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α-Halo Amides as Competent Latent Enolates: Direct Catalytic Asymmetric Mannich-type Reaction

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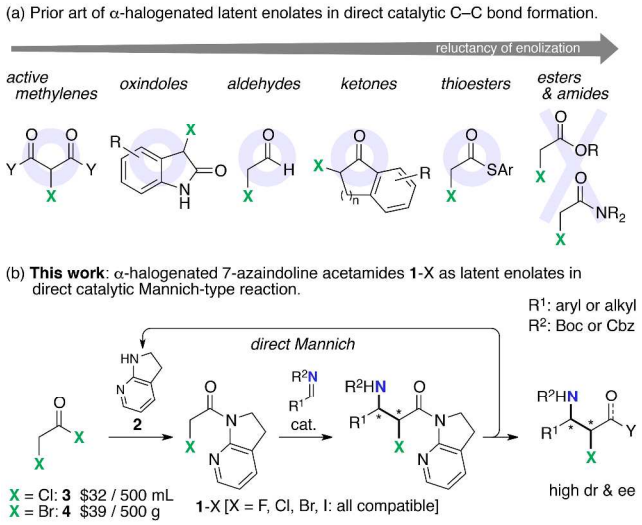
ABSTRACT: α-Halogenated carbonyl compounds are susceptible to dehalogenation and thus largely neglected as enolate precursors in catalytic enantioselective C–C bond forming reactions. By merging the increased stability of the α-C-halogen bond of amides and the direct enolization methodology of the designed amide, we explored a direct catalytic asymmetric Mannich-type reaction of α-halo 7-azaindoline amides with *N*-carbamoyl imines. All α-halo substituents, α-F, -Cl, -Br, -I amides, were tolerated to provide the Mannich-adducts in a highly stereoselective manner without undesirable dehalogenation. The diastereoselectivity switched intriguingly depending on the substitution pattern of the aromatic imines, which is ascribed to stereochemical differentiation based on the open transition state model. Functional group interconversion of the 7-azaindoline amide moiety of the Mannich-adducts and further elaboration into a diamide without dehalogenation highlight the synthetic utility of the present protocol for accessing enantioenriched halogenated chemical entities.

Introduction

Chlorinated and brominated compounds comprise a large family of biologically active natural products,[1] leading to the pursuit of halogen-containing drug candidates as well as their fluorinated analogs. The growing interest and demand for halogenated chemical entities motivated the development of new protocols to incorporate halogen atoms into the carbon frameworks of interest in a highly stereoselective manner. A commonly adopted method of accessing this class of compounds, particularly those bearing halogen atoms at the stereogenic carbon, is functionalization of double bonds triggered by halenium cations and their equivalents.[1g] For target-oriented synthesis of these halogenated compounds, merging the C–C bond construction stage and the introduction of halogen atoms offers a more direct option with better step economy. In light of the wide applicability of enolate chemistry, enantioselective coupling of α-halogenated enolate and electrophiles is a viable option toward achieving this aim. Although catalytic enolization of highly reactive 2-halo-1,3-dicarbonyl compounds[2] and 3-halooxindoles[3] is well-explored for producing halogen-bearing enolate precursors, α-halogenated monocarbonyl compounds are rarely exploited in reactions triggered by catalytic enolization (Scheme 1a). The C-halogen bond at the α-position of carbonyl is labile and this has been exploited for catalytic dehalogenative enolization.[4] Catalytic deprotonative enolization of α-halo thioesters with retention of the C-halogen bond was demonstrated by Coltart et al. for diastereoselective aldol reactions using a $MgBr_2$/amine binary catalytic system.[5] Enantioselective entry was reported using α-chloroaldehydes via enamine catalysis, which allowed for direct Michael reactions with reactive 1,1-

Scheme 1. The Art of Enolization of α-Halocarbonyls



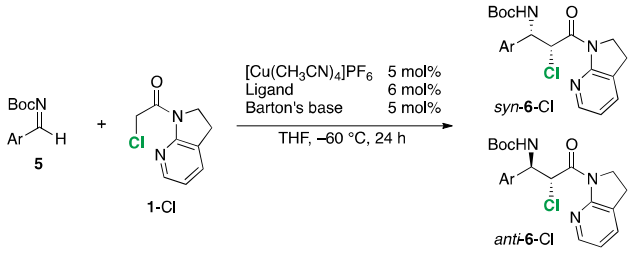
bissulfonylethene[6] or fluorination with NFSI.[7] Recently, Trost et al. documented catalytic enolization of cyclic ketones bearing α-chloro and bromo substituents in this Mannich-type reaction manifold with high stereoselectivity.[8] The scarcity of catalytic enantioselective C–C bond forming reactions involving in situ catalytic enolization of α-halo monocarbonyl compounds, however, prompted us to apply our amide enolization protocol to produce enantioenriched products with halogens on a stereogenic carbon. 7-Azaindoline amides, which we developed as latent enolates operative in a cooperative catalytic system,[9,10] can be readily prepared with an α-chloro or α-bromo substituent from inexpensive haloacetyl halides (Scheme 1b). Amide carbonyl is the least reactive of the series of carbonyl functionalities, and likely suppresses undesired dehalogenation. Herein we report the proficiency of α-halogenated 7-azaindoline acetamides **1** for catalytic enoliza-

tion in enantioselective Mannich-type reactions with *N*-carbamoyl imines;[11] *all* α-halo substituents, F, Cl, Br, and I were tolerated. In particular, α-Cl and α-Br amide **1**-Cl and **1**-Br, which conform to naturally abundant chlorinated and brominated compounds, were readily prepared from inexpensive commercial sources **3** and **4** with 7-azaindoline **2**,[12] which can be recovered after synthetic elaboration of the Mannich products.

