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Stereospecific *syn*-dichlorination of allylic amines enabled by identification of a superior stereo-directing group

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Alteration of a well-established reaction mechanism for access to different molecular structures is an inherently intriguing research subject. In that context, *syn*-stereospecific alkene dihalogenation draws attention as a long-standing problem in synthetic organic chemistry. The simplest approach would be the incorporation of an additional stereo-inverting step within the traditional *anti*-dihalogenation process. Surprisingly, this seemingly trivial idea turned out challenging, and no suitable stereo-directing group was known before our work. Herein, we describe a highly efficient *syn*-dichlorination of *N*-protected allylic amines through the anchimeric assistant phenomenon that has been inapplicable to alkene dihalogenation. Upon rational identification of a superior stereo-director, 1,8-naphthalimide, our practical reaction conditions with mild and convenient dichlorinating reagents can accommodate the formerly unemployable aryl alkenes in excellent yields (>95%) and stereospecificity (>50:1). DFT calculation suggests a concerted internal trapping mechanism without a discrete carbocationic species, which accounts for the conservation of the stereochemical integrity.

Vicinal dihalogenation of alkenes is *anti*-stereospecific under conventional reaction conditions, originating from the presence of a cyclic haliranium intermediate **1** (Fig. 1a)[1,2]. This innate stereochemical characteristic is highly reliable and thus indispensable for the stereoselective synthesis of organohalides[3–11]. Furthermore, the recent advancements in this field have even reached a remarkably sophisticated level of enantioselectivity control[12–23]. On the other hand, the alteration of the diastereochemical course turns out to be more challenging, and only limited examples can be found in the old chemical literature (Fig. 1b)[24–26]. It was described that the use of phosphorus pentachloride or sulfuryl chloride in nonpolar solvent could result in *syn*-dichlorination of 1,5-cyclooctadiene predominantly via a radical mechanism[24]. Also, a few metal chlorides were shown to transfer two chlorine atoms onto the same face of an alkene in a concerted manner[25,26]. However, despite these intriguing reports, *syn*-stereospecific alkene dihalogenation has been much less explored. Hence, multistep processes had to be employed as synthetic detours until recently[27,28]. In 2015, pioneering research on a catalytic, single-step *syn*-dichlorination was disclosed by the Denmark group (Fig. 1c)[29,30]. Instead of re-routing the fundamental reaction pathway, a common electrophilic *anti*-halofunctionalisation was allowed to proceed (**2**), and then the non-halogen substituent was activated in situ and replaced invertively by another halogen, leading to an overall *syn*-dihalogenation. This conceptually straightforward yet practically formidable approach was successfully realised by exploiting selenium's readily interconvertible oxidation states that could be adjusted either chemically[29,30] or electrically[31]. Similarly, examples of *syn*-difluorination were described by the groups of Jacobsen and Gilmour in the following year employing catalytically generated hypervalent iodine difluoride, which becomes a leaving group after the initial *anti*-addition to an alkene (**3**)[32,33]. Recently, an interhalogenation variant was developed by the Lennox group via incorporation of external chloride nucleophile for displacement of the *anti*-fluoroiodinated intermediate[34]. In 2024, our group developed an electrophilic vicinal double activation strategy utilising thianthrenium dication[35] that enabled the stereospecific installation of two leaving groups on the same alkene face through a concerted cycloaddition (Fig. 1d)[36]. Then, the carefully controlled nucleophilic halogenations afforded *syn*-dichlorination/dibromination as well as regiodivergent *syn*-bromochlorination.

Despite these advancements, the substrate scope has been largely limited to aliphatic alkenes that form configurationally stable cyclic intermediates, which is crucial for maintaining stereochemical integrity. For this reason, aryl alkenes are notoriously challenging reactants for stereospecific dihalogenation because the benzylic stabilisation leads to the generation of non-cyclised trigonal carbocation (Fig. 1e)[19,37]. We supposed that this problem could be resolved by utilising a tethered nucleophile, which can participate in an *anti*-addition (**4**) temporarily and then serve as a leaving group that can be displaced by an external halide (Fig. 1f). The concerted nature of such intramolecular trapping has been described by the Borhan

