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A Broad Substrate Scope of Aza-Friedel-Crafts Alkylation for the Synthesis of Quaternary α-Amino Esters

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Abstract

A versatile synthetic protocol of aza-Friedel-Crafts alkylation has been developed for the synthesis of quaternary α-amino esters. This operationally simple alkylation proceeds under ambient conditions with high efficiency, regioselectivity, and an exceptionally broad scope of arene nucleophiles. A key feature of this alkylation is the role associated with the silver(I) salt counteranions liberated during the reaction. Taking advantage of a phase-transfer counteranion/Brønsted acid pair mechanism, we also report a catalytic enantioselective example of the reaction.

Graphical Abstract

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Author Contributions

S.S.S. and J.M. contributed equally to this work. This project was conceived by S.P.R. The manuscript was written through contributions of S.P.R. and G.Z. All authors have approved the final version of the manuscript.

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Supporting Information

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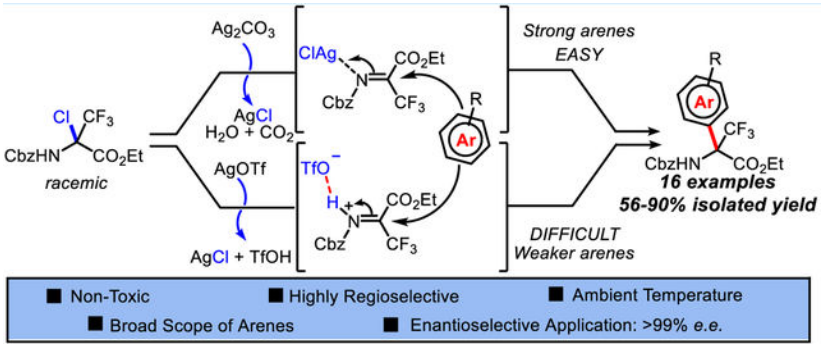
Tables of selected results from the reaction optimization screen at Eli Lilly, complete experimental procedures and characterization data, including ^{1}H, ^{13}C, and ^{19}F NMR spectra, and HPLC chromatograms for er determination (PDF)

The authors declare no competing financial interest.



α,α-Disubstituted α-amino acids found in carbonaceous chondritic meteorites[1] have been suggested to be at the origin of symmetry breaking (up to 20% ee) on earth, eventually leading to the homochirality (single enantiomeric form) of terrestrial proteinogenic α-amino acids.[2] Although several aspects of abiogenesis remain unclear, the role of α,α-disubstituted amino acids in transferring chirality to other proteinogenic α-amino acids renders these building blocks unique in nature. α,α-Disubstituted "quaternary" α-amino acids are also essential motifs of small molecules and nonribosomal peptides having a variety of biological activities (e.g., enzyme inhibitors, ion-channel blockers, or antibiotics).[3] Given that these building blocks are highly constrained compared to monosubstituted α-amino acids (Thorpe-Ingold effect), they impart valuable conformational rigidity when embedded in synthetic molecules.[4] Notably, α,α-disubstituted amino acids have a remarkable influence on peptide secondary structures, often producing well-defined helical conformations characteristic of many classes of biomolecules.[5] Even so, the asymmetric synthesis of this class of noncanonical amino acids remains mostly untapped and complicated.[6] On the other hand, fluorinated amino acids have recently attracted considerable attention owing to their unique medicinal and physicochemical properties (i.e., high stability to metabolic degradation, increased lipophilicity, and hydrogen bond acceptor ability).[7] Therefore, establishing a scalable and practical (optically active) synthesis of α,α-disubstituted α-trifluoromethyl amino esters is desirable.

