Communication

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Enantioselective Synthesis of α-Allyl Amino Esters via Hydrogen-Bond-Donor Catalysis

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Supporting Information Placeholder

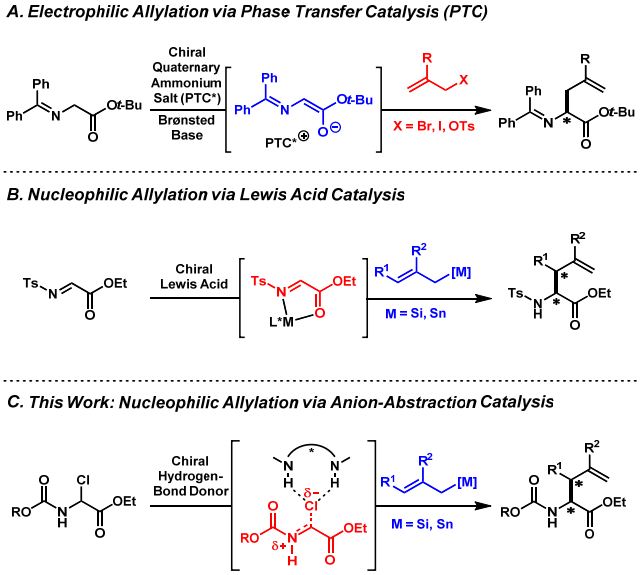
ABSTRACT: We report a chiral-squaramide-catalyzed enantio- and diastereoselective synthesis of α-allyl amino esters. The optimized protocol provides access to *N*-carbamoyl-protected amino esters via nucleophilic allylation of readily accessible α-chloro glycinates. A variety of useful α-allyl amino esters were prepared—including crotylated products bearing vicinal stereocenters that are inaccessible through enolate alkylation—with high enantioselectivity (up to 97% ee) and diastereoselectivity (> 10:1). The reactions display first-order kinetic dependence on both the α-chloro glycinate and the nucleophile, consistent with rate-limiting C–C bond formation. Computational analysis of the uncatalyzed reaction predicts an energetically inaccessible iminium intermediate, and a lower energy concerted S_N2 mechanism.

Among the many classes of unnatural amino acids devised by synthetic chemists, α-allyl amino acids have proven particularly valuable in a wide variety of contexts.[1-6] The alkenyl functional handle in these building blocks can be elaborated for site-selective protein modification,[1,2] preparation of glycopeptides,[3] or generation of peptide staples[4] and macrocycles. Noteworthy applications include construction of all-carbon analogs of disulfide-bridged macrocyclic peptides such as oxytocin,[5] and thioether-bridged lantibiotics such as nisin.[6]

As a result of their broad utility, α-allyl amino acids have been targets of widespread synthetic effort.[7-13] Among catalytic approaches, the phase-transfer-catalyzed (PTC) allylation of Schiff base, ester enolates was pioneered by O'Donnell[8] (Scheme 1A) and advanced to the current state-of-the-art by Maruoka through the discovery of highly effective, C_2 symmetric, quaternary ammonium salt catalysts.[9] This methodology provides access to unbranched α-allyl amino esters, but the preparation of branched products via PTC is generally not possible. Approaches involving transition-metal π-allyl intermediates have also been developed, but preparing branched products is hampered by requiring substitution to occur on a hindered electrophilic partner.[10] More effective approaches require the preparation of glycine allyl esters or allyl ammonium salts, which undergo enantioselective Claisen[11] or [2,3]-sigmatropic rearrangements,[12] respectively.