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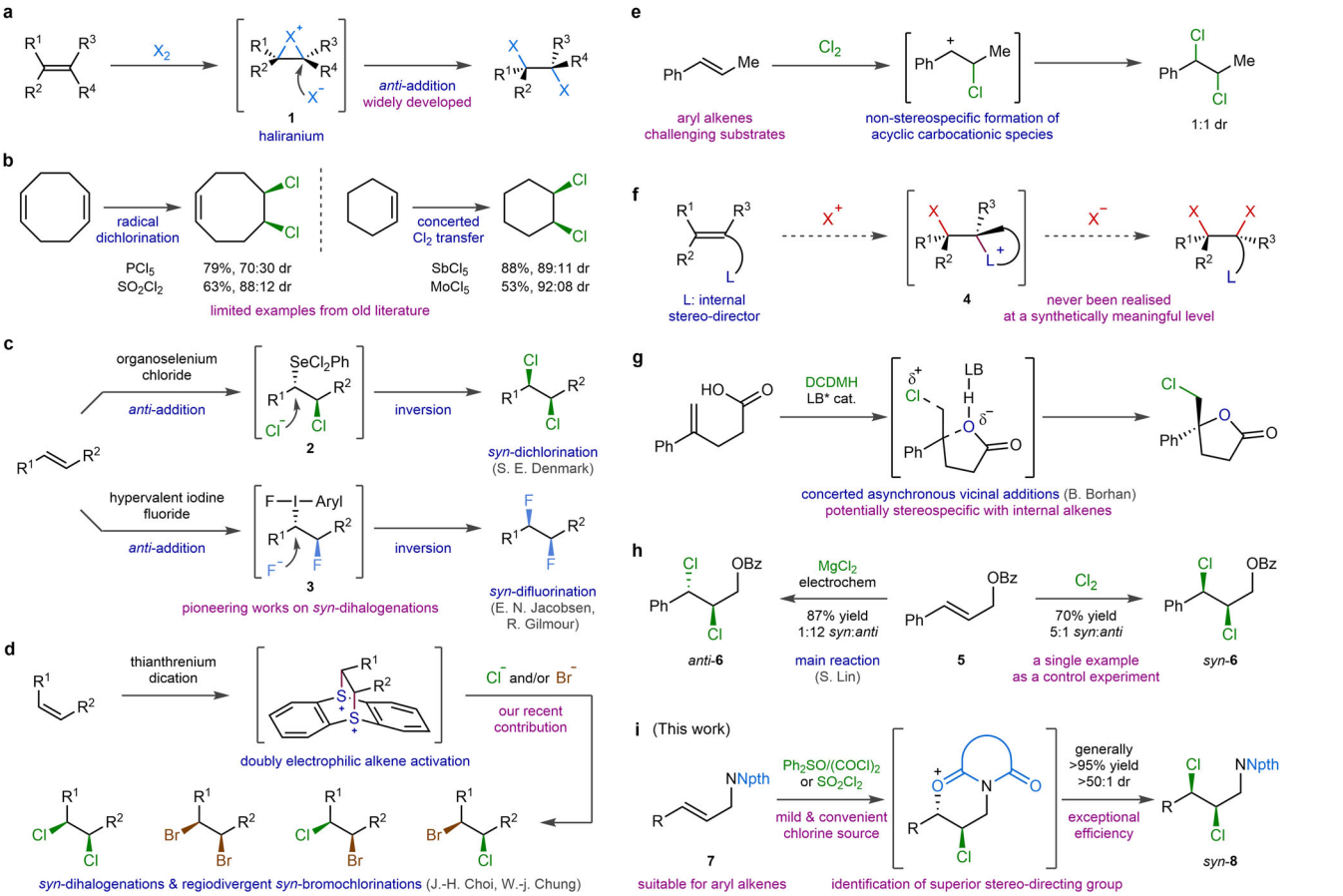


Fig. 1 | Vicinal *syn*-dihalogenation of alkenes. a Conventional *anti*-dihalogenation. **b** Old examples for *syn*-dihalogenation. **c** Pioneering modern works. **d** Our group's recent contribution to this field. **e** Unsuitability of aryl alkene substrates. **f** Proposed internal stereo-directing strategy. **g** Concerted nature of intramolecular trapping. **h** A relevant, overlooked precedent. **i** This work: *syn*-dichlorination of allylic amines enabled by identification of a superior directing group. (Bz benzoyl, Npth 1,8-naphthaloyl).

