized by intermolecular hydrogen bond interactions cannot be disregarded as a contributing factor. X-Ray diffraction analysis revealed that, contrary to our expectations, the heterodimer was stabilized through hydrogen bonding between the N–O and the acidic C(3)–H of the isoquinoline ring, instead of the NH.

Owing to this nonlinear effect, homoallylic alcohols were obtained in moderate to high yields and enantioselectivities of up to 99% ee with a non-racemic catalyst with 90% enantiopurity. This method was also extended to the crotylation of aromatic aldehydes, where a similar nonlinear effect was observed, affording the corresponding alcohols in high yields and diastereo- and enantiopurities.

Supporting Information Summary

Crystallographic data, spectroscopic data and experimental details are provided in the Supporting Information.

Deposition Number 2351851 (for *rac*-**C1**), contains the supplementarycrystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service.

The authors have cited additional references within the Supporting Information (Ref. [24–31]).

Acknowledgements

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Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: Organocatalysis · Nonlinear effects · *N*-oxides · Allylation · Trichlorosilanes

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[22] In these cases, a parallel non-productive reaction may occur, causing inactivation of the aldehyde (see ref.[1e,21]) It is also well known that the *N*-oxide-catalyzed allylation of non-aromatic aldehydes is difficult. This is especially true for aliphatic aldehydes, as conjugated systems still activate the carbonyl groups and few studies have successfully addressed the allylation of this type of substrate using this approach (for some exceptions see)[22,23].
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