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Synthesis and Reactivity of α-Haloglycine Esters: Hyperconjugation in Action

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Abstract

A general and efficient synthesis of α-haloglycine esters from commercially available feedstock chemicals, in a single step, is reported. The reactivity of these α-haloglycine esters with various nucleophiles was studied as surrogates of α-iminoesters upon activation with hydrogen-bond donor catalysts. DFT calculations on the α-haloglycine structures (X = F, Cl, Br) accompanied by an X-ray characterization of the α-bromoglycine ester support the existence of a "generalized" anomeric effect created by hyperconjugation. This peculiar hyperconjugative effect is proposed to be responsible for the enhanced halogen nucleofugality leading to a facile halogen abstraction by hydrogen-bond donor catalysts. This reactivity was exploited with thiourea catalysts on several catalytic transformations (aza–Friedel-Crafts and Mannich reactions) for the synthesis of several types of non-proteinogenic α-amino esters.

Keywords

Anomeric effect; Homogeneous catalysis; Hyperconjugation; Non-proteinogenic amino acids; Synthetic methods

Introduction

Non-proteinogenic α-amino acid residues are essential motifs of proteins, non-ribosomal peptides, natural products, and other marketed drugs.[1] Due to their exceptional array of structural and functional diversity, building blocks derived from non-proteinogenic α-amino acids are also found in numerous chiral auxiliaries, organocatalysts, ligands, and bioactive peptides, thus imparting them with a crucial role in modern organic chemistry.[2] This is why developing the most versatile and scalable synthesis of non-proteinogenic α-amino acids has attracted significant attention in the past decades. Conceptually, several synthons have been proposed and studied to achieve the amino acids α-stereocenter functionalization via the corresponding glycine-like radical, anion or carbocation.[3] Most recent efforts have focused either on a Schiff base approach (α-anion), or the activation of an iminoglycine **A** by BrØnsted or Lewis acids to unveil the glycinyl iminium **B** reactivity. Numerous

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functionalizations of α-iminoglycine esters **A** through Strecker,[4] Mannich,[5] aza-Friedel–Crafts[6] or Petasis[7] reactions have been reported to synthesize an exquisite variety of highly functionalized and optically active α-amino esters (Scheme 1). However, the innate instability of these iminoglycines **A** is a major limitation which often translates into cumbersome preparation techniques.[8] To counter this obstacle, α-amido sulfones[9] and α-haloglycine esters[10] have been tentatively exploited as in situ imine precursors.

For a long time, however α-haloglycine esters have been disregarded in the synthesis of α-amino esters because they were dubiously thought to be overly reactive, and moisture sensitive.[11] Not surprisingly, there have been only a few reports using α-haloglycine derivatives for the synthesis of non-proteinogenic α-amino acids or esters,[12] heterocycles[13] and peptides.[14] Important to our strategy, the works of Williams[15] and Davies[11b] validated that α-haloglycine bearing a chiral auxiliary moiety can be functionalized with nucleophiles to prepare a wide range of α-amino acids in a diastereoselective fashion. Until recently, the chemistry of α-haloglycines was largely unexplored because the asymmetric maneuvers for halogen abstraction by a chiral catalysts were limited. In 2014, Jacobsen reported the first asymmetric Mannich synthesis of α-amino esters via the halogen abstraction of a α-chloroglycine residue by thiourea anion-binding chiral catalysts.[16] Since this report, we have been particularly drawn to examine the role of halogens from α-haloglycine esters **4a-c** (X = F, Cl, and Br) in the abstraction mechanism leading to glycinyl iminiums **B** (Scheme 1 and Scheme 2). Herein, we are reporting for the first time the synthesis and characterization of three N-carbamoyl α-haloglycine **4a-c**, as well as their innate reactivity which is proposed to rise from a very unique “generalized” anomeric effect. Finally, we are demonstrating the efficiency of several hydrogen-bond donor catalysts in promoting noteworthy applications via halogen abstractions for the synthesis of two different classes of α-amino esters.

Results and Discussion

Synthesis of α-haloglycines.

While α-fluoroglycine ester **4a** has never been reported, α-haloglycine esters **4b** (X = Cl) and **4c** (X = Br) are typically synthesized in two steps which entail the isolation and purification of the hemiaminal **3** followed by a halogenation step (Scheme 2).[17]

We recently reported that α-chloroglycine ester **4b** can be prepared in a single step and further functionalized in the same reaction vessel to afford a general strategy to several classes of α-amino esters.[16,18] We proposed that the key to a multicomponent synthesis of α-haloglycine is the simultaneous activation of a glyoxylic ester **1** to facilitate the condensation with a selected primary carbamate **2** while enabling a facile deoxyhalogenation of the hemiaminal intermediate **3** (Scheme 3). Encouraged by our initial findings that the AcOH (cat.)/AcCl system promotes the synthesis of α-chloroglycine **4b** in a single step (Table 1, entry 1),[18] several other halogenation reagents have been evaluated to optimize the synthesis of **4a-c** (Scheme 3 and Table 1).[19] As we initially reported, water needs to be fully extruded to avoid the reaction reversibility via hydrolysis, and other oxidative side reactions.[20] Therefore, for each deoxyhalogenation reagent or “promoter” tested (Scheme

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3), the stoichiometry in promoters was carefully calculated to account for the initial dehydration of glyoxylate **1** (step 1) and to remove a second molecule of water during the deoxyhalogenation of hemiaminal **3** (step 3). For each successful promoter evaluated in Table 1, a reaction profile was established through the reactions' advancement monitoring by ^{1}H NMR.[21] As shown in our proposed mechanism (Scheme 3), all the promoters release stoichiometric amounts of acid (H-X) during the initial dehydration of glyoxylate hydrate **1** thus facilitating further the condensation producing hemiaminal **3** (step 2). A second molecule of water is then extruded during deoxyhalogenation (step 3) to access α-haloglycines **4a-c**. The preliminary kinetic studies[21] confirmed what could be intuitively assumed, that N-carbamoyl iminium formation **5**→**6** is the rate-limiting step of the cascade reaction.[22] We also observed a correlation between the Lewis acid strength of the promoters (nucleofugality of leaving groups transiently formed in **5**) and the overall rate of halogenation, as it would be expected from a typical S_N1 reaction via the N-carbamoyl iminium **6**.[23] Thus, the net reactivity increase observed may be rationalized by considering the promoter strength from TMSCl, AcCl, $SiCl_4$ ≈ $(CO)_2Cl_2$ to the most reactive $SOCl_2$ (Table 1, entries 1–6). To sum-up the results presented in Table 1, thionyl chloride ($SOCl_2$: entry 2), and silicon tetrachloride ($SiCl_4$: entry 3) were found to be the most efficient promoters to synthesize **4b** in quantitative yields (r.t. or 35 °C). Along with the formation of HCl, by-products of these reactions are easily removed by evaporation or filtration respectively (SO_2 or SiO_2). Similarly, several promoters were evaluated to prepare α-bromoglycine ester **4c** (entries 7–9). As expected, bromination reagents are more reactive, and $SOBr_2$ was found to be extremely efficient to produce **4c** at −20 °C in a quantitative manner and only 20 min. Finally, numerous attempts to synthesize α-fluoroglycine ester **4a** have been unsuccessful with only small amounts of hemiaminal **3** observed in some cases (entries 10–11). Therefore the synthesis of substrate **4a** was optimized via a stepwise process in one-pot: First, the initial condensation leading to hemiaminal **3** was achieved using catalytic amounts of AcOH at 40 °C which was followed by an in situ deoxyfluorination promoted by DAST (entry 12).[24] The addition of molecular sieves (4Å MS) or Ag_2O as acid scavengers severely slows down reactions (2–3 folds), suggesting that the condensation–deoxyhalogenation reactions toward **4a-c** are likely catalyzed by acid (HX).