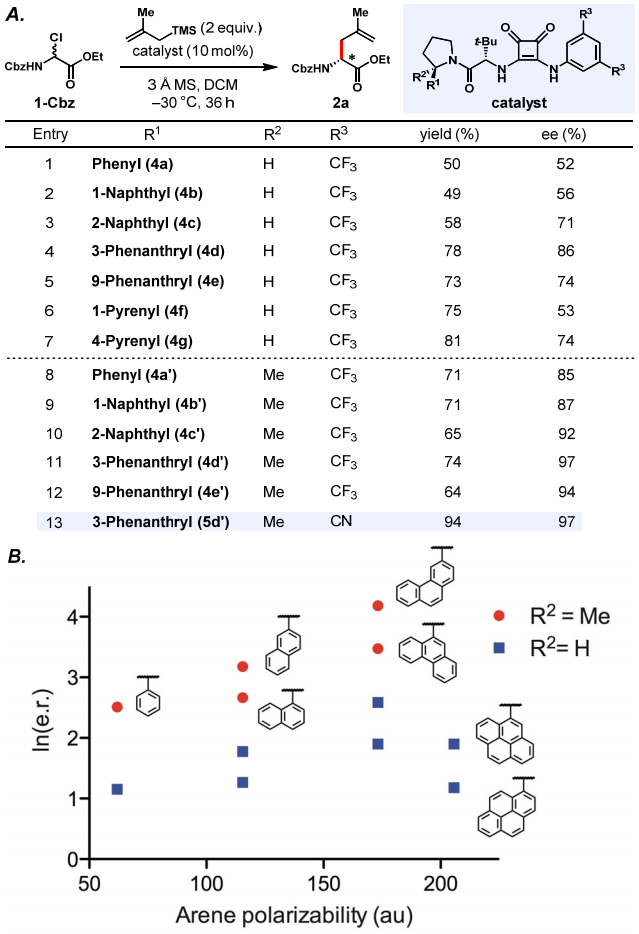
The use of nucleophilic allylating agents allows stereocontrolled construction of β-branched α-allyl amino acid derivatives, as elegantly demonstrated by Lectka and Jørgensen in Lewis-acid-catalyzed allylations of *N*-tosyl α-imino esters using chiral copper complexes (Scheme 1B).[13] Inspired by this precedent, we envisioned a new approach involving nucleophilic allylation of α-halo amino esters catalyzed by chiral hydrogen-bond-donor catalysts (Scheme 1C). This strategy benefits from the ready accessibility of *N*-carbamoyl α-chloro amino esters as α-imino ester equivalents.[14,15] The products resulting from the proposed nucleophilic allylation protocol would possess readily cleavable carbamate protecting groups, facilitating further manipulations.[16] Herein, we report the highly enantioselective and diastereoselective synthesis of α-allyl amino esters via anion-abstraction catalyzed addition of allylsilane and allylstannane nucleophiles to *N*-carbamoyl-α-chloro amino esters.

Scheme 1. Approaches to the Asymmetric Catalytic Synthesis of α-Allyl Amino Esters



We selected the allylation of α-chloro glycinate **1-Cbz** with 2-methallyltrimethylsilane as a model reaction for catalyst optimization (Figure 1). An extensive survey of chiral dual-hydrogen-bond-donors revealed that arylpyrrolidinosquaramides **4a-g**[17] catalyzed the formation of **2a** with promising levels of enantiocontrol. As observed previously in reactions involving stabilized cationic intermediates, enantioselectivity was strongly responsive to the polarizability of the arene substituent on the pyrrolidine.[18] Such effects have been ascribed to stabilizing π interactions between the catalyst and positively charged intermediates and/or transition states, in which the diastereomeric transition state leading to the major product is stabilized preferentially. However, arene polarizability alone does not account for the effects on reaction enantioselectivity in the allylation reaction (Figure 1B).[19] The point of attachment of the arene to the pyrrolidine is also important, with arenes bearing sub-

stitution ortho to the pyrrolidine group affording lower enantioselectivity. Such sensitivity to the spatial disposition of the aryl group is consistent with a highly ordered network of attractive non-covalent interactions in the enantioselectivity-determining transition state assembly.[18]

