Communication

Catalytic Asymmetric Construction of Halogenated Stereogenic Carbon Centers by Direct Vinylogous Mannich-Type Reaction

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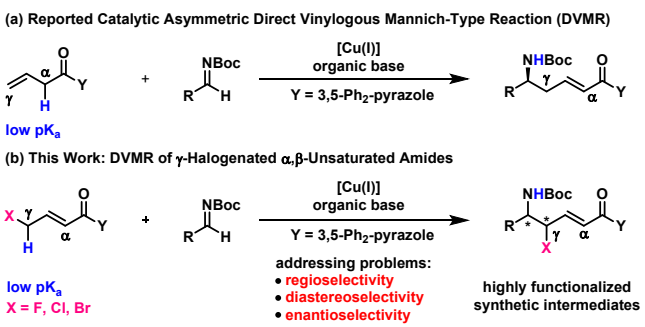
Supporting Information Placeholder

ABSTRACT: A catalytic asymmetric vinylogous Mannich-type reaction of γ-halo-α,β-unsaturated *N*-acylpyrazoles and *N*-Boc-aldimines was disclosed, which afforded an array of halogenated (F-, Cl-, and Br-) allylic stereogenic carbon centers in high yields with good to high regio-, diastereo- and enantioselectivity. The brominated product served as a suitable electrophile for common S_N2 nucleophilic substitution and copper-mediated S_N2' allylic alkylation with metal reagents. The utility of present methodology was demonstrated by the asymmetric synthesis of a common intermediate towards the synthesis of two chiral 2,3-disubstituted piperidine pharmaceuticals.

Halogenated stereogenic carbon centers are found in naturally occurring compounds.[1] Although the chiral carbon centers bearing fluorine or iodine in natural products are few, the molecules containing chlorine or bromine are much more. For examples, one chiral quaternary center containing chlorine and one chiral tertiary carbon center with bromine present in (+)-halomon, an anticancer lead.[2] Clindamycin, used to treat a variety of bacterial infections, owns a chiral chlorinated tertiary carbon center as well.[2] In manmade bioactive molecules, the chiral carbon centers with fluorine are much more frequently encountered.[3] Some of them exhibited significant bioactivity, such as LY-503430[4] (used to treat Parkinson's disease). Actually, halogenation, as well as the stereochemistry of the halogen-bearing carbons, can significantly alter the bioactivity of molecules.[2] Moreover, halogen atoms have a profound effect on the bonding through halogen bonding interactions.[2] Therefore, exploring effective stereoselective construction of halogenated chiral carbon centers is an important synthetic task.[5]

Alkyl halides are among the most versatile compounds in synthetic chemistry and regularly employed in alkylation reactions, radical cascades, and alkyl cross-coupling chemistry.[2b,6] As one special type of alkyl halides, allyl halides attract the most attention of synthetic community due to its high reactivity and abundant transformation chemistry. First, allyl halides were employed in transition metal-free asymmetric allylic alkylation using Grignard reagents.[7] Second, allyl halides were utilized in transition metal-catalyzed asymmetric allylic substitution with various nucleophiles.[8] Third, allyl halides were utilized in nickel-catalyzed asymmetric Negishi cross-coupling and palladium-catalyzed enantioselective allyl-allyl cross-coupling.[9] Moreover, asymmetric Nozaki-Hiyama-Kishi allylation of carbonyl compounds afforded synthetically versatile homoallylic alcohols, which can go further structure elaboration if multiply halogenated allylic halides were utilized.[10] However, the allyl halides employed in literature mainly focused on the racemic compounds or the ones without stereogenic carbon center. The preparation of chiral allyl halides would offer a new opportunity for the asymmetric allylation of various nucleophiles with or without transition metal catalysts.[11]

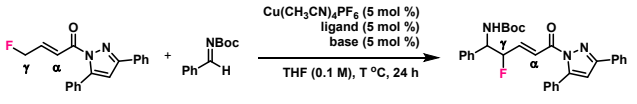
Scheme 1. Catalytic Asymmetric Direct Vinylogous Mannich-Type Reaction (DVMR) of γ-Halogenated α,β-Unsaturated *N*-Acylpyrazoles Catalyzed by a Copper(I) Complex