To gain mechanistic insight into the condensation-deoxyhalogenation cascade, the reaction with AcOH(cat.)/AcCl at 60 °C in $CDCl_3$ (Table 1, entry 1) was monitored in situ by ^{1}H NMR (Figure 1). Interestingly, while the starting material Cbz-carbamate **2** disappearance followed a typical exponential decay, the plot for the conversion of α-chloroglycine ester **4b** over time best fit a sigmoid-like curve, suggesting a complex reaction mechanism (Figure 1A). Indeed, the slow formation of product **4b** in the initial 100 minutes corresponds to the time-frame of glyoxylate dehydration (step 1) and a plausible oxonium formation which further initiates the condensation to the hemiaminal intermediate **3** (step 2). During this initial dehydration, the first equivalent of HCl and AcOH are released which appeared to further catalyze the reaction. The maximum conversion in **3** can be seen after 150 minutes suggesting that the rate-determining step is the deoxyhalogenation via the intermediacy of iminium **6**. From there on, the formation of AcOH and **4b** (monitored by ^{1}H NMR) followed similar kinetics (sigmoid curve) with an acceleration phase followed by a deceleration

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characteristic of an autocatalysis-like mechanism (Figure 1A).[25] The rate in AcOH formation (d[AcOH]/dt) was plotted against time which confirmed that the acceleration phase proceeded from 100 to 250 minutes at which time the rate of formation in **4b** is maximal before decelerating toward the end of the reaction. Given that similar kinetic profiles (autocatalysis-like) were not observed in other reactions (Table 1, entries 2–9) suggested that the rate-determining step could be shifted based on the promoter strength.[21] As such, in the reactions of condensation–deoxybromination to synthesize **4b** (Table 1, entries 7–9), hemiaminal **3** was not observed by ^{1}H NMR throughout the entire reaction course.

Reactivity of α-haloglycines.

Our next goal was to study the reactivity of α-haloglycines **4a-c** under the control of hydrogen-bond donor thiourea catalysts $\mathbf{T_{A,B}}$ (Figure 2).

A comparative reactivity was examined via a competitive cross functionalization experiment in an aza-Friedel–Crafts reaction (Table 2). Using an equimolar mixture of α-haloglycines (**4a**-F, **4b**-Cl and **4c**-Br) with N-methylindole as π-nucleophile, the innate reactivity of α-haloglycines (Condition A: entry 1) was investigated and compared under the presence of 10 mol-% of the achiral Schreiner's thiourea $\mathbf{T}_A$ (Condition B: entry 2). Under both reactions' conditions, α-fluoroglycine **4a** remained mostly untouched ([**4a**] deviation over time is due to substrate degradation[26]) which suggested that **4a** is unreactive under these conditions. More interestingly, in the initial hour of the uncatalyzed reaction (entry 1), α-chloroglycine **4b** reacted the fastest (57 % consumed) while α-bromoglycine **4c** slowly initiated a reaction (14% consumed). After this mark, from 1.5 to 3.5 h, α-chloroglycine **4b** was surprisingly regenerated (blue box in Table 2), which might be the result from an anion exchange (Br^- to Cl^-). Indeed, after the first hour of reaction, ≈ 60 % of α-chloroglycine was consumed therefore the concentration of chloride in the reaction media is significant. It is likely that the degree of conversion in chloride enhanced an external ion return mechanism **4c** → **4b** (as [Cl^-] increased), which also contributed to retard the glycinyl iminium **6** trapping by the indole nucleophile, therefore, promoting the regeneration of α-chloroglycine **4b** (through ionic-pair exchange).[27] When similar reaction conditions were applied to evaluate the anion-binding catalysis with thiourea $\mathbf{T}_A$ (10 mol-%), α-chloroglycine **4b** was not consumed faster (entry 2). In contrary, α-bromoglycine **4c** appeared to interact with the hydrogen-bond donor catalyst $\mathbf{T}_A$ which translated in an overall rate acceleration in product formation. Indeed, during the first hour of reaction, the consumption of **4c** is largely increased (49% vs. 14%: entry 2 vs. 1). In this case, the counteranion exchange occurred much later, after 6 hours of reaction. Overall, under the reaction conditions tested at −20 °C, both α-haloglycines **4b** and **4c** have shown an innate propensity to heterolysis, forming the glycinyl iminium **6** in either contact or solvent-separated ion pairs.[18b]

The direct comparison between catalyzed and uncatalyzed reactions demonstrated that the Schreiner's thiourea catalyst $\mathbf{T}_A$ has a pronounced halide-binding effect on α-bromoglycine **4c** (Figure 3). In addition, it is proposed that a "generalized" anomeric effect (vide infra) in **4c** develops a partial negative-charge on the halogen leaving group, which promotes an early event of halogen-binding by thiourea $\mathbf{T}_A$ resulting in a more facile C-Br bond cleavage and a

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greater equilibrium concentration in glycinyl iminium **6**, favorable to the ensuing C-C bond-forming step.

To test this hypothesis, a side by side comparison of α-chloro and α-bromoglycines **4b** and **4c** reactivity catalyzed by an H-bond donor thiourea was deemed necessary. Thus the reactivity of α-haloglycine esters **4b** and **4c** as iminoglycine precursors were tested by kinetic profiling in our previously reported Mannich reaction (Scheme 4). While the uncatalyzed reaction between **4b** and dibenzoylmethane afforded the expected Mannich product **8** in only 14% yield, thiourea catalyst $\mathbf{T}_A$ was found to exert a profound effect on the reaction, affording **8** in 90 % yield. As a control, the course of the uncatalyzed reactions of **4b** and **4c** with dibenzoylmethane were monitored in situ by ^{1}H NMR in CD_2Cl_2 and shown that product **8** was formed in less than 7 % yield in both cases (initial rate constant k_{obs} of 75 and 0 × 10^{-5} M^{-1}•min^{-1} respectively). Similarly to the Friedel–Crafts reaction, the uncatalyzed reaction of **4b** seemed to be faster than the reaction of **4c**. Furthermore, both reactions proved to be catalyzed by the Takemoto's tertiary aminothiourea $\mathbf{T}_B$ leading to about 25 % yield in **8** from α-chloroglycine **4b** in the first hour, while only 15 % yield was observed from α-bromoglycine **4c**. From these initial reactions profile, it appears that the crucial tertiary amine moiety in catalyst $\mathbf{T}_B$ might be rapidly quenched by the in situ formation of an HBr salt. Nonetheless, catalyst $\mathbf{T}_B$ displayed a markedly enhanced reactivity toward **4b**, affording good conversion in product **8** as previously reported[16] (conv. > 35 % at 2 h).[21]

Having established some interesting trends in reactivity, between **4b** and **4c**, we further investigated some potential modes of activation for α-fluoroglycine ester **4a** (Table 3). Even though the fluoride anion is known to be the strongest hydrogen-bond acceptor halide, the activation of covalently bound organofluorines by hydrogen-bond donors for nucleophilic substitution remains a particularly challenging reaction.[28] Inspired by the original study from Bull and Davies on the reactivity of α-haloglycine and their halogen exchange reactions,[11b] we hypothesized that **4a** could be converted into **4b** under an appropriate set of conditions. Upon exposure with TMSCl, **4a** was chlorinated with high conversions in 2 hours at 0 °C (entries 1–2). When a similar reaction was carried out at −78 °C for 30 min, product **4b** was obtained in 20 % yield (entry 3). In comparison, the chlorination of **4a** was catalyzed smoothly at −78 °C by thiourea $\mathbf{T_A}$ to deliver **4b** in 60 % yield (entry 4). Remarkably the catalyzed reaction proceeded to full conversion in only one hour to afford **4b** in 96% yield after a practical and simple evaporation (entry 5).

The overall results of functionalization in both the aza-Friedel–Crafts and in the Mannich reactions suggest that α-chloroglycine **4b** reacts innately faster than the α-bromo-analogue **4c** leading to an unexpected order of reactivity (Cl > Br >> F).[34d]

Structural Studies.