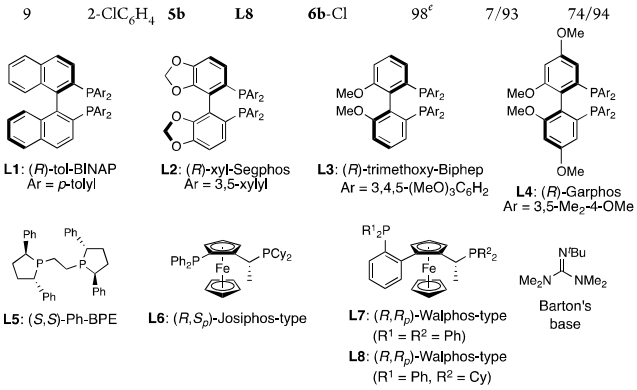
Results and Discussion

Given the abundance of chlorinated natural products, we began our study with a Mannich-type reaction of α-chloro-7-azaindoline amide **1**-Cl with *N*-Boc-imine **5a**. Based on our previous findings that Cu(I)/Barton's base catalytic system facilitated the enolization of 7-azaindoline amides,[9] suitable reaction conditions quickly emerged following a brief survey of chiral ligands (Table 1). While biaryl-type bisphosphine ligands **L1**–**L4** afforded encouraging enantioselectivity, the diastereoselectivity was generally poor and variable conversions were observed (entries 1–4). Chiral alkylphosphine ligand (*S*,*S*)-Ph-BPE **L5** afforded *syn*-**6**-Cl with excellent enantioselectivity, albeit with a small preference for the *syn* isomer (entry 5). A possible primary reason for the low diastereoselectivity is the less tractable prochiral face selection of imine **5a**; the absolute configuration at the α-position was mostly identical for both *syn*/*anti* diastereomers and the prochiral face-selection of in situ-generated Cu(I)-enolate of **1**-Cl was generally well-controlled. This tendency led us to use structurally distinct chiral phosphine ligands **L6**–**L8** with a ferrocene framework. Although a poor outcome was realized with (*R*,S_p)-Josiphos **L6** (entry 6), Walphos-type ligands **L7** and **L8** outperformed other chiral ligands, and in particular, **L8,** having a dicyclohexylphosphine unit, delivered *syn*-**6a**-Cl in 87% isolated yield with high diastereo- and enantioselectivity (entries 7,8). Unexpectedly, aromatic imine **5b** with a Cl-substituent at the *o*-position switched the diastereoselectivity to predominantly afford *anti*-**6b**-Cl with high enantioselectivity.[13] The identical absolute configuration at the α-position

Table 1. Evaluation of Chiral Ligands[a]

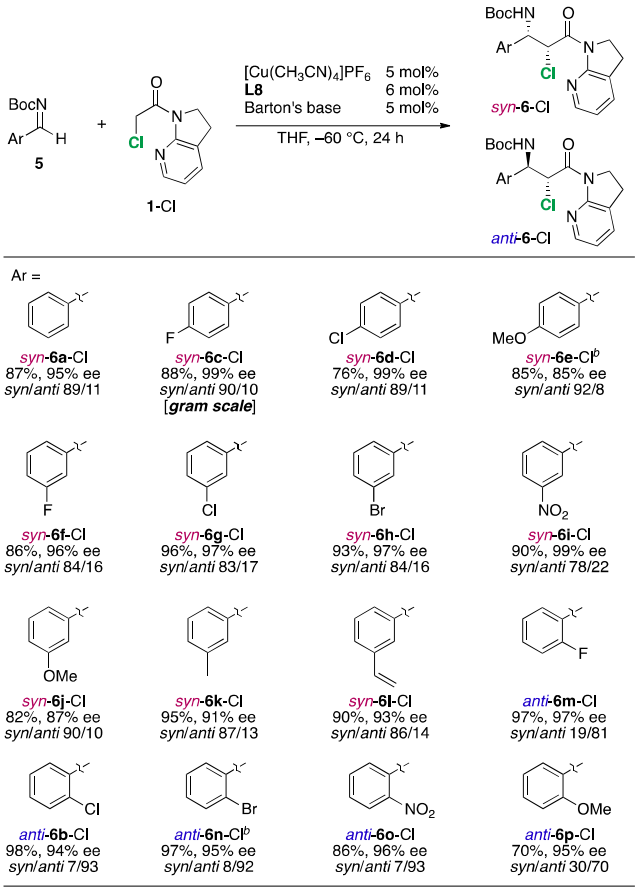


entry	imine **5** Ar =		Ligand	product	yield (%)[b]	*syn*/*anti*[c]	ee (%)[d] *syn*/*anti*
1	Ph	**5a**	**L1**	**6a**-Cl	5	39/61	80/91
2	Ph	**5a**	**L2**	**6a**-Cl	90	52/48	–6/72
3	Ph	**5a**	**L3**	**6a**-Cl	3	22/78	95/95
4	Ph	**5a**	**L4**	**6a**-Cl	67	54/46	53/77
5	Ph	**5a**	**L5**	**6a**-Cl	81	62/38	98/64
6	Ph	**5a**	**L6**	**6a**-Cl	7	43/57	84/73
7	Ph	**5a**	**L7**	**6a**-Cl	93	76/24	94/65
8	Ph	**5a**	**L8**	**6a**-Cl	87[e]	89/11	95/96
9	2-ClC_6H_4	**5b**	**L8**	**6b**-Cl	98[e]	7/93	74/94



[a]**5**: 0.2 mmol, **1**-Cl: 0.1 mmol, 0.4 M on **1**-Cl. [b]Determined by ^{1}H NMR analysis of the crude mixture with 3,4,5-trichloropyridine as an internal standard. [c]Determined by HPLC analysis. [d]Determined by HPLC analysis. Negative sign indicates opposite enantiomer was obtained as a major product. [e]Isolated yield.