In stark contrast to the activation of α-iminoglycinate **A** into iminium **B**, which is one of the most studied and versatile enantioselective strategies for synthesizing monosubstituted nonproteinogenic α-amino esters,[8] few diastereo-[9] and enantioselective[10] methods are currently available for the synthesis of acyclic α,α-disubstituted α-trifluoromethyl amino esters **4**. Indeed, the important electrophilicity of α-imino ester **3** results in a weak Lewis basicity of the imine nitrogen, seemingly contributing to a lack of reactivity toward Lewis and Brønsted acid catalysts (Scheme 1). Of particular interest, the synthesis of α,α-trifluoromethyl-aryl amino esters by Friedel-Crafts reactions remains challenging by both diastereo-[11] and enantioselective strategies.[12] Seemingly, the relatively harsh acidic conditions required for condensing amines with α-trifluoromethyl ketoesters often limit the choice of N-protecting groups, leading to a two-step condensation/dehydration with water scavengers via hemiaminal **1**.[13] A milder alternative was also devised from the direct aza-Wittig reaction with phosphazenes to prepare the most moisture-sensitive α-imino ester **3**.[14] The lack of convenient synthesis and reactivity of α-trifluoromethyl α-imino esters **3** (weak

Lewis basicity) combined with a high moisture sensitivity (hydration, **3** → **1**) are factors that largely hindered the use of this approach. To address this methodological gap, we initially envisioned avoiding the isolation of **3** by studying the direct reactivity of chloroaminal **2**. Given that glycinyl chloroaminals were successfully exploited as effective surrogates of α-iminoglycinates **A** by halide abstraction and anion binding catalysis for carbon-carbon bond formation at the α-center,[15] we intuitively hypothesized that if a similar maneuver could be achieved from a tetrasubstituted chloroaminal **2**, several classes of α,α-disubstituted α-trifluoromethyl amino esters **4** could become synthetically accessible. Herein, we report a highly practical and general Friedel-Crafts alkylation via a silver(I)-mediated halide abstraction combined with hydrogen bonding that enables the addition of a broad range of arene nucleophiles to the α-trifluoromethyl α-iminopyruvate **3**.[16]

The starting material, α-trifluoromethyl chloroaminals (±)-**2a** and (±)-**2b** bearing common *N*-carbamoyl protecting groups (Cbz or Fmoc), can be synthesized in >90% yield and kept intact for >8 weeks under low-moisture conditions. In collaboration with scientists from Eli Lilly, a silver(I)-mediated Friedel-Crafts alkylation of chloroaminal (±)-**2a** was extensively assessed through the screening of solvents, nucleophiles, and other reaction parameters on the Automated Synthesis laboratory (ASL) platform.[17,18] As a result of this screen, a couple of silver(I) salts emerged as efficient stoichiometric reagents capable of generating Friedel-Crafts products cleanly via a putative halide abstraction mechanism.[19] The initial results obtained via the robot synthesizer were further optimized manually to study both reaction intermediates (e.g., **3**) and any potential byproducts formed during the reaction by ^{1}H and ^{19}F NMR (Table 1). Indeed, using Ag_2CO_3 as a promoter, the halide abstraction took place rather slowly, leading to ~60% conversion of imine **3** after 4 h (entries 1 and 2). The reaction carried out without a desiccant (entry 1) produced imine **3**, which rapidly transformed into hemiaminal **1** (~1:1 ratio after 4 h), leading to a >95% yield of **1** after 24 h. The same reaction in the presence of molecular sieves delivered imine **3** in a quantitative manner as the sole reaction product (entry 2). Initial Friedel-Crafts conditions were tested with rather weak π-nucleophile arenes (entries 3 and 4) such as furan **5a** (N ~ 1.3) and 1,3-dimethoxybenzene **5b** (N ~ 2.5).[20] In both cases, the desired arylation did not take place as suggested by the large amount of imine **3** being formed over time (>95% NMR yield). These results suggest that arenes **5a** and **5b** are not nucleophilic enough to engage in the Friedel-Crafts alkylation with imine **3**. Therefore, a stronger nucleophile, *N*-methylindole **5c** (N ~ 5.8), was tested under the same reaction conditions. While small amounts of imine **3** were observed, the desired product **4c** formed rapidly over the course of the reaction (entry 5, ≤98% NMR yield after 24 h). To circumvent the lack of reactivity of weak arene nucleophiles and expand the initial success to a broader scope of arenes, other common silver salts were evaluated.[18] While reactions with AgOAc or the more ionizing $AgBF_4$ and $AgSbF_6$ do not deliver the desired Friedel-Crafts products, several silver salts such as $AgNO_3$, AgOTs, and AgOTf enabled the reaction to occur with **5b** as the nucleophile. Optimum reactivity was observed with AgOTf, leading to the formation of arylated product **4b** in a 36% yield (entry 6). Reaction conditions were further optimized by evaluating several solvents and concentrations.[18] Reactions in diethyl ether showed a cleaner profile, leading to the formation of **4b** in 54% and 71% yields at concentrations of 0.1 and 0.3 M, respectively (entries 7 and 8, respectively). The presence of molecular sieves in addition to AgOTf did