The fact that α-haloglycines **4a-b** engaged so easily in heterolysis at cryogenic temperatures, prompted us to draw similarities with the reactivity of pyranosyl halides[29] and the well-established anomeric effect in carbohydrate chemistry[30] Functionalizations of Csp^3–F bonds are sparse with the exception of the facile C-F bond cleavage at the anomeric

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center of glycopyranosyl fluorides to achieve glycosylation reactions.[31] This reactivity is facilitated by the anomeric effect embedded at the C1-position of fluorinated carbohydrates through favorable dipole-dipole repulsion and hyper-conjugation $n_{(O)} \rightarrow \sigma^*_{(C\text{-}F)}$.[32] Hyperconjugative effects in the series of pyranosyl halides have been extensively studied and characterized by abnormal bond lengths. X-ray crystallographic data have shown that O-C(1) bonds are typically shortend, and C(1)-X_{ax} elongated.[33] Even though hyperconjugation is widely accepted as a major stereoelectronic effect that contributes to organic reactivity,[34] examples of hyperconjugative effect on acyclic molecules - so-called "generalized" anomeric effect - are limited.[35] Having access to the α-haloglycine esters **4a-c** in pure form, spectroscopic data were obtained to correlate the ease of these substrates toward heterolysis with a potential hyperconjugative effect. Crude material **4c** was crystallized in toluene and the X-ray crystal structure of **4c** provided several interesting structural features (Figure 4A). For instance, the bond angles around the central C_α are larger than expected for a sp^3-hybridized carbon. Also, all dihedral angles observed in the crystal structure correlated well with our conformational analysis of **4b** obtained by density functional theory computations (DFT) at the B3LYP 6-311++G (3df,3pd) level of theory (including solvent corrections)[21] Torsion angle Φ, which is a key dihedral angle in the conformational analysis of peptides[36] was found to be unusually large which is characteristic of a fully extended conformation like in *trans*-amides ($\Phi_{X\text{-}ray}$ = 150.5°; Φ_{calc} = 159.3°). Also, torsion angle θ between the H-N-C(2) and N-C(2)-H planes which can be determined experimentally from the vicinal scalar coupling constant $^3J_{NH\text{-}H\alpha}$ in ^{1}H NMR was well estimated by the DFT calculations ($\theta_{X\text{-}ray}$ = 161.9°; θ_{calc} = 160.8°).

Indeed, this peculiar large torsional angle in **4c** matches the abnormally large vicinal coupling constant in $CDCl_3$ ($J_{NH\text{-}H\alpha}$ = 10.2 Hz), thus supporting the argument that the low-lying conformation in the crystal lattice reflects closely the major conformer of **4c** in solution (Figure 4B)[37,38] Similarly, the $J_{NH\text{-}H\alpha}$ coupling constants for **4a**, **4b**, and **4c** are abnormally large in both apolar and polar protic solvents $CDCl_3$ and CD_3CN (J > 9.2 Hz), suggesting that the three α-haloglycines experience a comparable solvent exposure and have a similar *gauche*-conformation.[39] In such *gauche*-conformation, **4c** is also stabilized by a weak intramolecular hydrogen bond NH•••O=C (2.491 Å) leading to the alignment of the C-Br bond with the carbonyl π* antibonding orbital of the ester.[37] Furthermore the quasi-orthogonality of the α dihedral angle C(3)-N-C(2)-Br (α = −92.6°) supports the fact that the nitrogen lone pair not only engaged in conjugation with the carbonyl π* orbital (Cbz carbamate) but more importantly aligned impeccably in an antiperiplanar manner to the $\sigma^*_{C\text{-}Br}$ antibonding orbital to allow a spatial electronic donation through hyperconjugation ($n_{(N)} \rightarrow \sigma^*_{(C\text{-}Br)}$). This proposed phenomenon of hyperconjugation in **4c** is further characterized by abnormal bond lengths: (C2)–N and C(2)–Br (see X-ray crystal structure and the DFT minimized models).[21] With a 140.6 pm length, the (C2)–N bond is substantially shorter than the reported average length for C_{sp3}–N_{sp2} of 145.4 pm in acyclic amides,[40] suggesting that the C(2) carbon of **4c** has a partial sp^2-character. Finally, the C(2)–Br bond length of 200.6 pm is the longest ever reported C_{sp3}–Br bond in the CCDC database (Cambridge Crystallographic Data Centre), +4 pm longer than the average C_{sp3}–Br bond lengths reported in the literature (196.6 pm) which is consistent with a bond elongation magnitude caused by hyperconjugative effects in pyranosyl bromides (avg +2 pm).[21,41]

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Taken altogether, these spectroscopic and structural results suggest that a “generalized” anomeric effect might take place in the α-haloglycines studied **4a-c** due to an hyperconjugation that stabilizes gauche conformations in which the C–X bonds are unusually elongated.

CCDC 1878828 (for **4c**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

Conclusions

In conclusion, some highly practical and efficient preparations of α-haloglycine esters **4a-c** in one-pot have been developed to generate useful precursors of non-proteinogenic α-amino esters. X-ray characterization and other spectroscopic data combined with the DFT calculations support the existence of an anomeric effect in these acyclic α-haloglycines **4a-c**, which is the first reported example of hyperconjugation initiated by a nitrogen heteroatom bearing an electron-withdrawing carbamoyl protecting group ($n_{(N)} \rightarrow \sigma^*_{(C–Br)}$). This peculiar hyperconjugative effect is proposed to be responsible for the innate reactivity of the α-haloglycines studied herein by developing a partial negative-charge on the halogen leaving group, thus enhancing nucleofugality and binding by hydrogen-bond donor catalysts. Interestingly, α-chloroglycine **4b** reacts faster than the bromoanalog **4c** leading to an innate order of reactivity Cl > Br >>F. The unique “generalized” anomeric effect was therefore advantageously exploited to enable several types of transformations (halogen exchange, and C-C bond formations) catalyzed by two thiourea catalysts $\mathbf{T_{A\text{-}B}}$. This work resulted in the synthesis of two kinds of non-proteinogenic α-amino esters **7** and **8** as proof of principle. While a catalyzed halogen exchange was achieved with the Schreiner thiourea on α-fluoroglycine **4a**, the catalyzed Friedel–Crafts reaction was found to be optimum not from α-chloroglycine **4b** as it was initially reported,[18] but from α-bromoglycine **4c**. In the other end, the kinetic study for the direct asymmetric Mannich reaction catalyzed by the Takemoto bifunctional thiourea was found to proceed more smoothly from α-chloroglycine **4b**. Given the importance of haloacetals in glycosylation chemistry and other C-C bond formation in small molecules,[42] as well as the role of stereoelectronic factors in glycosylation mechanisms,[43] we anticipate that the characterization of the hyperconjugative effect herein and its implication for halogen binding will stimulate new catalytic coupling reactions to be developed with H-bond donor catalysts.[44]

Experimental Section

Instrumentation and methods:

All reactions were performed in flame-dried glassware under a positive pressure of argon. Yields refer to chromatographically and spectroscopically pure compounds, unless otherwise noted. Analytical TLC was performed on 0.25 mm glass-backed 60 Å F-254 TLC plates (Silicycle, Inc.). The plates were visualized by exposure to UV light (254 nm). Infrared spectra were recorded on a Nicolet IS5 FT-IR spectrophotometer. ^{1}H NMR spectra were recorded on a Varian Mercury400 and a Bruker Biospin GmbH (400 MHz) spectrometers and are reported in ppm using solvent as an internal standard ($CDCl_3$ at 7.26 ppm, or

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CD_3CN at 1.96 ppm). ^1H NMR spectra were performed using standard parameters, and data are reported as b = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet; coupling constant(s) in Hz, integration. ^{13}C NMR spectra were recorded on a Varian Mercury400 (100 MHz) spectrometer. Chemical shifts are reported in ppm, with solvent resonance employed as the internal standard ($CDCl_3$ at 77.2 ppm, or CD_3CN at 1.3 and 118.3 ppm).

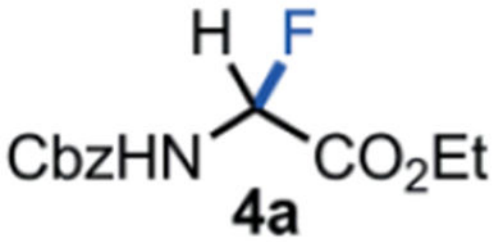
Reagents and solvents:

All reagents used in this paper were acquired from Alfa Aesar or Sigma Aldrich. All bulk solvents were acquired from Fischer Scientific. Freshly distilled solvents were used in the reactions presented herein. Chloroform was dried with CaCl2 overnight prior to distillation and transferred under argon to a dark glass bottle with 3 Å molecular sieves for storage. Tetrahydrofuran was purified by refluxing with sodium metal and benzophenone and transferred under argon to a dark glass bottle with 3 Å molecular sieves for storage. Dichloromethane was dried with $CaCl_2$ over-night, prior to distillation and transferred under argon to a dark glass bottle with 4 Å molecular sieves for storage. Full procedures can be found in Purification of Laboratory Chemicals by Armarego, W. L. F.; and Chai C. L. L., Elsevier (Sixth Edition).

Products **7** and **8** have been reported and fully characterized by us in ref.[18,16] respectively.