Table 2. Substrate Scope of Monosubstituted *N*-Boc Imines 5 in Direct Catalytic Asymmetric Mannich-type Reaction of 1-Cl[a]

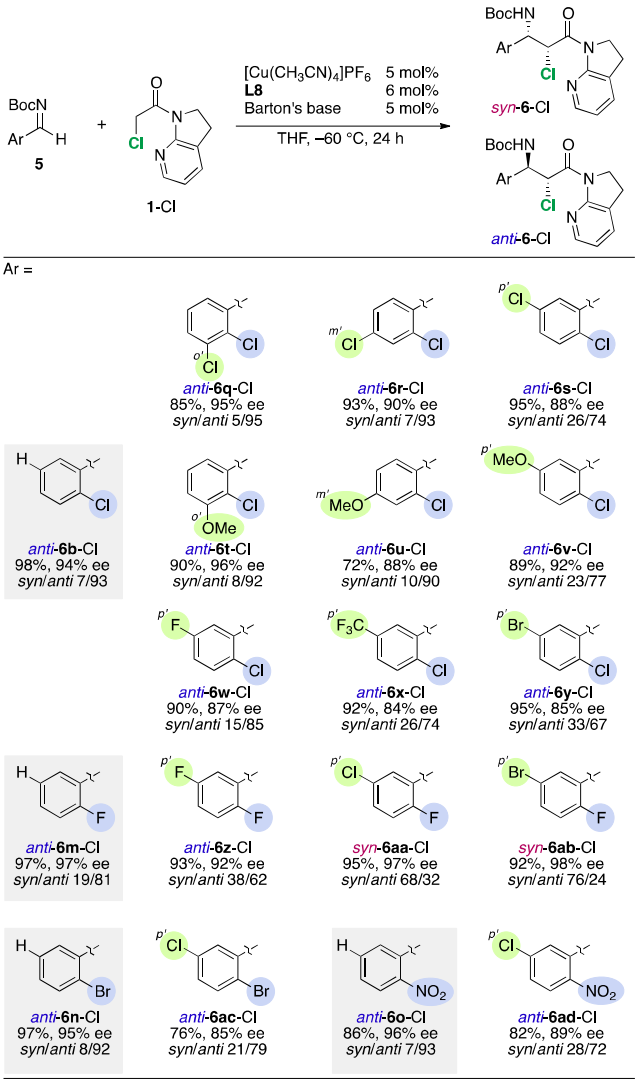


[a]**5**: 0.2 mmol, **1**-Cl: 0.1 mmol, 0.4 M on **1**-Cl. Isolated yields are reported. Enantioselectivity of the major diastereomers is presented. [b]Run with 10 mol% of catalyst.

of the major enantiomers implied that the prochiral face selection was altered by the presence of an *o*-substituent (*vide-infra*). The catalyst comprising Cu(I)/**L8**/Barton's base was widely effective for the direct Mannich-type reactions of **1**-Cl with both aromatic and aliphatic imines (Table 2–4). In contrast to the highly labile nature of α-Cl carbonyl compounds, the thus-obtained α-Cl-β-NHBoc amides exhibited sufficient stability, and no substitution/β-elimination/aziridination was detected during the work-up and chromatographic separation. Table 2 summarizes the scope of aromatic imines preferentially affording the *syn*-adduct when imines **5** without *o*-substituents were used. Generally high enantioselectivity was observed with imines bearing halogen (**5c**,**d**,**f**–**h**), nitro (**5i**), Me (**5k**), and vinyl (**5l**) substituents at the *m* or *p*-positions, while MeO substituted imines (**5e**,**j**) afforded somewhat lower enantioselectivity. The present Mannich protocol was scalable to at least a gram scale without any detrimental effects on conversion or stereoselectivity (**5c**). As noted above, the presence of *o*-substituents altered stereoselection to give the *anti*-adduct as the major diastereomer, not only for *o*-Cl (**5b**) but also for *o*-F (**5m**), *o*-Br (**5n**), *o*-NO_2 (**5o**), and **5p,** having an electron-donating *o*-MeO substituent.

To gain further insight into the switched diastereoselectivity, an in-depth study of the substituent effect was performed as summarized in Table 3. Using *o*-Cl-substituted imine **5b** as a reference, a series of dichloro-substituted imines **5q**–**s** was subjected to the optimized conditions of the Mannich-type reaction. This comparative study revealed that the position of another Cl-substituent with respect to the anchoring *o*-Cl substituent affected the diastereoselectivity; *p*'-Cl substitution (**5s**) led to a significant loss in *anti*-selectivity,[14] whereas *o*'- or *m*'-Cl substitution (**5q**,**r**) gave the products with a comparable level of diastereo- and enantioselectivity (*o*', *m*', and *p*' denote the relative position of the additional substituent with respect to the anchoring *o*-substituent). This tendency was also observed in the series of disubstituted imines **5t**-**v** having *o*-Cl-*o*'-OMe, *o*-Cl-*m*'-OMe, and *o*-Cl-*p*'-OMe substitution patterns. The magnitude of the decrease in *anti*-selectivity was largely proportional to the sterics of the *p*'-substituents, from *syn*/*anti* = 15/85 for *p*'-F (**5w**) to *syn*/*anti* = 33/67 for *p*'-Br (**5y**). The *o*-F substituent (**5m**) exerted a smaller anchoring effect to cause *anti*-diastereoselectivity (*syn*/*anti* = 19/81), which was weakened by *p*'-F substituents (**5z**) in a similar manner as observed for disubstituted imines bearing the *o*-Cl substituent. Intriguingly, larger *p*'-Cl (**5aa**) and *p*'-Br (**5ab**) substituents overrode the anchoring effect of the *o*-F substituent, preferentially affording the *syn*-product.