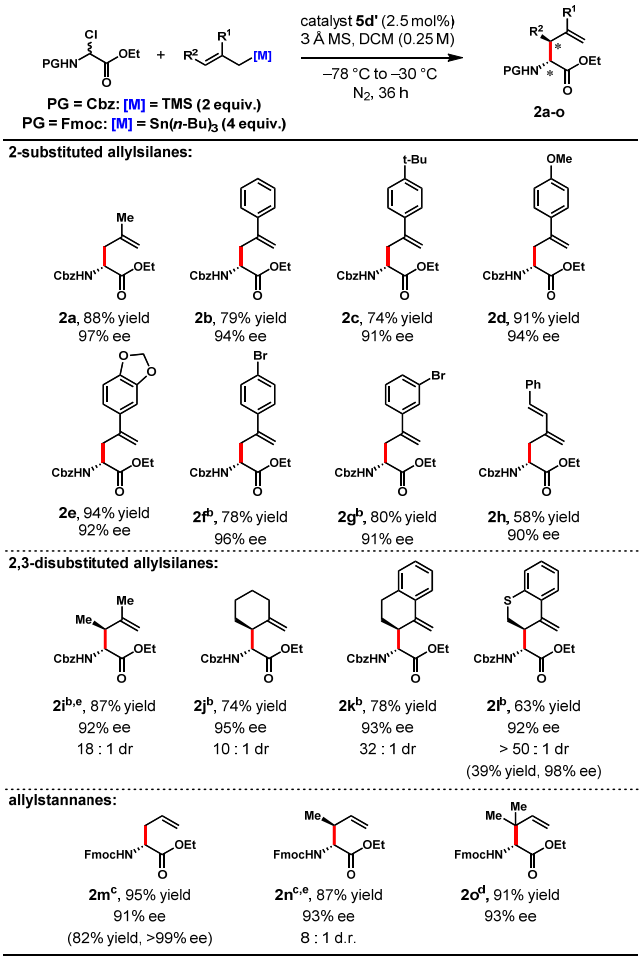


Entry		R^1	R^2	R^3	yield (%)	ee (%)
1	**Phenyl (4a)**	H	CF_3	50	52
2	**1-Naphthyl (4b)**	H	CF_3	49	56
3	**2-Naphthyl (4c)**	H	CF_3	58	71
4	**3-Phenanthryl (4d)**	H	CF_3	78	86
5	**9-Phenanthryl (4e)**	H	CF_3	73	74
6	**1-Pyrenyl (4f)**	H	CF_3	75	53
7	**4-Pyrenyl (4g)**	H	CF_3	81	74
8	**Phenyl (4a')**	Me	CF_3	71	85
9	**1-Naphthyl (4b')**	Me	CF_3	71	87
10	**2-Naphthyl (4c')**	Me	CF_3	65	92
11	**3-Phenanthryl (4d')**	Me	CF_3	74	97
12	**9-Phenanthryl (4e')**	Me	CF_3	64	94
13	**3-Phenanthryl (5d')**	Me	CN	94	97

Figure 1. (A) Yield and enantioselectivity of **2a** for a series of 2-arylpyrrolidine- and 2-aryl-2-methylpyrrolidine-substituted catalysts. Yields were determined by ^{1}H NMR by integration against an internal standard. (B) Relationship between the enantiomeric ratio of **2a** and the polarizability of the arene substituents on the catalysts **4a–4g** (R^2 = H, blue series) and **4a'–4e'** (R^2 = Me, red series).

Further evidence for the importance of the conformational properties of the arylpyrrolidine in enantioinduction was provided through the evaluation of 2-aryl-2-methyl-substituted pyrrolidine-derived catalysts. Dual H-bond-donor catalysts bearing such fully substituted arylpyrrolidine derivatives have been found to exist predominantly as the amide (*Z*)-rotamer, whereas the unsubstituted analogs exist as rotameric mixtures.[20] In the model allylation reaction, catalysts bearing fully substituted arylpyrrolidines (R^2 = Me, **4a'–4e'**, Figure 1B, red circles) all induce higher enantioselectivities than the corresponding unsubstituted catalysts (R^2 = H **4a–4e**, Figure 1B, blue squares). A dependence of ee on arene group polarizability and positioning was observed with the fully substituted arylpyrrolidine catalysts similar to that of the unsubstituted catalysts. At this stage it may be concluded that the properties of the arylpyrrolidine have a strong influence on reaction enantioselectivity, but that full elucidation of the bases for these effects and their relative importance will require a sophisticated multiparameter analysis.[21] Finally, optimization of the aniline-derived portion of the catalyst revealed that the more electron deficient dicyano derivative **5d'** afforded comparable enantioselectivities but substantially improved rates and product yields than the bis-trifluoromethyl derivative **4d'**.