group for chlorolactonisation of geminally disubstituted aryl alkenes (Fig. 1g)[38,39]. If a similar reaction mechanism could also be operative for internal alkenes, it would be possible to form a reactive intermediate without compromising the stereospecificity. This idea may look deceptively trivial at first glance, but surprisingly, such anchimeric assistance had not been developed into a viable synthetic strategy for alkene dihalogenation prior to our work. Precedents are scarce[40,41], and one relevant example can be found in the Lin group's report on electrochemical alkene dichlorination (Fig. 1h)[42]. As a control experiment, a representative substrate, *E*-cinnamyl benzoate (**5**) was treated with molecular chlorine (Cl_2), which might be an active species. However, in contrast to the production of *anti*-dichloride (*anti*-**6**) under their electrolytic conditions, the opposite *syn*-dichloride (*syn*-**6**) was obtained as the major diastereomer probably via the participation of the benzoate ester as the authors suggested. Thus, a mechanistic insight was acquired, but this interesting stereochemical dichotomy was overlooked.

Our group revisited the anchimeric assistance phenomenon in the context of stereospecific alkene dihalogenation, and careful analysis of the reaction outcome led to the identification of a superior stereo-directing group that could almost completely dictate the stereochemical course. Herein, we present a highly efficient *syn*-dichlorination of allylic amines with emphasis on aromatic alkene derivatives (Fig. 1i). The use of *N*-naphthalimide (**7**) as well as the mild and convenient dichlorinating conditions enabled the practical synthesis of stereo-defined 2,3-dichloroamines (**8**) in excellent yields with outstanding diastereoselectivities (generally >95% yield and >50:1 dr) through unconventional stereochemical correlation.

Results and discussion

Preliminary experiments

We pursued our proposed internal stereo-directing strategy by re-evaluating the dichlorination of **5** (Fig. 2a). At the outset, safer and more user-friendly dichlorinating reagents that can replace the toxic chlorine gas were looked for, and two suitable reaction conditions were found. By employing either $Ph_2SO/(COCl)_2$[43] or SO_2Cl_2[44–49], the alkene dichlorination could be conducted smoothly at an ambient temperature without any special apparatus. SO_2Cl_2 is particularly practical as it leaves essentially no by-products. However, in addition to the desired *syn*-**6**, two other isomeric products, *anti*-**6** and 2,3-dichloride **9** were also generated. To address these competing side pathways that diminished the reaction efficiency, the mechanistic courses were analysed (Fig. 2b). The formation of *anti*-diastereomer (*anti*-**6**) implied that the neighbouring group participation of benzoate was not effective enough to completely surpass the external chloride attack for the initial *anti*-addition. Thus, the nucleophilicity of the stereo-directing group should be increased. On the other hand, the constitutional isomer **9** arose from the presence of two similarly electrophilic oxocarbenium-bound carbons in the intermediate **10**, having caused the site-selectivity issue. Hence, the electronic properties of the two heteroatoms on the stereo-directing group should be sufficiently differentiated. Both problems could be rationally resolved by replacing one of the oxygens with nitrogen, which is a stronger electron-donor and a poorer leaving group, and therefore, *N*-protected allylic amines would be ideal substrates for this purpose (Fig. 2c).

Stereo-directing group survey

To test our hypothesis, common nitrogen-protecting groups were examined (Table 1). As anticipated, the use of phthalimide (**11**) resulted in much

improved diastereoselectivity and nearly complete site-selectivity under both dichlorinating conditions (entries 3 and 4). However, these reactions were accompanied by variable amounts of chloroalkene side products. With a commercially available polyhalogenated derivative (**12**), the attenuated nucleophilicity led to substantially decreased diastereo-discrimination, being consistent with our expectation (entries 5 and 6). It was presumed that, for the facilitation of the desired internal stereo-directing, the putative intermediate such as **I** should be stabilised. To that end, the use of naphthalimide was conceived as the larger six-membered cyclic imide structure **II** would relieve the angle strain around the trigonal carbocationic centre. Moreover, the extended aromatic system could also be beneficial for charge delocalisation. Gratifyingly, a clean conversion to a single isomeric *syn*-1,2-dichloride took place from the 1,8-naphthalimide substrate (**7**) without any detectable side products including chloroalkenes (entries 7 and 8).