Table 3. Substrate Scope of Disubstituted *N*-Boc Imines 5 in Direct Catalytic Asymmetric Mannich-type Reaction of 1-Cl[a]



[a]**5**: 0.2 mmol, **1**-Cl: 0.1 mmol. 0.4 M on **1**-Cl. Isolated yields are reported. *o*', *m*', and *p*' denote the relative position of the additional substituent with respect to the anchoring *ortho*-substituents. Enantioselectivity of the major diastereomers is presented.

The deterioration of *anti*-selectivity by the presence of the *p*'-substituent was similarly valid for imines **5ac** and **5ad** sharing identical substitution patterns with *o*-Br-*p*'-Cl and *o*-NO_2-*p*'-Cl, respectively.

Together, these data led us to propose a plausible rationale for the observed divergent diastereoselectivity (Figure 1). Similar to other previously studied 7-azaindoline amides,[9] abnormally downfielded α-protons (4.92 ppm) were observed for **1**-Cl in ^{1}H NMR (THF-d_8) due to hydrogen bonding with the inherent pyridyl nitrogen, which is indicative of the preferred *E*-conformation of **1**-Cl in solution. Activation of **1**-Cl through bidentate coordination with the Cu(I) complex was evidenced by the upfield shift of the α-protons (4.71 ppm) as well as NOE correlation with the protons at the 2-position of the indoline.[15] Subsequent deprotonation by Barton's base generated the corresponding enolate, which engaged in a Mannich-type addition to *N*-Boc imines **5**. In the simplest case (i), given the coordinatively saturated Cu(I)-enolate and steric bulk of

neighboring ligand **L8**, *m*- or *p*-substituted imines **5**-(**i**) presumably reacted via open transition state model **I**, where the smallest steric barrier and dipole interactions were anticipated. In model **I**, the reaction proceeded through the *Re*-face of imine **5**-(**i**), affording the product **6**-Cl in a *syn*-selective fashion. On the other hand, imines **5**-(**ii**) bearing an *o*-substituent followed a different scenario (case (ii)). Due to electrostatic repulsion with the neighboring imine nitrogen, **5**-(**ii**) prefers the *s-trans* conformation over the *s-cis* counterpart, which eventually rendered model **III** for *Re*-face attack considerably less attainable because of the peripheral steric repulsion. Instead, model **IV** for the C–C bond formation via the *Si*-face of the imine **5**-(**ii**) was more likely, predominantly affording *anti*-**6**-Cl. The unexpectedly lower *anti*-selectivity of imine **5p** with an *o*-OMe group is ascribed to the fact that the hydrogen bonding interaction between the imine nitrogen and the *o*-OMe group mediated by a proton rendered the *s-cis* conformation more feasible, which prefers a *Re*-face attack, as shown in model **III'**, to deliver a considerable amount of the *syn*-configured product. The Cu(I)-enolate ligated with **L8** effectively exposed one face accessible for the reaction with imines, and the identical *2R* configuration was favored for both *syn*- and *anti*-**6**-Cl. The reaction via the *Si*-face for *anti*-selectivity was compromised by the presence of the *p*'-substituent (case (iii)), as delineated in model **VI** for the *Si*-face attack in which steric repulsion was predicted based on the presence of the *p*'-substituent. In the case of *p*'-substituted *o*-Cl imines **5s**,**v**,**w**–**y**, *o*-Br-*p*'-Cl imine **5ac**, and *o*-NO_2-*p*'-Cl imine **5ad**, the *Si*-face model **VI** was generally favored to give *anti*-**6**-Cl with gradual erosion of the *anti*-selectivity proportional to the steric bias of the *p*'-substituents. In contrast, for imines **5m**,**z**,**aa**,**ab** with the smaller *o*-F substituent, *anti*-selectivity was generally lower and the reaction through model **V** for the *Re*-face attack was a major pathway to give a higher fraction of *syn*-**6**-Cl when the *p*'-substituent was *p*'-Cl or *p*'-Br, larger than a fluoro-substituent (imines **5aa**,**ab**).

The present Cu(I)/Barton's base catalytic system accommodated the use of aliphatic imines **5ae**–**aj** as applicable substrates by changing the chiral bisphosphine ligand from **L8** to (*S*,*S*)-Ph-BPE **L5** (Table 4). All imines tested, including non-branched (**5ae**–**ag**), α-branched (**5ah**,**ai**), and β-branched (**5aj**) imines, were converted to the corresponding Mannich products in a *syn*-selective fashion, likely through model **I** depicted in Figure 1. To overcome the inherent lower reactivity, both higher catalyst loading (10 mol%) and higher temperature (0 °C)