Table 1. Reaction Scope[a]

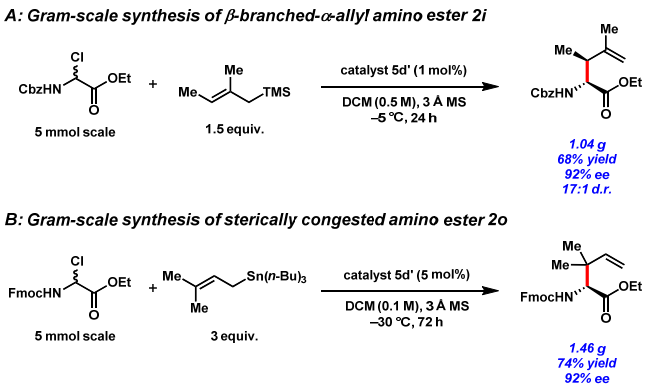


[a] Conditions: substrate (0.5 mmol), catalyst (0.0125 mmol), nucleophile (1.0 mmol), 3 Å MS (60 mg), DCM (2 mL), under N_2, initially cooled to –78 °C and stirred at –30 °C, 36 h. Enantiomeric excess determined by HPLC. Diastereomeric ratio determined by ^{1}H NMR of the crude product, yield reflects isolation of major diasteromer. [b] –5 °C. [c] catalyst (0.05 mmol), nucleophile (2.0 mmol), DCM (5 mL), –50 °C, 72 h. [d] catalyst (0.05 mmol), nucleophile (1.5 mmol), DCM (5 mL), –30 °C, 72 h. [e] (*E*)-trimethyl(2-methylbut-2-en-1-yl)silane and (*E*)-crotylstannane employed as the nucleophiles. Yields and enantioselectivities in parentheses are of crystallized products.

The scope of the α-allyl amino ester synthesis was investigated with optimal catalyst **5d'** (Table 1).[22] Consistently high yields and excellent enantioselectivities were obtained with several different 2-substituted allylsilane nucleophiles. 2-Arylallyltrimethylsilanes with electronically neutral or donating substituents furnished the corresponding products **2b–g** in 90-96% ee. β-Branched-α-allyl amino esters were produced with high diastereoselectivities and enantioselectivities using 2,3-disubstituted allylsilanes as nucleophilic reacting partners (Table 1, **2i–l**). As noted above, these products are generally inaccessible using electrophilic allylation reagents in traditional enolate allylations.[9,10] The enantio- and diastereoselectivies of branched products **2i-l** and **2n** are generally higher than those obtained with previously reported catalytic asymmetric methods.[13] Additional benefits of this method include a larger range of reported nucleophiles, as well as products containing easily

cleavable *N*-protecting groups. In contrast, allylsilane nucleophiles lacking 2-substituents were completely unreactive under the catalytic conditions, an observation consistent with the fact that allyltrimethylsilane (N = 1.68)[23] is substantially less nucleophilic than 2-methylallylsilane (N= 4.41).[24] The more nucleophilic allyltributylstannanes (N= 5.46 for the parent compound)[23] were evaluated and found to be effective reacting partners, allowing construction of α-allyl amino esters **2m–o** with high yields and enantioselectivities. Reoptimization of the reaction conditions and carbamate protecting group was necessary for reactions employing stannane nucleophiles; in particular the Fmoc-protected analog of **1** was found to provide improved enantioselectivities (e.g., 93 vs 74% ee with prenylstannane nucleophile). Crotylstannanes underwent reaction to furnish the branched product **2n**. Both the (*E*)- and (*Z*)-crotyltributylstannane afforded the syn diastereomer predominantly (8:1 with the (*E*)-isomer, 4:1 with the (*Z*)-isomer). A similar outcome was observed using silane nucleophiles leading to product **2i**, indicating that the allylation reactions proceed through open transition states. Reaction of prenyl tributylstannane with **1-Fmoc** generated the reverse-prenyl amino ester **2o** in 93% ee.

Scheme 2. Gram-scale reactions



The new catalytic protocol proved to be readily adaptable to the preparative-scale synthesis of α-allyl amino esters. For example, using either the α-chloro amino ester **1-Cbz** or **1-Fmoc** and appropriate allylsilane or allylstannane nucleophiles, the β-branched products **2i** and **2o** were generated on gram scale (Scheme 2). The reaction of 2,3-dimethylallylsilane with **1-Cbz** could be conducted at relatively high concentrations (0.5 M in DCM) with 1.5 equiv. of the nucleophile and 1 mol% catalyst with no compromise in enantioselectivity relative to the smaller scale reaction. The addition of prenylstannane to **1-Fmoc** could not be conducted at higher concentration due to the limited solubility of **1-Fmoc** in DCM, but the catalyst loading could be lowered to 5 mol% while preserving the high enantioselectivity of the reaction.