The catalytic asymmetric construction of halogenated chiral carbon centers consists of two pathways. One is catalytic asymmetric introduction of a halogen into prochiral compounds, including electrophilic halofunctionalization of alkenes[12] and halogenation of various nucleophiles and electrophiles.[13] Denmark,[12b,12d] Burns[14] and many others[15] are pioneers in the former case. In the latter case, methods for enantioselective α-chlorination or α-bromination of carbonyl compounds and related reactions have rapidly progressed in the last decade.[16] The other is the catalytic asymmetric functionalization of a halogenated prochiral carbon, comprising of enantioselective transformation with halogenated alkenes,[5b,17] asymmetric allylation with halogenated allyl metal reagents,[18] asymmetric α-functionalization of α-halo enolsilanes or enolates,[19] and asymmetric β-elimination of trihalides.[20] However, to the best of our knowledge, the chemistry of γ-halo dienolates has never been investigated in literature. Herein, we disclosed a copper(I)-catalyzed direct asymmetric vinylogous Mannich-type reaction of γ-halo(F, Cl or Br)-α,β-unsaturated *N*-acylpyrazoles and *N*-Boc-aldimines, constructing chiral halogenated allylic carbon centers in high yields with good to high regio-, diastereo-, and enantioselectivity.

Previously, we reported a copper(I)-catalyzed direct catalytic asymmetric vinylogous Mannich-type reaction of β,γ-unsaturated *N*-acylpyrazole and various aldimines (Scheme 1a).[21] Combination of an *N*-acyl-3,5-Ph_2-pyrazole and a bulky bisphosphine ligand ((*R*)-DTBM-SEGPHOS) was found to be the key to perfectly control the regioselectivity. It was envisioned that a weakly electron-withdrawing halogen (F, Cl and Br) would acidify the γ-protons but would not reduce the nucleophilicity of the γ-carbon significantly, which would allow an atom-economic[22] vinylogous Mannich-type reaction to construct halogenated stereogenic carbon centers in the presence of a copper catalyst[23] (Scheme 1b).

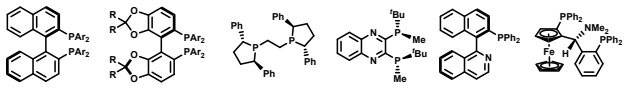
Table 1. Optimization of the Reaction Conditions[a]



1 2a, 2 equiv 3a

entry	ligand	base	T	total yield[b]	γ/α[b]	dr (*syn*/*anti*)[b]	ee (%)[c]
1	(*R*)-BINAP	Et_3N	rt	39	1/1	1/2	23/28
2	(*R*)-TOL-BINAP	Et_3N	rt	20	1.5/1	1/2.7	-10/18
3	(*R*)-SEGPHOS	Et_3N	rt	<5	-	-	-
4	(*R*)-QUINAP	Et_3N	rt	<5	-	-	-
5	(*R*)-DIFLUORPHOS	Et_3N	rt	69	1/1.8	1/2.3	53/21
6	(*R*,*R*)-QUINOXP*	Et_3N	rt	29	1/3	<1/20	-/4
7	(*R*,*R*)-Ph-BPE	Et_3N	rt	36	1/3	1/2	-37/-46
8	(*R*,R_p)-TANIAPHOS	Et_3N	rt	66	>20/1	3/1	11/66
9	(*R*)-DTBM-SEGPHOS	Et_3N	rt	75	>20/1	>20/1	98
10[d]	(*R*)-DTBM-SEGPHOS	Et_3N	0	87	>20/1	>20/1	>99
11	(*R*)-DTBM-SEGPHOS	$^iPr_2NEt$	0	83	>20/1	>20/1	98
12	(*R*)-DTBM-SEGPHOS	Cy_2NMe	0	61	>20/1	>20/1	99
13	(*R*)-DTBM-SEGPHOS	Et_3N	-20	76	>20/1	>20/1	98
14[e]	-	Et_3N	0	0	-	-	-
15	(*R*)-DTBM-SEGPHOS	-	0	0	-	-	-

[a]**1**: 0.1 mmol, **2a**: 0.2 mmol. [b]Determined by ^1H NMR analysis of reaction crude mixture using CH_3NO_2 as an internal standard. [c]Determined by chiral-stationary-phase HPLC analysis. [d]Isolated yield. [e]Performed without copper(I)-complex.