$C_{12}H_{14}FNO_4$

$MW = 255.2\ g.mol^{-1}$



4a

N-Cbz-α-fluoroglycine ethyl ester 4a:

In a polypropylene vial, a mixture of benzyl carbamate **2** (76 mg, 0.50 mmol, 1.0 eq.), ethyl glyoxylate hydrate in 50 % toluene (w/v) **1** (120 μL, 0.50 mmol, 1.0 equiv.) and acetic acid (3 μL, 0.05 mmol, 0.10 eq.) were stirred in anhydrous dichloromethane (5.0 mL) for 15 h under argon at 40 °C. The reaction was monitored by the ^1H NMR for the full conversion to the corresponding hemiaminal. The reaction mixture was then cooled to −78 °C and diethylaminosulfurtrifluoride (DAST: 132 μL, 1.0 mmol, 2.0 eq.) was added dropwise over 5 min to the reaction mixture. At the end of the addition, the reaction mixture was allowed to slowly warm up to room temperature over another 2 h. After consumption of all starting materials (observed by the ^1H NMR), the reaction mixture was quenched with ice-cold water

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(10 mL) and extracted with CH_2Cl_2 (3 × 5.0 mL). The combined organic layers were then dried with sodium sulfate, filtered and concentrated under vacuum in a glass scintillation vial to obtain the desired product **4a** as a pale yellow liquid (144 mg containing residual CH_2Cl_2, 0.50 mmol, >95 % yield overall) which is finally transferred in a polypropylene vial for storage. [Note: Complete removal of the residual CH_2Cl_2 in a scintillation vial leads to rapid decomposition of compound **4a**]. $\boldsymbol{R_f}$ = 0.25 (EtOAc/hexanes, 30:70; UV active, stains green-yellow with vanillin). Caution!! α-Fluoroglycine **4a** is not stable, neither on silica nor on neutral alumina; It decomposes rapidly into **3**, but **4a** can be stored in a polypropylene vial under argon in a freezer at −78 °C for 4 days with a minimum decomposition <10 %. **IR** (Neat) ν_{max} = 697, 736, 779, 857, 970, 1021, 1205, 1335, 1374, 1399, 1455, 1520, 1732, 2982, 3320 cm^{-1}. **^{1}H NMR** (400 MHz, CD_3CN): δ (ppm) 7.44–7.33 (m, 5H), 7.08 (bs, 1H, NH), 5.96 (dd, *J* = 53.7, 9.5 Hz, 1H), 5.15 (s, 2H), 4.24 (q, *J* = 7.1 Hz, 2H), 1.26 (t, *J* = 7.2 Hz, 3H). **^{19}F NMR** (377 MHz, $CDCl_3$) δ (ppm) −140.2 (d, *J* = 54.0 Hz). (Standard hexafluorobenzene δ = −164.9 ppm). **^{13}C NMR** (100 MHz, CD_3CN): δ (ppm) 166.1 (C; d, *J* = 33.3 Hz), 137.2 (C), 129.5(2 CH), 129.3(CH), 129.1 (2 CH), 88.34 (C-F: d, *J* = 205.1 Hz), 68.2 (CH_2), 63.3 (CH_2), 14.2 (CH_3). **HRMS (ESI)**: Compound **4a** hydrolyzed into the corresponding hemiaminal **3** in the mass spectrometer with m/z Calcd. for $[C_{12}H_{15}NO_5+Na]^+$ = 276.0842, found 276.0848 (+2.2 ppm).

SMILES: FC([H])(C(OCC)=O)NC(OCC1=CC=CC=C1)=O.

4b

$C_{12}H_{14}ClNO_4$

MW = 271.1 g.mol^{-1}

N-Cbz-α-chloroglycine ethyl ester 4b:

In a flame dried scintillation vial, a mixture of benzyl carbamate 2 (76 mg, 0.50 mmol, 1.0 eq.), ethyl glyoxylate hydrate in 50 % toluene (w/v) 1 (143 μL, 0.60 mmol, 1.2 eq.) and thionyl chloride (109 μL, 1.50 mmol, 3.0 eq.) were stirred under argon in anhydrous chloroform (5.0 mL) for 6 hours at 60 °C. The reaction mixture was cooled down to r.t. and directly evaporated under vacuum to obtain the desired product **4b** as a white solid (135 mg, 0.50 mmol, quant. yield). Compound **4b** can be stored in an amber glass container at r.t. for 14 days in a desiccator without major decomposition <5–10%). $\boldsymbol{R_f}$ = Caution!! Compound **4b** is not stable on silica gel; it hydrolyses back to the corresponding hemiaminal **3** which can be observed by TLC at the R_f mentioned above. **M.P.** = 117–119 °C. **IR** (Neat) ν_{max} =

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660, 694, 753, 778, 976, 1023, 1056, 1204, 1240, 1337, 1529, 1700, 1742 cm^{-1}. **^{1}H NMR** (400 MHz, CD_3CN): δ (ppm) 7.48–7.22 (m, 5H), 7.03 (bs, NH), 6.18 (d, *J* = 10.4 Hz, 1H), 5.16 (s, 2H), 4.26 (q, *J* = 7.1, 2H), 1.27 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ (ppm) 165.9 (C), 153.9 (C), 135.3 (C), 128.7 (2 CH), 128.6 (CH), 128.4 (2 CH), 68.1 (CH), 63.4 (CH2), 63.2 (CH_2), 13.9 (CH_3). **HRMS (ESI)**: Compound **4b** hydrolysed into the corresponding hemiaminal **3** in the mass spectrometer with m/z Calcd. for $[C_{12}H_{15}NO_5+Na]^+$ = 276.0842, found 276.0835 (−2.5 ppm). SMILES: ClC([H])(C(OCC)=O)NC(OCC1=CC=CC=C1)=O.

N-Cbz-α-bromoglycine ethyl ester 4c:

N-Protected α-bromoglycine **4c** was synthesized using the either following procedures:

In a flame dried scintillation vial, a mixture of benzyl carbamate **2** (76 mg, 0.50 mmol, 1.0 eq.), ethyl glyoxylate hydrate in 50 % toluene (w/v) 1 (143 μL, 0.60 mmol, 1.2 eq.), acetyl bromide (111 μL, 1.50 mmol, 3.0 eq.) and acetic acid (3 μL, 0.05 mmol, 0.1 eq.) were stirred in anhydrous chloroform (5.0 mL) for 6.5 hours under argon at room temperature. The reaction mixture was then evaporated under vacuum to obtain the desired product **4c** as a pale brown solid (157 mg, 0.50 mmol, quant. yield).

Alternatively, the title compound can be prepared in a flame dried scintillation vial, with a mixture of benzyl carbamate **2** (76 mg, 0.50 mmol, 1.0 eq.), ethyl glyoxylate hydrate in 50% toluene (w/v) 1 (143 μL, 0.60 mmol, 1.2 eq.) which were stirred in anhydrous chloroform (5.0 mL) under argon at −20 °C. Into the reaction mixture thionyl bromide (116 μL, 1.50 mmol, 3.0 eq.) was added dropwise and stirred for 15 min until full consumption of all starting materials. The reaction mixture was then evaporated under vacuum to obtain the desired product **4c** as a pale brown solid (158 mg, 0.50 mmol, quant. yield).

Compound **4c** can be stored in a brown glass container at r.t. in a desiccator for 7 days without major decomposition < 5 %). ***R*f** = Caution!! Compound **4c** is not stable on silica gel; it hydrolyses back to the corresponding hemiaminal **3** which can be observed by TLC at the R_f mentioned above. **M.P.** = 63–65 °C. **IR** (Neat) ν_{max} = 661, 752, 762, 776, 814, 844, 861, 910, 950, 992, 1112, 1144, 1230, 1274, 1333, 1367, 1381, 1396, 1525, 1700, 1736,

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3032, 3292 cm^{-1}. **^{1}H NMR** (400 MHz, CD_3CN): δ (ppm) 7.47–7.27 (m, 5H), 7.08 (bs, NH), 6.38 (d, *J* = 10.8 Hz, 1H), 5.17 (s, 2H), 4.26 (q, *J* = 7.1 Hz, 2H), 1.27 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ (ppm) 166.2 (C), 153.5 (C), 135.3 (C), 128.7 (2 CH), 128.7 (2 CH), 128.4 (CH), 68.2 (CH), 63.2 (CH_2), 53.4 (CH2), 13.9 (CH_3). **HRMS (ESI)**: Compound **4c** hydrolysed into the corresponding hemiaminal **3** in the mass spectrometer with m/z Calcd. for $[C_{12}H_{15}NO_5+Na]^+$ = 276.0842, found 276.0855 (+4.7 ppm).