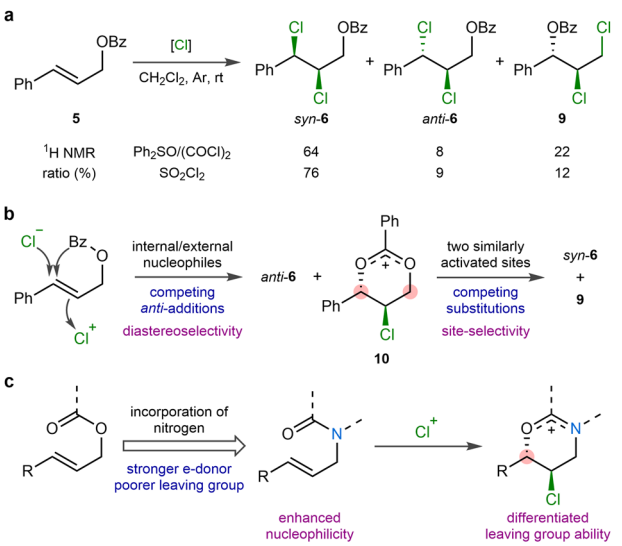
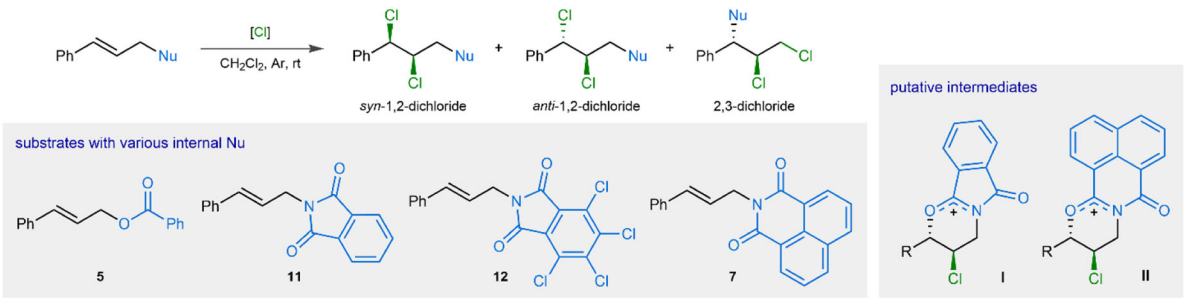


Fig. 2 | Initial observation of selectivity problems and analyses. a Product distribution in dichlorination of *E*-cinnamyl benzoate. **b** Mechanistic analysis of the side-product formations. **c** Rational modification of the stereo-directing group. (Bz benzoyl).

Substrate scope

Subsequently, a wide range of allylic naphthalimides were surveyed (Fig. 3). The relative configuration of 1,2-dichloride was assigned by comparison with the known $^3J_{HH}$ coupling constants (4.9–6.4 Hz for *syn*, 7.8–9.8 Hz for *anti*)[29]. The presence of a benzylic methyl group (**8b**) was tolerated without causing benzylic C–H chlorination[50]. Even the *ortho*-methyl substitution (**8c**) was only marginally influential on yield, and the excellent diastereoselectivity was maintained. Electron-deficient substrates turned out to be suitable for our *syn*-dichlorination conditions. A trifluoromethyl group (**8d**) and halogens (**8e**–**8h**) could be installed at any position without problems. The relative *syn*-configuration was confirmed by X-ray diffraction analysis of **8 h**. On the other hand, electron-donating groups appeared to have varying degrees of compatibility. The strongly electron-releasing *para*-methoxy group (**8i**) was detrimental to the stereospecificity as it could interfere with the nucleophilic addition at the benzylic position by providing the electron density via resonance through the aromatic ring (**III**). Such an adverse effect was not sufficiently alleviated by employing the less electron-rich phenoxy group (**8j**). Fortunately, the high level of diastereoselectivity was restored when acetate was introduced (**8k**), and the trifluoromethoxy group allowed the reaction to proceed uneventfully (**8l**). Strangely, although the methoxy group at a *meta*-position did not harm the stereochemical integrity, the *syn*-dichlorinated product (**8m**) was contaminated by inseparable unidentified impurities, affording diminished yields and purity. On the other hand, the stereospecificity was lost with a *Z*-cinnamyl substrate (**8n**), which implied that the approach of the tethered nucleophile had been