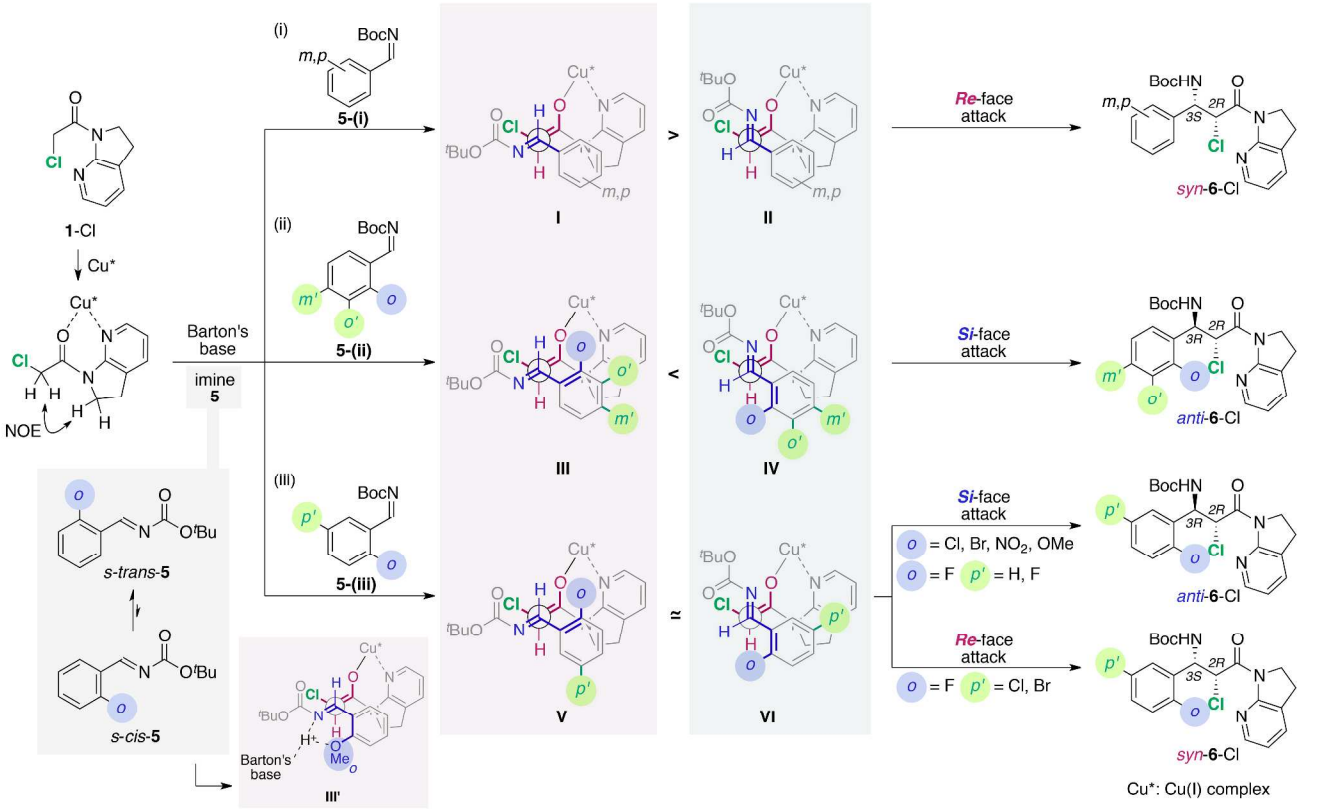
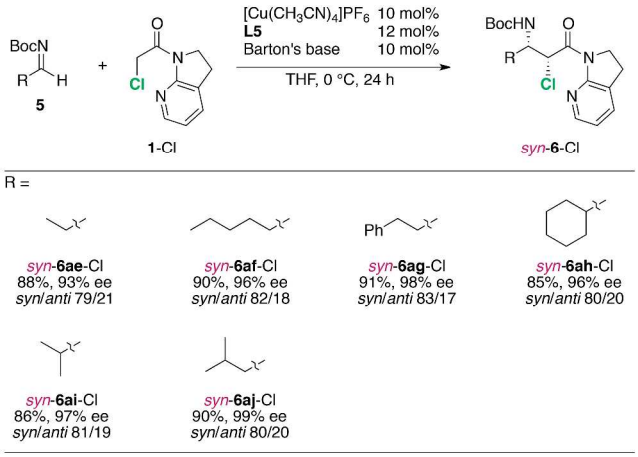


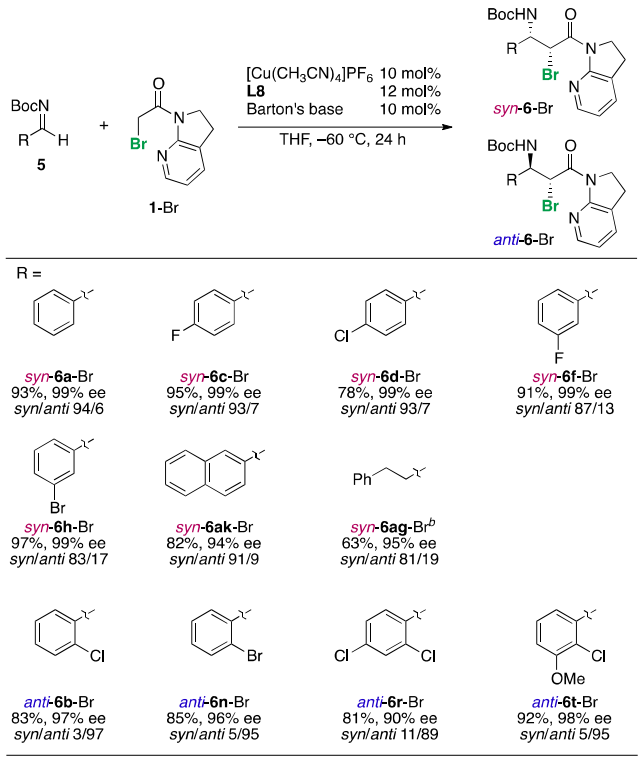
Figure 1. Schematic representation of the origin of diastereoselectivity based on the substitution pattern of aromatic imines **5**. (i) *syn*-Selective reaction of *m*- or *p*-monosubstituted imines **5**-(**i**). (ii) *anti*-Selective reaction of *o*,*o*'- or o,*m*'-disubstituted imines **5**-(**ii**). (iii) *o*,*p*'-disubstituted imines **5**-(**iii**) showed divergent diastereoselectivity depending on the steric factor of substituents. *o*', *m*', and *p*' denote the relative position with respect to the *o*-substituent.