SMILES: BrC([H])(C(OCC)=O)NC(OCC1=CC=CC=C1)=O.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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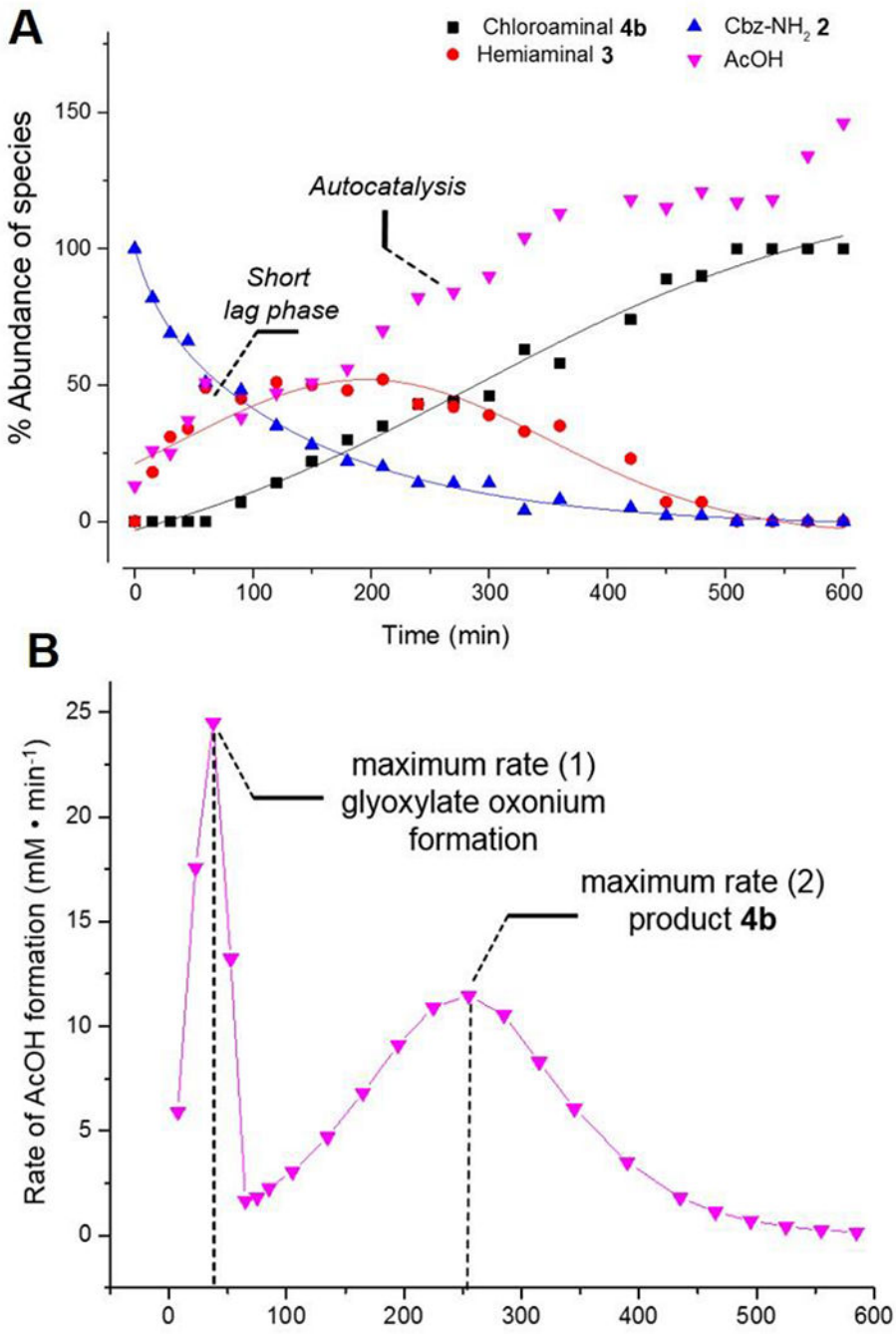

Figure 1.

Panel A: kinetic profile for the synthesis of α-chloroglycine **4b** at 60 °C (Table 1, entry 1) with best-fitted curves. **Panel B:** rate of AcOH formation with time suggesting an autocatalysis-like mechanism.

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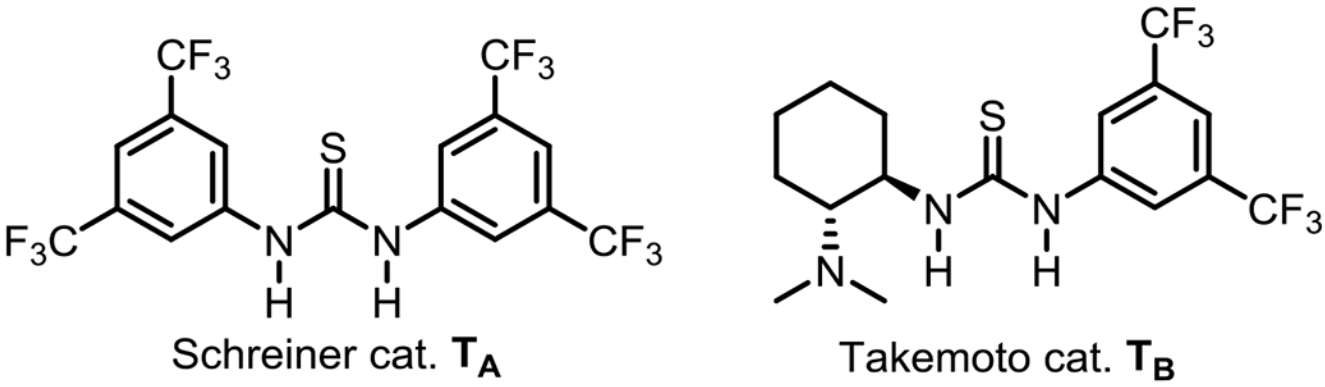

Figure 2.
Thiourea catalysts $\mathbf{T_{A,B}}$ used in this study.

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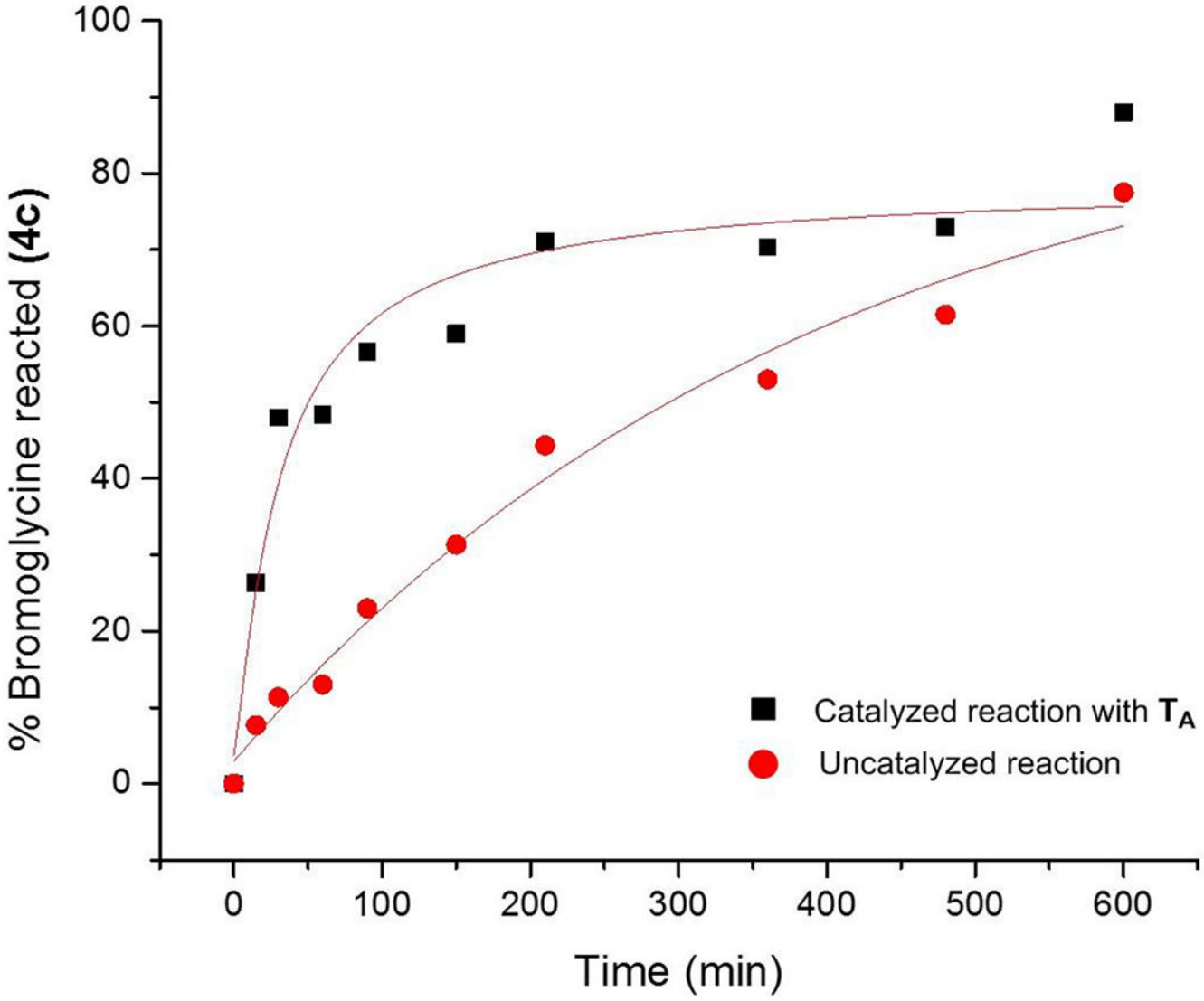