Table 1 | Survey of tethered nucleophiles.[a]



entry	internal Nu	conditions[b]	conversion[c]	dr (*syn*/*anti*)[c]	rr (1,2/2,3)[c]
1	OBz (**5**)	A	>99%[d]	8.5:1	3.3:1
2	OBz (**5**)	B	>99%[d]	8.7:1	7.1:1
3	NPhth (**11**)	A	>99%[d]	27:1	>50:1
4	NPhth (**11**)	B	>99%[d]	28:1	>50:1
5	NPhth-Cl_4 (**12**)	A	>99%[d]	6.4:1	>50:1
6	NPhth-Cl_4 (**12**)	B	57%	2.8:1	>50:1
7	NNpth (**7**)	A	>99% (97%)	>50:1	>50:1
8	NNpth (**7**)	B	>99% (98%)	>50:1	>50:1

Bz benzoyl, *Phth* phthaloyl, *Npth* 1,8-naphthaloyl.
[a]1.0 mmol scale at 0.1 M concentration.
[b]Conditions A: Ph_2CO (1.2 equiv), $(COCl)_2$ (1.2 equiv), 10 min; conditions B: SO_2Cl_2 (1.2 equiv), 30 min.
[c]Determined by ^1H NMR spectroscopic analysis after silica gel chromatography. Isolated yields of homogeneous materials in parenthesis.
[d]Contaminated by varying amounts of chloroalkenes (3–15%).

hampered by the geometrically constrained structure. In addition, the putative cyclic intermediate **IV** has a favourable *anti*-periplanar arrangement for facile E2 elimination, resulting in the formation of chloroalkenes (6%). Less activated aliphatic alkenes still provided high yields and synthetically useful diastereoselectivities for linear (**8o** and **8p**) and β-branched (**8q** and **8r**) alkyl substituents. The absence of a benzylic site may have been responsible for the slight erosion of stereospecificity by slowing down the neighbouring group participation, thus giving more chance to competing *anti*-addition of external chloride. In these cases, the $Ph_2SO/(COCl)_2$ combination is more effective, and the alkene geometry has only minimal impact on the reaction outcome unlike the aryl substrates likely due to the less pronounced steric difference.

Computational study

To gain insight into the observed structure-selectivity relationship, the internal stereo-directing process was analysed by DFT calculation at the M06-2X/6-31 + G(d,p)/PCM(CH_2Cl_2) level of theory (Fig. 4)[51–56]. In the transition state of the chlorination step with SO_2Cl_2 for the representative