not affect the reaction outcome, leading to the full conversion of (±)-**2a** after only 1 h, but significant amounts of hemiaminal intermediate **1** persisted [entries 6–8 (*vide infra*)]. The fact that imine **3** was not observed in these reactions suggested that AgOTf or TfOH, a byproduct of halide abstraction, might account for activating imine **3** in the Friedel-Crafts alkylation.

Two silver-mediated methods therefore emerged to cover a broad scope of arene nucleophiles encompassing (a) electron-rich substrates using Ag_2CO_3 and (b) electron-poor arenes by switching the reagent to AgOTf (Scheme 2). For reactions mediated by Ag_2CO_3 (0.75 equiv), reaction times varied from 18 to 72 h to deliver the quaternary α-trifluoromethyl amino esters **4c-j** in a range of yields of 56–89% with high regioselectivity in most cases. Using the same method, Fmoc-chloroaminal (±)-**2b** can also be functionalized in good yield, as shown by the synthesis of **4f** in 89% yield. Interestingly, reactions with 1,3-dimethoxybenzene ($N \sim 2.5$) did not proceed after 3 days under these conditions, or at a higher temperature, thus delineating the limit of reactivity of Ag_2CO_3-mediated Friedel-Crafts alkylation. Even so, the reactivity of **3** with weaker π-nucleophiles ($N \leq 2.5$) requires the use of AgOTf (2.0 equiv) to promote the Friedel-Crafts reactions. Under the optimum reaction conditions described in Scheme 2, reaction times could be decreased (<3 h) and α-trifluoromethyl amino esters **4a**, **4b**, and **4k-p** were obtained in a remarkable range of yields of 71–90% with high regioselectivity.

Given the innate sensitivity of the ^{19}F nucleus, and the large chemical shift dispersion $\delta_F(CF_3)$ observed among the starting material **2** (−76.14 ppm), products **4b** and **4c** (−71.20 and −71.70 ppm, respectively), imine **3** (−70.05 ppm), and hemiaminal **1** (−80.63 ppm), reactions can be easily and quantitatively monitored by ^{19}F NMR spectra calibrated on C_6F_6 (see Scheme 3A).[21] To test our reactivity hypothesis, imine **3** was synthesized, isolated (highly hydroscopic → **1**), and further reacted with the moderately reactive arene **5b** ($N \sim 2.5$) and stoichiometric amounts of either AgOTf, Ag_2CO_3, or catalytic TfOH (Scheme 3B). Analysis of reaction progress by ^{19}F NMR revealed no measurable formation of **4b** in the presence of silver salts, while using 30 mol % TfOH afforded product **4b** in 37% yield. The innate electrophilicity of imine **3** was further evaluated with arenes **5b**, **5h**, and **5i** without any external additive. Arenes **5b** and **5i** were shown to be unreactive, while pyrrole **5h** ($N \sim 4.6$) reacted adequately with **3** (20% yield). The electrophilicity factor of imine **3** can therefore be roughly estimated to be $E = -5.0 - [(3.6 + 4.6)/2] = -9.1$,[20b] which is in line with some of the most electrophilic imines reported to date in the empirical Ofial-Mayr reactivity scale.[22] Taken together, these results suggest that the TfOH byproduct formed during halide abstraction on **2** plays a pivotal role in catalyzing the Friedel-Crafts alkylations.[11a] With this piece of mechanistic information, a catalytic enantioselective activation of imine **3** was evaluated with (*R*)-TRIP as the Brønsted acid catalyst and indole **5d** as the arene nucleophile.[23] While the uncatalyzed reaction yielded (±)-**4d** in 20% as a single C3 regioisomer, the TRIP-catalyzed reaction delivered the same regioisomer product (+)-**4d** (79:21 er) along with the C2 regioisomer in a 86:14 ratio. The C2/C3 regioisomers could not be separated by either silica gel chromatography or reverse-phase HPLC, but the comparable er and rr suggest that (+)-**4d** might be obtained with high enantiomeric purity.[18]