Table 4. Substrate Scope of Aliphatic *N*-Boc Imines 5 in Direct Catalytic Asymmetric Mannich-type Reaction of 1-Cl[a]



[a]**5**: 0.3 mmol, **1**-Cl: 0.1 mmol. 0.33 M on **1**-Cl. Isolated yields are reported. Enantioselectivity of the major diastereomers is presented.

Table 5. Substrate Scope of *N*-Boc Imines 5 in Direct Catalytic Asymmetric Mannich-type Reaction of 1-Br[a]



[a]**5**: 0.2 mmol, **1**-Br: 0.1 mmol, 0.33 M on **1**-Br. Isolated yields are reported. Enantioselectivity of the major diastereomers is presented. [b]Run using **L5** instead of **L8** at –20 °C for 72 h with 0.3 mmol of imine **5ag**.

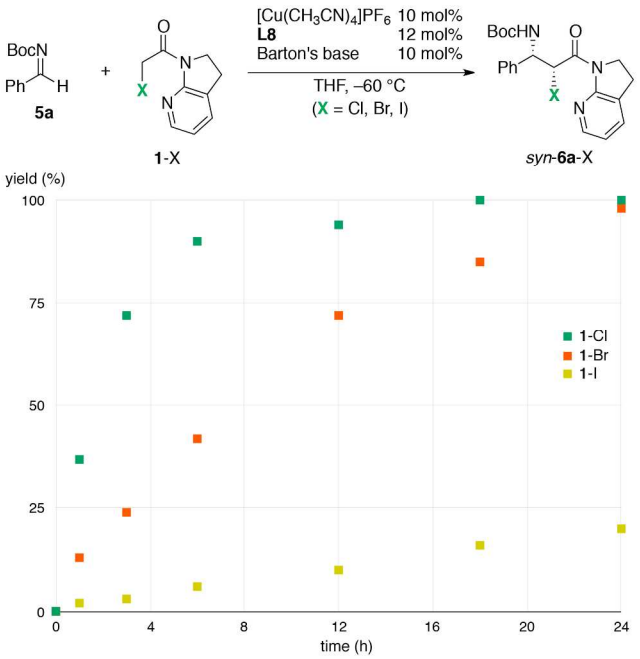


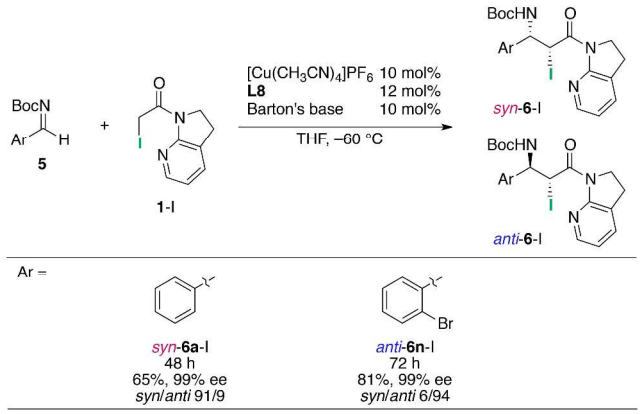
Figure 2. Reaction profile of amides **1**-Cl, **1**-Br, and **1**-I in catalytic asymmetric Mannich-type reaction. 0.2 M on **1**-X. 2.0 equiv of imine **5a** was used.

were essential for completion. Enantioselectivity was generally high, while *syn*-selectivity was moderate, presumably due to the increased sterics of the flanking alkyl chains.

Notably, α-Br and α-I 7-azaindoline amides (**1**-Br, **1**-I) served as competent latent enolates in the catalytic asymmetric Mannich-type reactions. Although a somewhat slower reaction rate was observed, face-selectivity of the in situ-generated enolate of **1**-Br had the same propensity observed for **1**-Cl; products *syn*-**6**-Br were predominantly obtained with *m*- or *p*-substituted imines **5a**,**c**,**d**,**f**,**h**,**ak** via a *Re*-face attack (model **I**, Figure 1), while *anti*-**6**-Br was the major diastereomer when *o*-substituted imines **5b**,**n**,**r**,**t** were used. Cu(I)/**L5**/Barton's base catalytic system accommodates aliphatic imine **5ag** at a higher reaction temperature (–20 °C). For comparison, the kinetic profile of the Mannich-type reaction was traced for **1**-Cl, **1**-Br, and **1**-I using imine **5a** (Figure 2). Under identical conditions with 10 mol% of catalyst loading at –60 °C and 0.2 M concentration, **1**-Cl produced the highest reaction rate and **1**-Br followed to reach completion within 24 h, while the reactivity of **1**-I was insufficient. A higher concentration (0.3 M) and extended reaction time allowed **1**-I to provide the desired product **6**-I in a reasonable yield (Table 6). The empirical tendency for diastereoselectivity shown in Figure 1 was also valid for **1**-I; imine **5a** with no substituent and **5n** with an *o*-Br substituent exhibited *syn*- and *anti*-selectivity, respectively. α-F azaindoline amide **1**-F has a stable C–F bond and its use in the direct Mannich-type reaction was previously addressed with *N*-Cbz-imines **7** (Scheme 2).[16,17] Compared with other α-halo azaindoline amides, **1**-F exhibited very slow reaction kinetics, and no product was obtained at –60 °C. A higher reaction temperature with Taniaphos-type ligand **L9** having a similar architecture afforded the corresponding products **8** in an *anti*-selective manner. It is noteworthy that the absolute configuration at the α-position was opposite that observed for **1**-Cl, **1**-Br, and **1**-I,

which could be ascribed to the reaction through *E*-enolate in the specific case of **1**-F. The involvement of the *E*-enolate is rationalized by minimal steric factor of the fluorine atom and smaller dipole moment.[18] Subsequent addition to imine **7** bearing *m*- or *p*-substituents likely proceeded through model **VII** to preferentially afford *anti*-configured product *anti*-**8**-F.[19]