While the direct generation of carbamate-protected amino esters provides amino acid derivatives in conveniently protected form, we were naturally concerned about the likely incompatibility of the alkenyl group in the allylated products with typical protocols for Cbz group removal. Indeed, under standard hydrogenolysis conditions, compound **2i** underwent competitive reduction of the alkene. However, reduction with triethylsilane under $Pd(OAc)_2$ catalysis left the alkenyl group intact and afforded the corresponding free amine in 87% yield with no measurable racemization.[25]

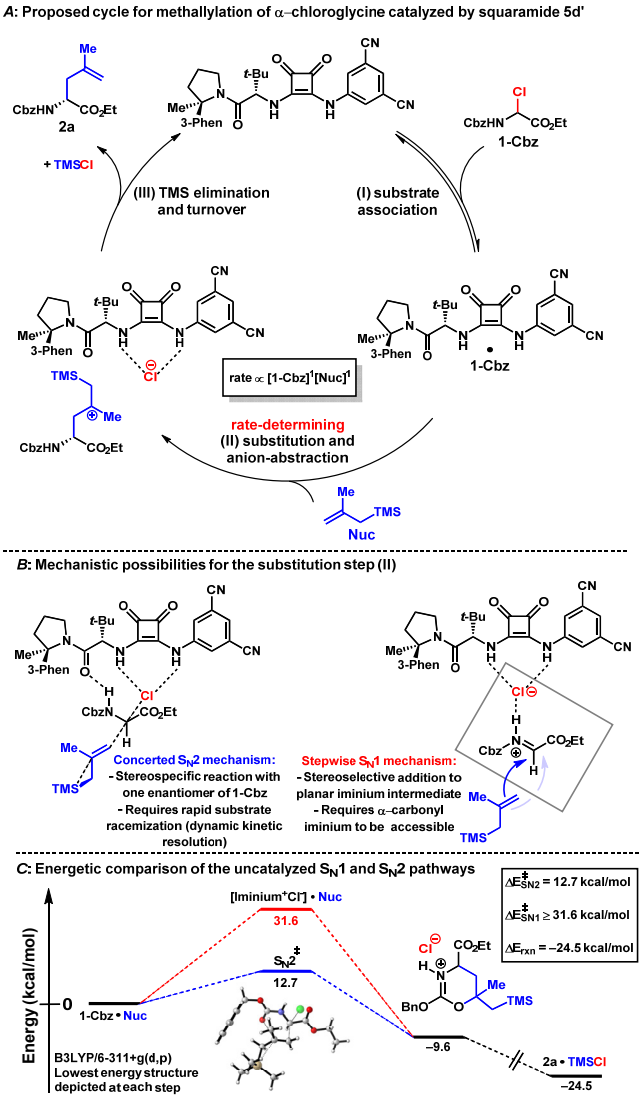


Figure 2: (A) Proposed catalytic cycle. Observed first order dependence on **1-Cbz** and **Nuc** indicate that nucleophilic addition is the rate-determining step. (B) Concerted S_N2 and stepwise S_N1 mechanisms require different mechanisms for enantioinduction. (C) Computational evaluation of the uncatalyzed reaction predicts that the S_N1 pathway is much higher in energy than the S_N2 pathway. All DFT calculations were performed at the B3LYP-D3(BJ)/6-311+G(d,p) level of theory including solvent corrections PCM(DCM). For a fuller discussion of the computational study, see SI.