Figure 3.

Effect of the hydrogen-bond donor catalyst $\mathbf{T_A}$ on the arylation of α-bromoglycine **4c** with N-methyl indole.

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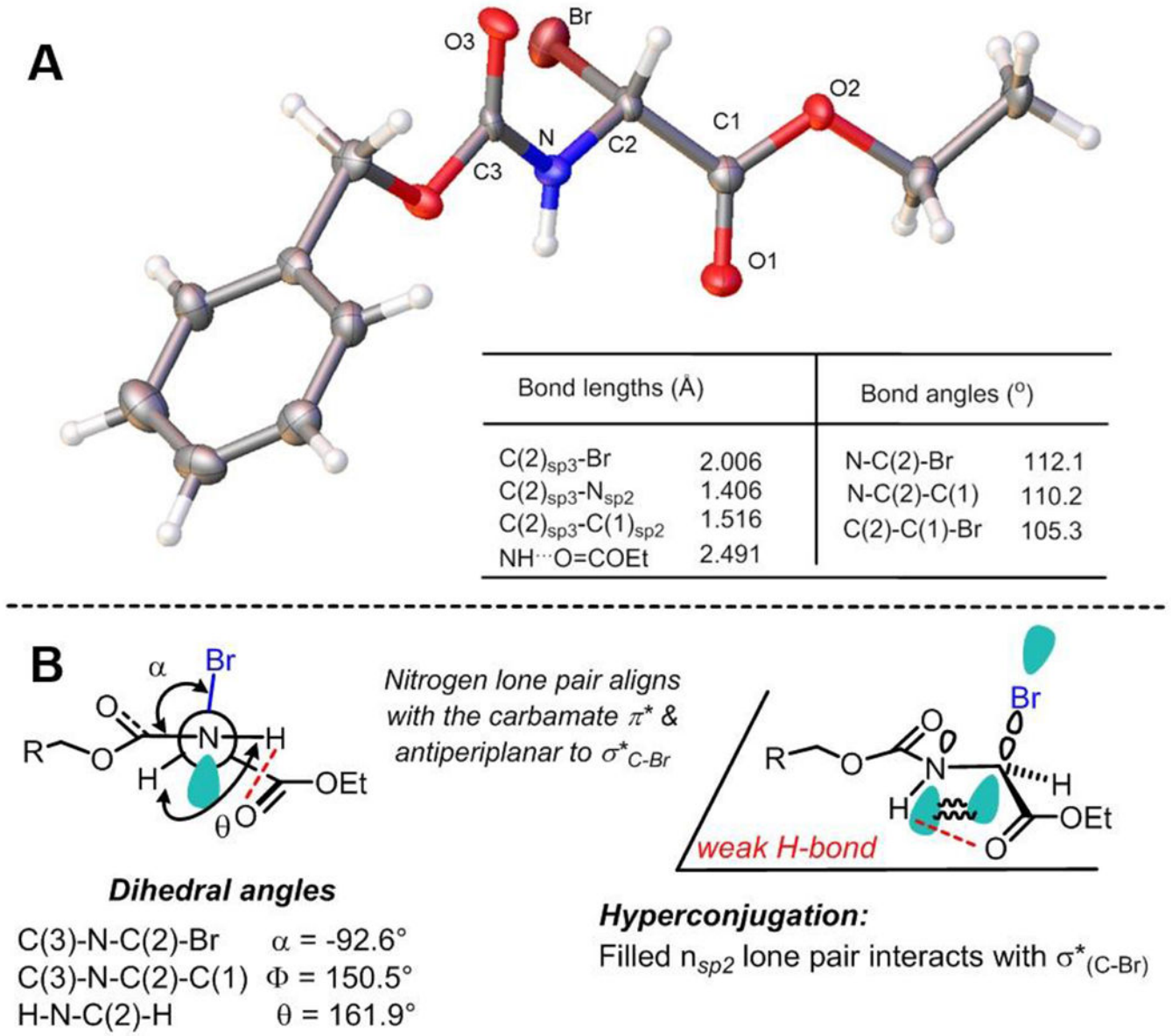

Figure 4.

Panel A: X-ray structure of α-bromoglycine ester **4c**. Ellipsoids are shown at the 50 % probability level. **Panel B:** model for hyperconjugation for the major conformer of **4c** in solution.

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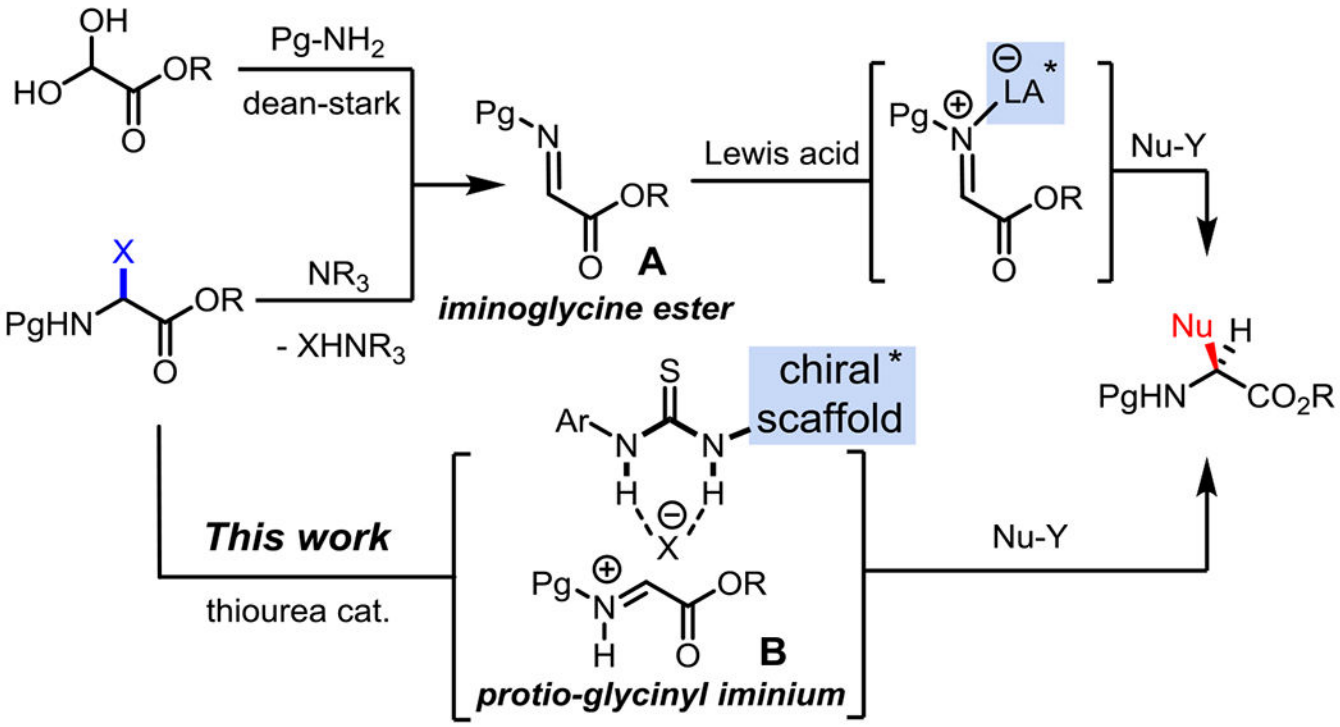

Scheme 1.