Given the role played by TfOH and (*R*)-TRIP as Brønsted acid catalysts in the key C-C bond-forming step from imine **3**,[24] we became interested in evaluating such a catalyst in combination with Ag_2CO_3 for halide abstraction. In principle, the cooperative action of an achiral transition metal with a chiral Brønsted acid could translate into a chiral counteranion catalysis approach (Scheme 4).[25] In this reaction, (*R*)-TRIP should be easily deprotonated by Ag_2CO_3, leading to a transient silver phosphate catalyst which could further achieve the halide abstraction and a phase transfer resulting in a chiral iminium-phosphate pair **6**. An iminium/imine equilibrium **6**/**6′** might be operating due to the low Brønsted basicity of imine **6′**, likely leading to a H-bonding catalysis for the facial enantiodiscrimination of imine **6′**. The addition of indole **5d** was selected as a model reaction. We tested this approach with the enantiopure (*R*)-TRIP phosphoric acid catalyst (10 mol %) and observed that lower loadings of Ag_2CO_3 (0.6 equiv) and molecular sieves (50 wt %) reduced the proportion of the undesired C2 regioisomer.[18] Under the optimized conditions, (+)-**4d** was obtained in 85% yield with a 90:10 er and a 91:09 rr. Crystallization of an EtOAc/EtOH solution of **4d** by slow evaporation delivered (+)-**4d** in the mother liquor as a single regioisomer with an er of >99.5:0.5. The residual solid was analyzed and shown to be rich in the C2 regioisomer (80:20 rr), similar to the measured er of 78:22. Taken together, these results suggest that the enantiodiscrimination induced by the TRIP catalyst is remarkable at rt (>99% ee), yet further optimizations will be necessary to avoid the formation of regioisomers. The Friedel-Crafts alkylation with indole **5d** was successfully scaled up to 1.0 mmol of (±)-**2a** with 5 mol % TRIP catalyst loading to afford product (+)-**4d** in 70% yield and >99% ee, which is more efficient than the original reaction of Bolm at −78 °C.[11] In comparison to this study, the absolute configuration of α-amino ester (+)-**4d** should be (*R*) as depicted.