A simplified catalytic cycle for the new allylation reaction is outlined in Figure 2A. The catalytic mechanism is proposed to involve three fundamental steps: 1) complexation of the electrophile **1-Cbz** to catalyst **5d'**, 2) substitution involving C–Cl bond breaking and C–C bond formation, and 3) trimethylsilyl elimination from the β-silyl cation to form product **2a** and TMSCl. The detailed mechanism of the substitution step and the role of the catalyst in promoting it are of greatest interest, since that process results in formation of the new C–C bond and is enantiodetermining. Although enantioselective anion-binding catalysis has been applied successfully to many reactions proceeding via *N*-acyliminium ion intermediates,[18b,26] several considerations led us to question whether such species are involved in the system under consideration here. α-Chloro carbonyl compounds such as **1** are generally activated toward S_N2 substitution pathways and deactivated toward dissociative S_N1 mechanisms.[27] Optimal enantioselectivities are obtained using DCM as

solvent in the allylations of **1** (Figure S7). In contrast, nonpolar ethereal or aromatic solvents are generally required to achieve high enantioselectivities in ion-pairing catalysis promoted by chiral H-bond donors. Indeed, DCM has been found to promote solvent separation of ion pairs in these systems, resulting in severe diminution of enantioinduction.[28]

Two plausible mechanisms for the substitution step are outlined in Figure 2B. If a stepwise S_N1 is operant, anion abstraction would precede C–C bond formation with the intermediacy of a discrete, highly electrophilic iminium ion intermediate. The unexpected solvent effect noted above might be reconciled with a secondary attractive interaction holding the ion-pair together, such as the iminium–Cl H-bond depicted in Figure 2B (right). If the reaction proceeds through a concerted, stereospecific nucleophilic displacement, a dynamic kinetic resolution with rapid racemization of the α-chloro glycinate would be required to account for the observed high yields and enantioselectivies. Such a racemization could occur via chloride dissociation, bimolecular chloride displacement, or sequential tautomerization pathways. The catalytic reaction was determined to obey a second-order rate law, with first-order dependence on both the α-chloro glycinate and allylsilane concentrations, consistent with either a concerted S_N2 mechanism or rate-determining allylation of an iminium intermediate in an S_N1 pathway.

Clear differentiation of the two mechanisms and determination of the basis for enantioinduction will require considerable further study and are under active investigation. However, a preliminary computational analysis of the uncatalyzed transformation predicts that the concerted S_N2 substitution proceeds through a substantially lower-energy pathway than the stepwise S_N1 mechanism.[29,30] The global ground state was identified as a dipole-dipole interaction complex between **1** and **Nuc**. Six staggered S_N2 transition states were located with activation barriers < 20 kcal/mol, with the lowest at 12.7 kcal/mol (Figure 2C). In contrast, the iminium–chloride ion-pair implicated in the S_N1 mechanism was 31.6 kcal/mol above the ground state. Recognizing that nucleophile addition is rate-determining and therefore must involve a discrete activation barrier, the concerted S_N2 pathway is thus computed to be more than 18.9 kcal/mol lower in energy than the S_N1 pathway.[31,32]

In summary, an enantio- and diastereoselective synthesis of α-allyl amino esters was accomplished via allylation of α-chloro glycine esters with a chiral squaramide hydrogen-bond donor as an anion-abstraction catalyst. Using either allylsilane or allylstannane nucleophiles, 15 representative α-allyl amino esters were constructed in high enantio- (up to 97% ee) and diastereoselectivities (> 10:1 dr). The silane addition reaction was carried out on gram-scale at 0.5 M concentration using 1 mol% catalyst. Experimental observations, kinetic data, and DFT calculations all point to an energetically inaccessible acyliminium ion intermediate and a relatively favorable, concerted S_N2 mechanism for the substitution step. Our current efforts are directed toward elucidating the racemization mechanism, the origin of enantioselectivity, and the specific noncovalent interactions involved in the selectivity-determining transition state. We anticipate that a full mechanistic understanding of the origin of selectivity in the allylation of **1** could enable extension of the methodology to other classes of nucleophiles, providing a broadly applicable approach to the enantioselective synthesis of α-substituted amino esters.

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI:

Experimental and Characterization Data of Catalyst and Substrate Syntheses (PDF)

Procedures and Analytical Data for the Enantioselective Reactions (PDF)

Details of Kinetic Studies (PDF)

Computational Studies (PDF)

Crystallographic Data for **2l** (CIF)

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Author Contributions

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Notes

The authors declare no competing financial interests.

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(32) Using a water PCM, we found the S_N2 pathway to be favored by an even greater margin, 22.8 kcal/mol, providing a strong indication that the high energy predicted for the iminium ion intermediate was not simply an artifact of comparing unbenchmarked covalent and ionized energies in a solvent PCM.

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