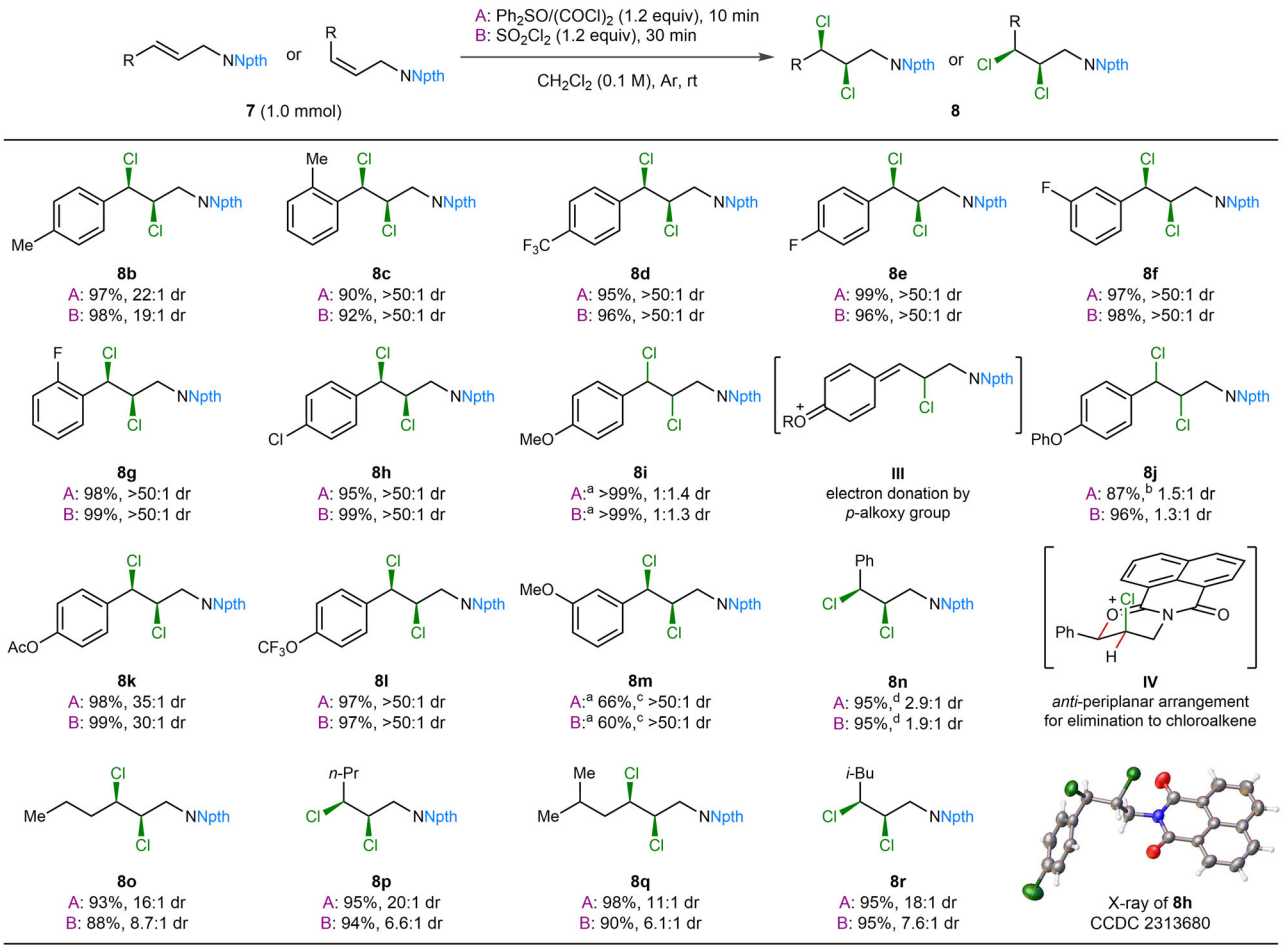


Fig. 3 | Substrate scope for *syn*-dichlorination of allylic naphthalimides. Yields of the isolated materials after column chromatography are given, and diastereomeric ratios (dr) were determined by ^{1}H NMR analysis of the purified materials, unless noted otherwise. [a]Analysed by ^{1}H NMR spectroscopy of the crude mixture with an internal standard. [b]Contaminated by chlorohydrins (15%). [c]Contaminated by unidentified compounds (34–40%). [d]Contaminated by chloroalkenes (6%). (Npth 1,8-naphthaloyl).

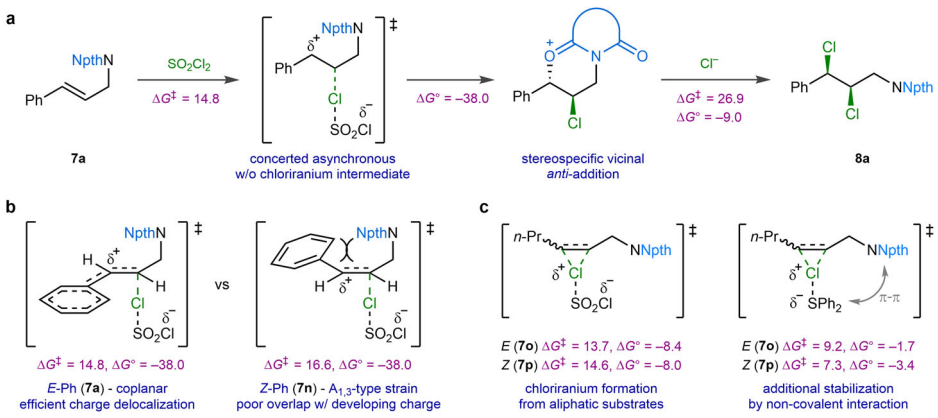


Fig. 4 | Computational analysis. a Characteristics of the internal stereo-directing process. **b** Influence of the alkene geometry. **c** Different behaviour of the aliphatic substrates. (M06-2X/6-31 + G(d,p)/PCM(CH_2Cl_2), free energies in kcal · mol^{-1}) (Npth 1,8-naphthaloyl).