In summary, a versatile aza-Friedel-Crafts alkylation has been developed for the synthesis of quaternary α-trifluoromethyl-aryl amino esters. The combined halide abstraction/alkylation process is operationally simple under ambient conditions, highly efficient, regioselective, and amenable to a remarkable broad scope of arenes, spanning 6 orders of magnitude in nucleophilicity (indole, $5.5 \geq N \geq -1.2$, anisole). The key feature of this reaction is the role associated with the silver(I) salt counteranions. In the course of silver-mediated halide abstraction, the silver counteranion is liberated as a conjugated Brønsted acid, likely resulting in an H-bond activation of the trifluoromethyl imine intermediate. This putative mechanism was exploited by replacing the achiral silver counteranion with a chiral phosphate in a catalytic enantioselective phase-transfer counteranion/Brønsted acid pair system to achieve an initial example of halide abstraction and aza-Friedel-Crafts alkylation with high stereoinduction (>99% ee). Further development of this asymmetric aza-Friedel-Crafts methodology for the synthesis of novel quaternary α-amino esters is of ongoing interest to our group. Ultimately, we anticipate that the present study will offer a useful new approach for the asymmetric synthesis of several classes of quaternary α-trifluoromethyl α-amino esters.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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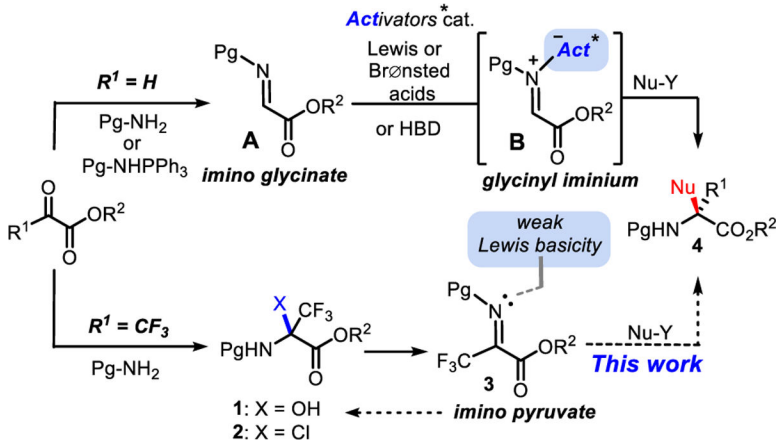
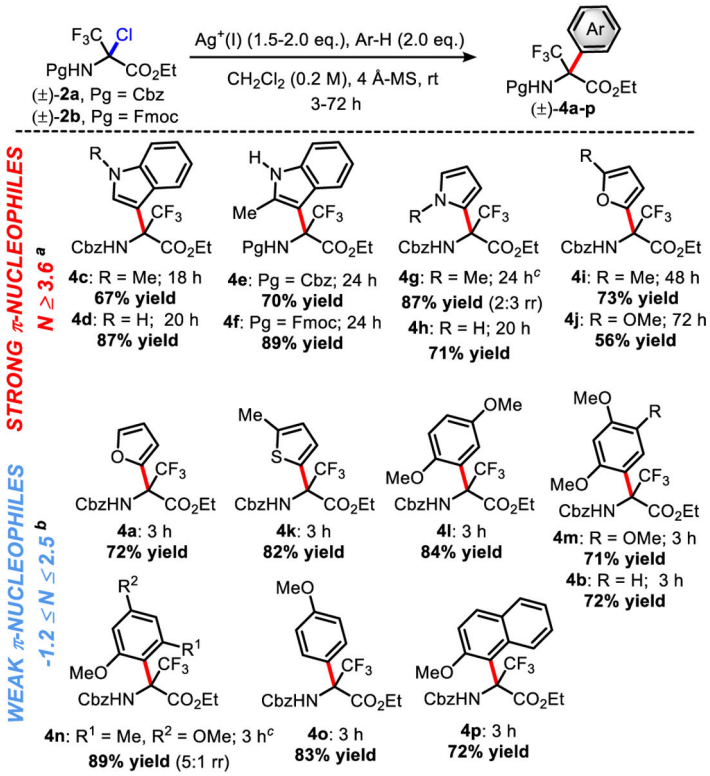


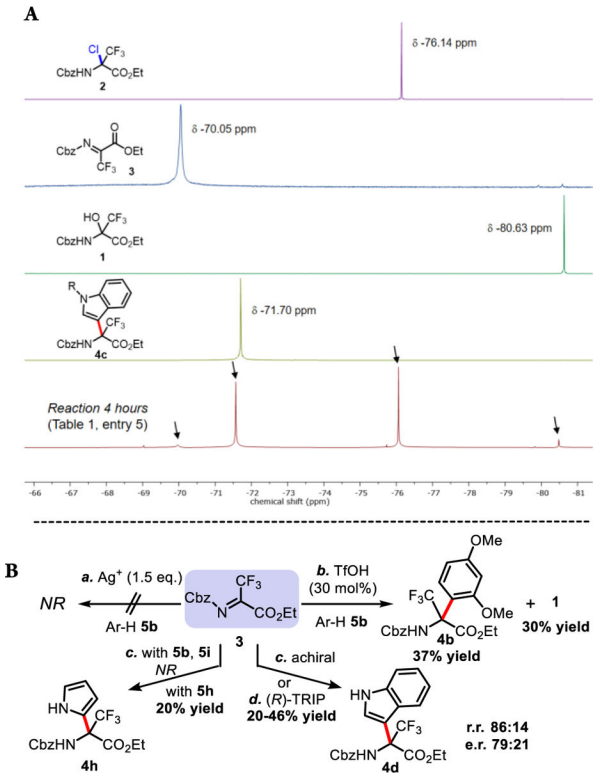
Scheme 1.