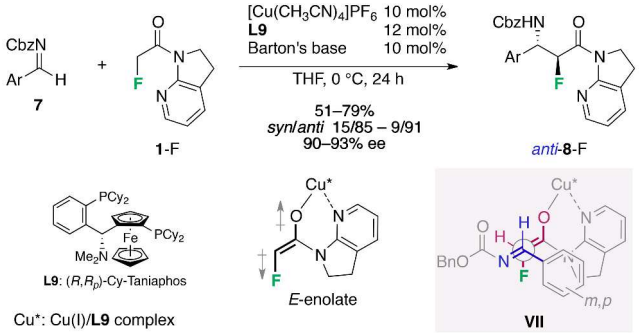
Table 6. Substrate Scope of *N*-Boc Imines 5 in Direct Catalytic Asymmetric Mannich-type Reaction of 1-I[a]



[a]**5**: 0.2 mmol, **1**-I: 0.1 mmol. 0.33 M on **1**-I. Isolated yields are reported. Enantioselectivity of the major diastereomers is presented.

Chart 1 shows the exclusive nature of 7-azaindoline amide for the present direct enolization methodology. Derivatives of the most reactive **1**-Cl among **1**-X were synthesized and evaluated in a Mannich-type reaction with imine **5a** under optimized conditions. All of the derivatives tested, including 7-azaindole amide **9**, indoline

Scheme 2. Direct Catalytic Asymmetric Mannich-type Reaction of 1-F with *N*-Cbz Imines 7[a]



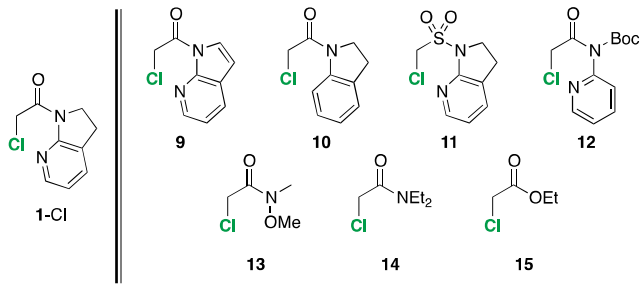
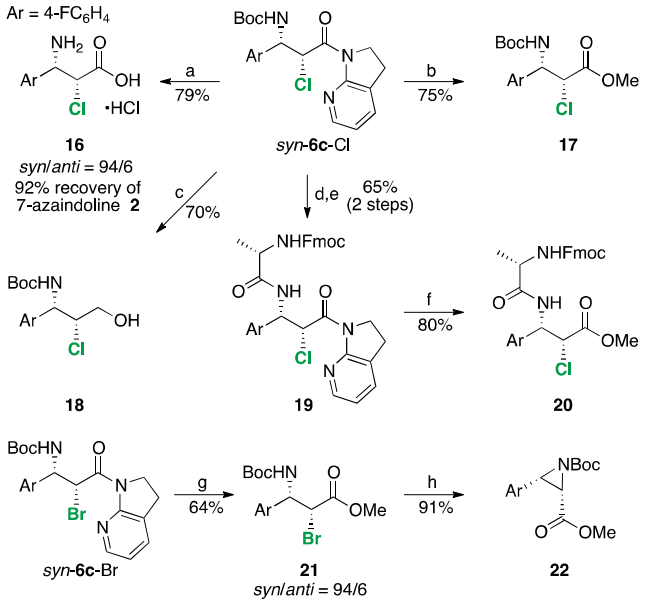


Chart 1. Unsuccessful Latent Enolates

Scheme 3. Transformation of Mannich-adducts[a]



[a]*Reagents and conditions*: (a) 6N HCl aq., 60 °C, 24 h; (b) CuCl, MeOH, 80 °C (bath temp.), 48 h; (c) BH_3•NH_3, LDA, THF, 0 °C to rt, 1 h. (d) TFA, CH_2Cl_2, rt, 20 min; (e) Fmoc-Ala-OH, PyBOP, 2,6-lutidine, CH_2Cl_2, rt, 18 h; (f) CuCl, MeOH, 80 °C (bath temp.), 42 h; (g) CuCl, CH_3CN/MeOH, 60 °C, 60 h; (h) Cs_2CO_3, CH_3CN, rt, 12 h.

amide **10**, 7-azaindoline sulfonamide **11**, *N*-Boc 2-pyridylamide **12**, and Weinreb's amide **13,** as well as simple amide and ester **14**,**15** failed to give the desired Mannich products.