Asymmetric synthetic strategies toward α-amino esters from iminoglycine ester **A**, and an N-acyliminium equivalent **B**.

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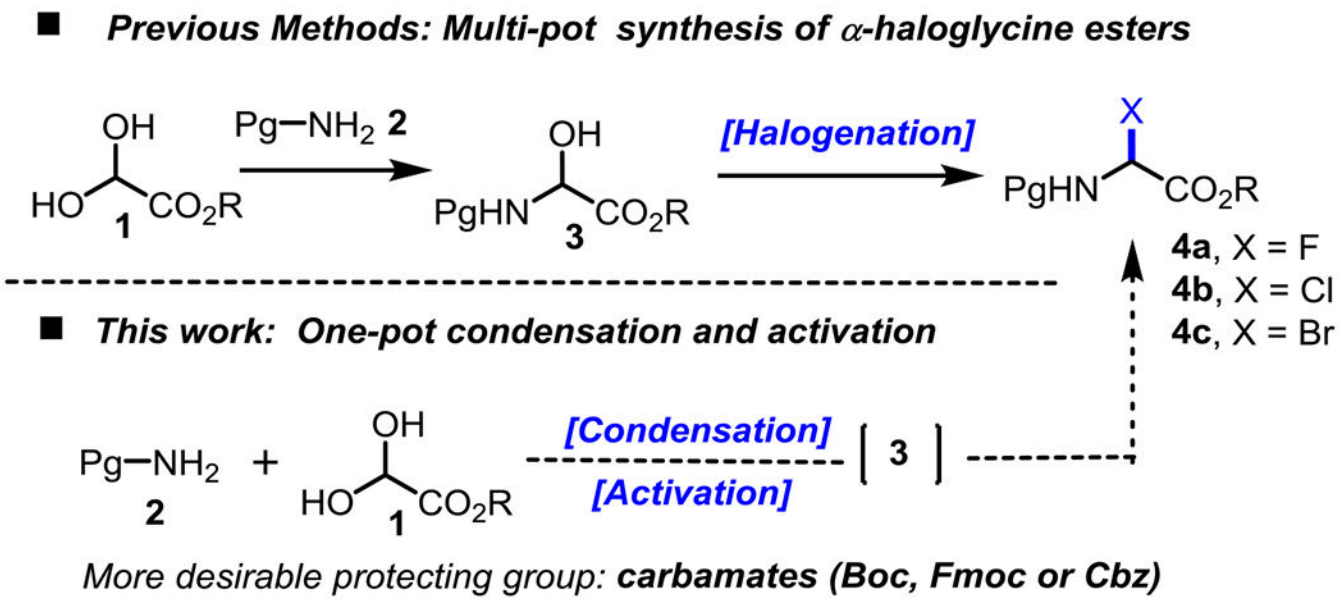

Scheme 2.
Synthesis of α-haloglycine esters.

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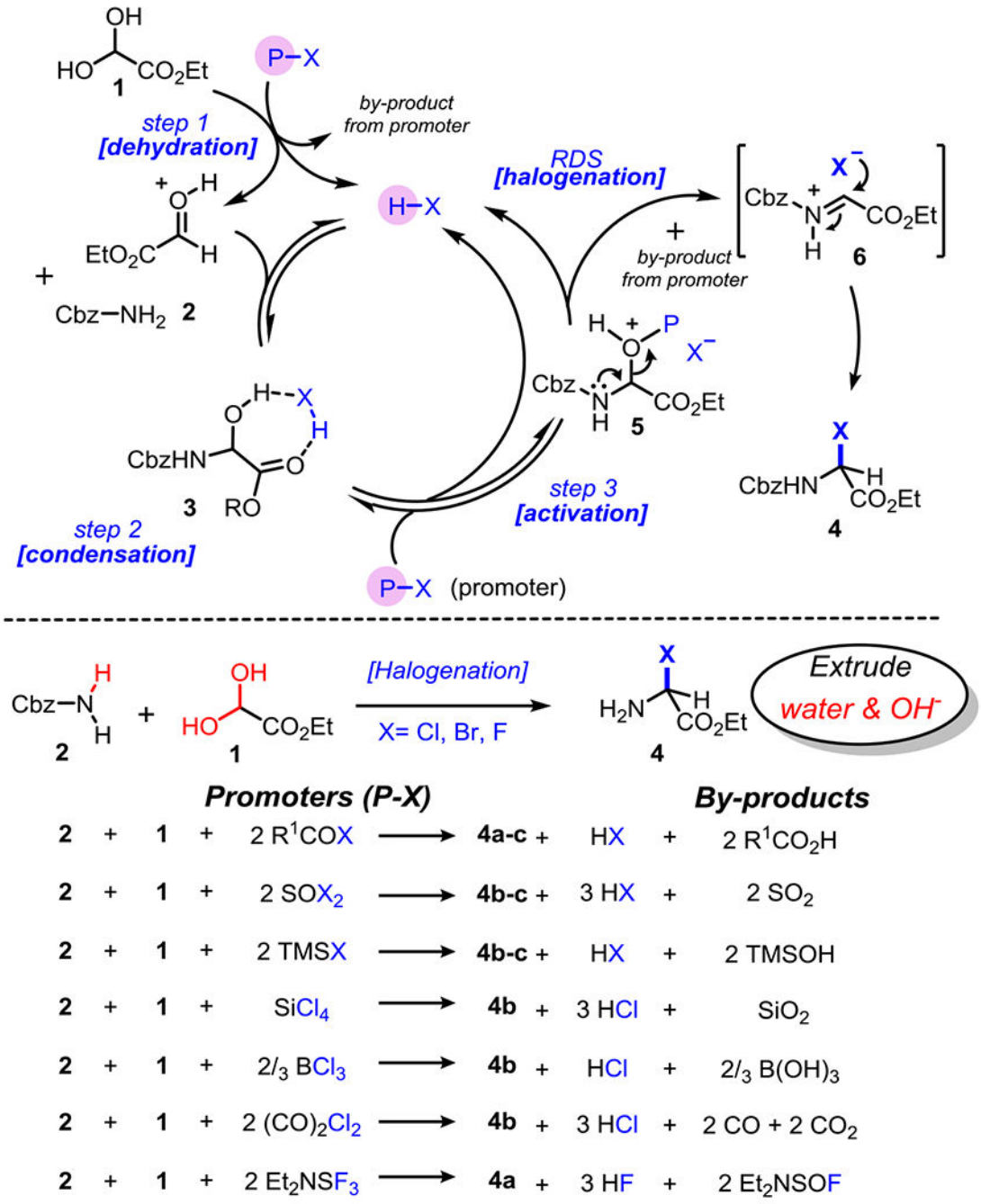

Scheme 3.
Proposed mechanism and reagents for the one-pot synthesis of α-haloglycine esters **4**.