Challenging Activation of α-Trifluoromethyl Imino Pyruvate versus the Typical Imino Glycinate Reactivity



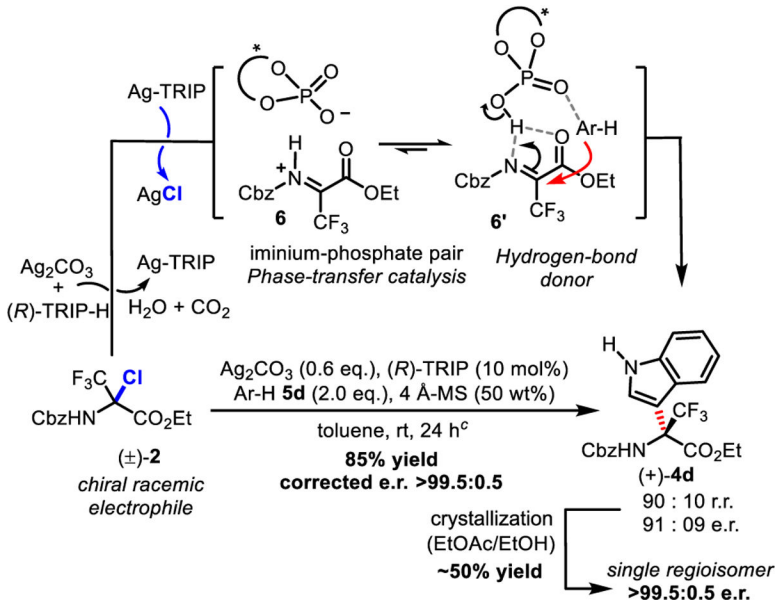
Scheme 2. Substrate Scope for the Synthesis of *α,α*-Disubstituted Amino Esters 4a-p by Friedel-Crafts Reactions[a–b–c]

[a]Standard reactions carried out on a 0.2 mmol scale for **2** (1.0 equiv) with arenes **5a-o** (2.0 equiv) in CH_2Cl_2 (0.2 M) with Ag_2CO_3 (0.75 equiv). Isolated yields reported. [b]Standard reactions carried out on a 0.2 mmol scale for **2** (1.0 equiv) with arenes **5a-o** (2.0 equiv) in CH_2Cl_2 (0.2 M) with AgOTf (2.0 equiv). Isolated yields reported. [c]Major regioisomers drawn for the sake of simplicity. Regioisomers separated by chromatography (see the Supporting Information).



Scheme 3. (A) Reaction Profile Monitored by ^{19}F NMR[a] and (B) Mechanistic Information from Control Experiments[b]

[a]Crude reactions analyzed by ^{1}H and ^{19}F NMR with C_6F_6 as the internal chemical shift reference set at −161.64 ppm in $CDCl_3$. [b]Reagents and conditions for imine **3** (1.0 equiv) with arenes **5b**, **5d**, **5h**, and **5i** (2.0 equiv) at rt: (a) AgOTf or Ag_2CO_3 (Ag^+, 1.5 equiv) in $CDCl_3$, no reaction observed; (b) TfOH (30 mol %) in $CDCl_3$; (c) 4 Å molecular sieves (50 wt %) in $CDCl_3$; (d) 4 Å molecular sieves (50 wt %) with (*R*)-TRIP (10 mol %) in $CDCl_3$ for 24 h, C3/C2 rr of 86:14, (+)-**4d** er determined by chiral NP-HPLC analysis.