substrate **7a**, while a chlorine is delivered to the β-position of the styryl moiety, the tethered nucleophile exhibits no apparent interaction with the developing benzylic carbocation (Fig. 4a). However, upon the intrinsic reaction coordinate calculation, an imide oxygen participates in the *anti*-addition spontaneously without generating a discrete carbocationic species (See the Supplementary Data 1). These results suggest that the stereo-direction operates via a concerted asynchronous mechanism. Then, the invertive displacement at the benzylic position by a chloride anion results in the overall *syn*-diastereospecificity. For the smooth execution of this process, the initial halocyclization should not be outcompeted by the external nucleophile. In that regard, the absence of free chloride reagents in our system appears advantageous. It also explains the lack of anchimeric assistance in Borhan's dichlorination of allylic amides, in which a large excess (100 equiv) of chloride anion is employed[12]. Subsequently, the influence of the alkene geometry was examined (Fig. 4b). In the case of *Z*-cinnamyl reactant **7n**, as one can imagine, the phenyl ring cannot accommodate co-planar conformation with the developing carbocation, thereby resulting in inefficient orbital overlap and thus less favourable transition state. In contrast, the alkyl derivatives **7o** and **7p** form the usual chloriranium species, and neither isomers experience serious steric encumbrance as supported by the comparable activation energies (Fig. 4c), which would lead to the similar level of diastereospecificity regardless of the alkene geometry. Moreover, an additional non-covalent π-π stacking interaction between the chlorinating species and the naphthalimide moiety appears to be responsible for the higher efficiency of the $Ph_2SO/(COCl)_2$ system. Furthermore, the non-concerted, two-step mechanism accounts for the less strict conservation of the stereochemical information as there presents an increased opportunity for the external chloride to intercept the chloriranium intermediate.

Conclusions

In conclusion, we have developed a highly stereospecific *syn*-dichlorination of allylic amine derivatives by exploiting the diastereo-altering ability of tethered nucleophiles. The mechanistic analysis of the side product formation led to the logical identification of 1,8-naphthalimide as the superior stereo-directing group, which provided both excellent yield and diastereoselectivity in most cases. Moreover, the simple and convenient conditions including easily handled reagents, short reaction time, and ambient temperature allowed the practical operation. Remarkably, our synthetic method is suitable for the previously unemployable aryl alkene substrates, which has been regarded as a noticeable limitation of the stereospecific alkene dihalogenations. In our strategy, the facile internal trapping of the benzylic carbocation enabled preservation of the stereochemical information. The DFT calculation suggested the concerted asynchronous nature of such processes. Through our current work, the neighbouring group participation phenomenon is successfully realised in diastereoselective alkene dichlorination chemistry.

Methods

Detailed reagent purifications and specific experimental procedures for individual compounds are described in the Supplementary Methods.

General procedure for the conditions A

To a stirred solution of *N*-protected allylic amine (1.00 mmol) and Ph_2SO (243 mg, 1.20 mmol, 1.2 equiv) in CH_2Cl_2 (10 mL) was added $(COCl)_2$ (103 μL, 1.20 mmol, 1.2 equiv) dropwise over 10 min under N_2. Then, the reaction mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, CH_2Cl_2/hexanes) to afford the corresponding *syn*-dichlorinated product.

General procedure for the conditions B

To a stirred solution of *N*-protected allylic amine (1.00 mmol) in CH_2Cl_2 (10 mL) was added SO_2Cl_2 (97 μL, 1.2 mmol, 1.2 equiv) in one portion under N_2. After 30 min, the reaction mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, CH_2Cl_2/hexanes) to afford the corresponding *syn*-dichlorinated product.

Data availability

The data supporting the findings of this study are available within this article and its Supplementary Information, which includes experimental details, characterisation data, and DFT calculation details. The computation output files are provided as Supplementary Data 1. The copies of NMR spectra for all new compounds are provided as Supplementary Data 2. Crystallographic data for **8h** are provided as Supplementary Data 3 and have been deposited at the Cambridge Crystallographic Data Centre (CCDC) under deposition number CCDC 2313680. These data can be accessed free of charge via https://www.ccdc.cam.ac.uk/structures/. All data are available from the corresponding author upon request.

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Author contributions

W.J.C. conceived the research concept. J.H.C. directed the computational study. W.J.C. and J.K.I. designed the synthetic strategy. J.K.I. performed the synthetic work. W.J.C. conducted the DFT calculation. W.J.C. and J.K.I. wrote the manuscript. All authors discussed the results and contributed to editing the manuscript and preparing the Supplementary Information.

Competing interests

The authors declare no competing interests.

Additional information

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