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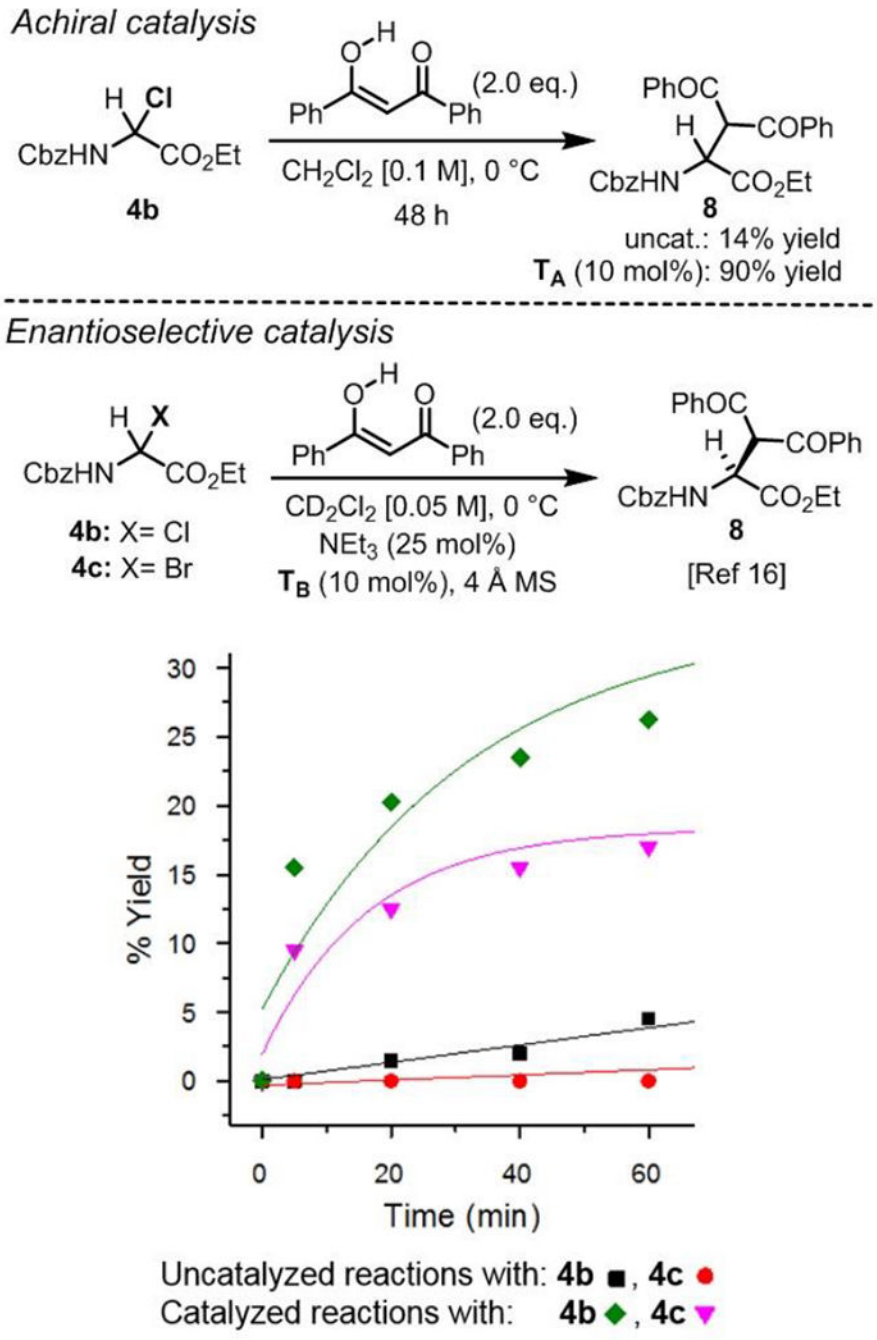

Scheme 4.

Effect of the hydrogen-bond donor catalyst $\mathbf{T_B}$ on the direct Mannich reaction of α-haloglycines **4b** and **4c**.

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Table 1.

Optimization studies to access α-haloglycines **4a-c** in one-pot.[a]

Entry	Promoter (eq.)	Temp	Time	Yield (%)[b]
1	AcCI (3.0)	RT	48 h	**4b** (62)
	AcOH (0.1)	60 °C	11 h	**4b** (100)
2	$SOCl_2$ (3.0)	RT	15 h	**4b** (100)
		60 °C	6 h	**4b** (100)
3	$SiCl_4$ (1.5)	35 °C	24 h	**4b** (100)
4[c]	BCl_3 (1.0)	0 °C	24 h	**4b** (0)
5	TMSCl (3.0)	RT	60 h	**4b** (89)
6	$(CO)_2Cl_2$ (3.0)	RT	18 h	**4b** (94)
7	AcBr (3.0)	RT	6.5 h	**4c** (100)
	AcOH (0.1)			
8	$SOBr_2$ (3.0)	−20 °C	15 mins	**4c** (100)
9	TMSBr (3.0)	RT	4 h	**4c** (100)
10[d]	BzF (3.0)	0 °C to 60 °C	72 h	**4a** (0)
	BzOH (0.1)			
11	Et_2NSF_3 (3.0)	0 °C to RT	72 h	**4a** (0)
12[e]	Et_2NSF_3 (3.0)	40 °C then −78 °C	15 h then 2 h	**4a** (100)
	AcOH(0.1)			

[a] ^{1}H NMR recorded in CD3CN, ^{a}H: **4a** (**F**), δ = 5.95 ppm (dd, J = 9.5, 53.7 Hz); **4b** (**Cl**), δ = 6.18 ppm (d, J = 10.4 Hz); 4c (**Br**), δ = 6.39 ppm (d, J = 10.8 Hz).

[b] Yields determined by ^{1}H NMR on crude reaction mixtures using mesitylene as internal standard.

[c] Complete decompostion of starting material Cbz-carbamate 2 was observed in presence of BCl_3.

[d] Hemiaminal **3** was formed (≈ 25 % conv.).

[e] Experiment run in in a a stepwise manner in CH_2Cl_2 for the condensation-deoxyfluorination.

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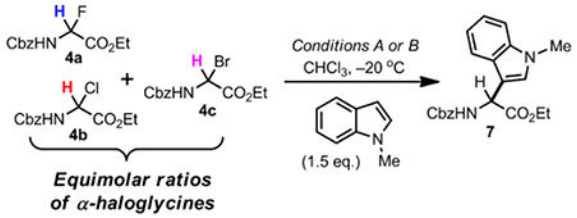
Table 2.

Cross-functionalization experiments to examine the competitive reactivity of α-haloglycine esters **4a–c**.[a–d]



Entry	Time (h)		0	0.25	0.5	1	1.5	2.5	3.5	6	8	10
1 Condition A *Uncat.*	α-haloglycine % consumption	**4a**	0	12	15	18	12	30	32	33	30	36
		4b	0	37	40	57	53	47	40[d]	47	50	43
		4c	0	8	14	14	24	32	43	54	59	76
	% Yield (**7**)		**0**	**9**	**11**	**12**	**14**	**19**	**20**	**28**	**29**	**37**
2 Condition B T_A (10 mol%)	α-haloglycine % consumption	**4a**	0	18	15	18	15	15	21	21	15	27
		4b	0	33	50	43	50	47	53	67	40	37[d]
		4c	0	27	49	49	57	59	70	70	73	86
	% Yield (**7**)		**0**	**20**	**23**	**25**	**29**	**32**	**36**	**40**	**43**	**45**

[a] Reactions performed on 0.5 mmol scale, conditions A: **4a–4c** (1.0 eq.), *conditions B:* **4a–4c** (1.0 eq.) with thiourea $\mathbf{T_A}$ (10 mol-%).

[b] The conversions were determined using ^{1}H NMR with mesitylene as internal standard, from reaction aliquots in $CHCl_3$ transferred in NMR tubes and adjusted to a mixture of $CHCl_3/CD_3CN$ (2:1) at low temperature.

[c] Average measurements are reported from triplicate experiments.

[d] A bromide-chloride exchange is likely occurring through an external ion-return between the two glycinyl iminium ion-pairs **6b:6c** (X = Br, Cl).

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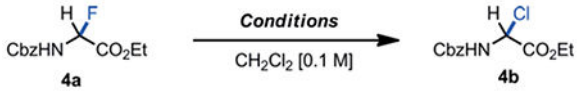
Table 3.

Halogen exchange on α-fluoroglycine esters **4a**.



Entry[a]	Conditions	Time	Temp	% Conv.[b]	% Yield[b,c]
1	TMSCl (66 mol%)	2 h	0 °C	72	45
2	TMSCl (100 mol%)	2 h	0 °C	82	82
3	TMSCl (130 mol%)	30 mins	−78 °C	23	20
4	TMSCl (130 mol%) **T_A** (10 mol%)	30 mins	− 78 °C	60	60
5	TMSCl (130 mol%) **T_A** (10 mol%)	1 h	*− 78 °C*	100	96[c]

[a] Reactions run on a 0.25 mmol scale.

[b] Conversions and Yields determined by ^{1}H NMR on crude reaction mixtures using mesitylene as internal standard.

[c] Isolated yield.