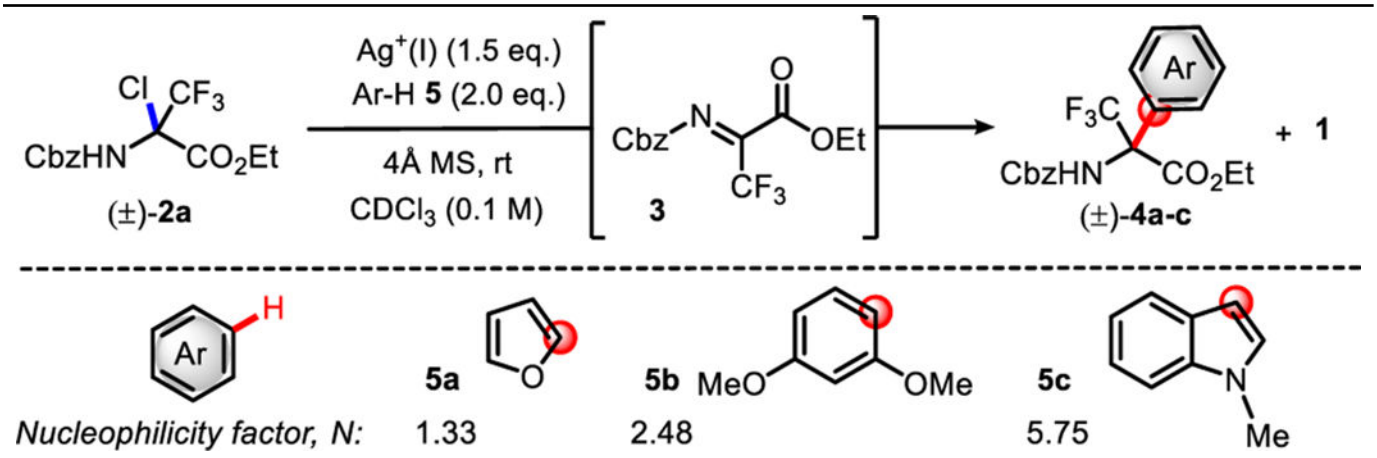


Scheme 4. Application to an Enantioselective Catalytic Aza-Friedel-Crafts Transformation[a–c]

[a]er determined by NP-HPLC using an enantiodiscriminating Chiralcel OD-H stationary phase, and rr determined by ^{19}F NMR. [b]The estimated er should be corrected on the basis of the measured rr given that the minor C3 regioisomer co-elutes with the minor enantiomer (−)-**4d** in NP-HPLC (see the text for explanations). [c]Reactions carried out at −20 and −78 °C afforded product (+)-**4d** with a similar er.

Table 1.

Reaction Optimization[a,b]



entry	arene	silver source	conversion ratio (2:3:1:4)[b] 1 h	conversion ratio (2:3:1:4)[b] 4 h	product yield[b,c] (%) 1 day
1[d]	-	Ag_2CO_3	66:34:0:0	25:40:35:0	>95 (**1**)
2	-	Ag_2CO_3	61:36:3:0	39:59:2:0	98 (**3**)
3	**5a**	Ag_2CO_3	53:45:2:0	17:78:5:0	>95 (**3**)
4	**5b**	Ag_2CO_3	70:2:2:0	26:70:1:0	>98 (**3**)[e]
5	**5c**	Ag_2CO_3	54:9:5:32	36:9:5:50	98 (**4c**)
6	**5b**	AgOTf	42:0:17:20	0:0:16:15	36 (**4b**)
7[f]	**5b**	AgOTf	0:0:32:42	0:0:52:33	54 (**4b**)
8[f,g]	**5b**	AgOTf	0:0:40:39	0:0:24:53	71 (**4b**)

[a]Reactions were carried out under argon with **2** (0.10 mmol) with arenes **5a-c**(2.0 equiv), silver reagent [1.5 equiv in Ag(I)], and 30 mg of 4 Å molecular sieves in $CDCl_3$ (2.0 mL).

[b]NMR ratios and yields determined for the crude reaction mixture by ^{19}F NMR with C_6F_6 as the internal standard.

[c]NMR yields determined for the crude reaction mixture by ^1H NMR with mesitylene as the internal standard.

[d]Reaction carried out without 4 Å molecular sieves.

[e]The reaction was also carried out at higher temperatures (up to 60 °C), and the formation of **4b** was not observed.

[f]Reaction carried out in anhydrous Et_2O.

[g]Reaction carried out at 0.3 M.