Transformation of the enantioenriched Mannich products with retention of the labile C–halogen bond at the stereogenic carbon highlights the synthetic utility of the present catalytic protocol (Scheme 3). The 7-azaindoline amide moiety of the diastereomerically pure *syn*-**6c**-Cl was hydrolyzed by 6N HCl aq. at 60 °C to give β-amino acid **16** in 79% yield with 92% recovery of 7-azaindoline **2**, albeit with marginal loss of the stereochemical integrity (*syn*/*anti* = 94/6). Transesterification of *syn*-**6c**-Cl mediated by CuCl in refluxing MeOH delivered the corresponding methyl ester **17**.[20] Myers' protocol using lithium amidotrihydroborate enabled direct reduction of the amide to primary alcohol **18**.[21] Of particular note is that a free amino group could be exposed without aziridination by treatment with TFA to remove the Boc group at room temperature, and subsequent addition of Fmoc-Ala-OH using PyBOP furnished amide **19**. CuCl-mediated transesterification of **19** gave methyl ester **20**, providing a general procedure to access peptides with an α-chloro-β-amino acid unit.[22] As expected, Mannich product *syn*-**6c**-Br bearing α-Br substituent was more susceptible to undesired reactions and a tiny amount of epimerized product was observed in the conversion to ester **21** under CuCl-mediated transesterification conditions.[20] The labile C–Br bond was exploited to furnish *cis*-substituted aziridine **22**.[8]

Conclusion

In conclusion, we determined that α-halogenated 7-azaindoline amides were amenable to catalytic enolization and subsequent enantioselective addition to *N*-carbamoylimines. All α-halo substituents, F, Cl, Br, and I, were successfully accommodated; considering that α-halogenated monocarbonyl compounds have been underexplored as latent enolates, the observed broad applicability of α-halogenated 7-azaindoline amides is noteworthy. The divergent diastereoselectivity depending on the substitution pattern of the aromatic imines was rationalized by the plausible open transition state models. Divergent functional group interconversion of the 7-azaindoline moiety of the Mannich product as well as *N*-acylation without dehalogenation highlight the synthetic utility of the reaction to access enantioenriched halogenated building blocks. Further developments toward an aldol reaction manifold and the application to natural product synthesis are underway.

ASSOCIATED CONTENT

Supporting Information

Experimental details and spectroscopic data of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

Crystallographic data for *anti*-**6b**-Cl (CIF)
Crystallographic data for *syn*-**6d**-Cl (CIF)
Crystallographic data for *anti*-**6m**-Cl (CIF)
Crystallographic data for *anti*-**6r**-Cl (CIF)
Crystallographic data for *syn*-**6ah**-Cl (CIF)
Crystallographic data for *syn*-**6d**-Br (CIF)
Experimental procedures and spectral data (PDF)

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12. Bulk purchase of **3** or **4** even lowers the cost shown in Scheme 1.
13. Absolute configuration of *anti*-**6b**-Cl was determined by X-ray crystallographic analysis. That of *syn*-**6a**-Cl was deduced from *syn*-**6d**-Cl (determined by X-ray crystallographic analysis) by analogy.
14. The use of the corresponding *N*-Cbz imine under otherwise identical conditions led to lower stereoselectivity (83% isolated yield, dr 55/45, 64% ee/77% ee).
15. Cu(I)/**L2** complex was used in NMR analysis to avoid overlapped peaks.
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17. For catalytic asymmetric Mannich-type reactions, only highly acidic α-fluoro-β-ketoesters, α-fluoro-β-ketoimides, α-fluoromalonates were used; see (a) Han, X.; Kwiatkowski, J.; Xue, F.; Huang, K.-W.; Lu, Y. *Angew. Chem. Int. Ed.* **2009**, *48*, 7604. (b) Pan, Y.; Zhao, Y.; Ma, T.; Yang, Y.; Liu, H.; Jiang, Z.; Tan, C.-H. *Chem. Eur. J.* **2010**, *16*, 779. (c) Yoon, S. J.; Kang, Y. K.; Kim, D. Y. *Synlett* **2011**, 420. (d) Kang, Y. K.; Yoon, S. J.; Kim, D. Y. *Bull. Korean Chem. Soc.* **2011**, *32*, 1195. (e) Kang, Y. K.; Kim, D. Y. *Tetrahedron Lett.* **2011**, *52*, 2356. (f) Zhao, Y.; Pan, Y.; Liu, H.; Yang, Y.; Jiang, Z.; Tan, C.-H. *Chem. Eur. J.* **2011**, *17*, 3571. (g) Wang, H.-Y.; Zhang, K.; Zheng, C.-W.; Chai, Z.; Cao, D.-D.; Zhang, J.-X.; Zhao, G. *Angew. Chem. Int. Ed.* **2015**, *54*, 1775. (h) Cosimi, E.; Engl, O. D.; Saadi, J.; Ebert, M.-O.; Wennemers, H. *Angew. Chem. Int. Ed.* **2016**, *55*, 13127.
18. In the case of α-CF_3-α-F 7-azaindoline amide, the α-F substituent located close to azaindoline upon complexation with a Cu(I)

complex, which was evidenced by HOESY analysis (see ref 16). This observation suggested that α-F substituent was accommodated in the *E*-enolate geometry without severe steric repulsion.

19. No epimerization of the Mannich product was observed during the course of the reaction and the anti configuration was kinetically determined.
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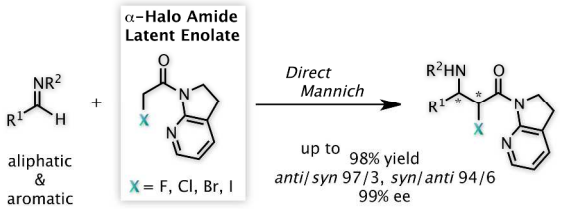
α-Halo Amide
Latent Enolate
aliphatic
&
aromatic
X = F, Cl, Br, I
Direct
Mannich
up to 98% yield
anti/syn 97/3, syn/anti 94/6
99% ee