Ar = Ph, (*R*)-BINAP; Ar = Tol, (*R*)-TOL-BINAP

R = H, Ar = Ph, (*R*)-SEGPHOS; R = F, Ar = Ph, (*R*)-DIFLUORPHOS; R = H, Ar = 3,5-$^tBu_2$-4-OMe-Ph, (*R*)-DTBM-SEGPHOS

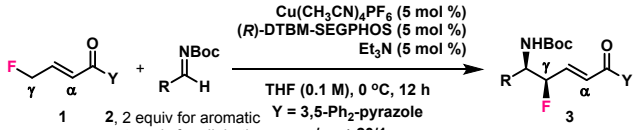
(*R*,*R*)-Ph-BPE (*R*,*R*)-QUINOXP* (*R*)-QUINAP (*R*,R_p)-TANIAPHOS

We began our investigation by using γ-F-α,β-unsaturated compound **1** and *N*-Boc-aldimine **2a** as model substrates for optimization of reaction conditions (Table 1). (*R*)-BINAP, (*R*)-TOL-BINAP, (*R*)-SEGPHOS, (*R*)-QUINAP, (*R*)-DIFLUORPHOS, (*R*,*R*)-QUINOXP* and (*R*,*R*)-Ph-BPE proved to be not suitable ligands in this reaction (entries 1-7). (*R*,R_p)-TANIAPHOS was found to be a good ligand in terms of excellent regioselectivity although both diastereo- and enantioselectivity were not high (entry 8). As previously reported,[21] bulky (*R*)-DTBM-SEGPHOS outperformed to give the vinylogous product **3a** in 75% yield with >20/1 regioselectivity, >20/1 diastereoselectivity and 98% ee (entry 9). Decreasing the temperature to 0 °C resulted in an increased yield (entry 10). Study of organic bases identified triethylamine as the best in terms of the reaction performance and its low price (entries 10-12). Further decreased reaction temperature led to extenuated reactivity (entry 13). Both copper(I) complex and organic base were indispensable for this reaction as no reaction occurred in the absence of either of them (entries 14-15).

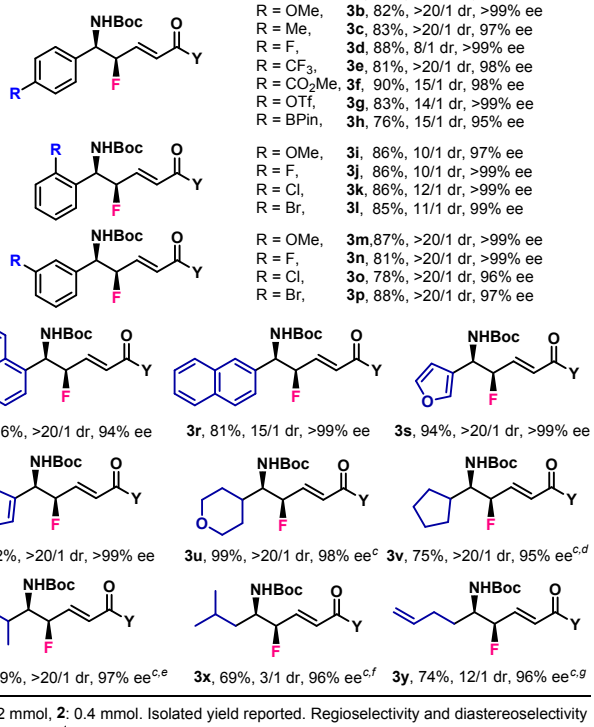
With optimized reaction conditions in hand, the catalytic asymmetric vinylogous Mannich-type reaction of **1** and various *N*-Boc-aldimines **2** was examined (Table 2). Aromatic imines reacted with **1** smoothly to deliver the vinylogous products in uniformly good results. Both electron-donating and withdrawing groups on the aromatic imines were well tolerated. The position of the substituents on the phenyl ring seemed to have little effect on both yield and enantioselectivity. However, sterically congested *ortho*-substituted aromatic imine led to inferior diastereoselectivity (**3i-3l**). A variety of functional groups, including methoxyl, methyl, fluoride, chloride, bromide, ester, triflate (OTf) and pinacolatoboron (BPin), were well tolerated. Particularly, the products with Cl, Br, OTf and BPin on the phenyl ring are noteworthy, as these functional groups allow for late-stage transition metal-catalyzed cross-coupling reaction.

The phenyl ring in aldimines **2** could be replaced by 1-naphthyl, 2-naphthyl, 3-furanyl, and 3-thienyl with the desired products obtained in high yield, regio-, diastereo- and enantioselectivity (**3q-3t**). Remarkably, aliphatic imines containing acidic α-protons and thus sensitive to basic conditions were also competent substrates in this reaction (**3u-3y**). However, α-addition inevitably occurred and α-adducts were observed as side products. A terminal olefin presented in the product offers the opportunity for further functional group manipulation to afford more complex molecules. The relative configuration of product **3** was determined to be *syn* by virtue of X-ray crystallographic analysis of **3b** (for details, see SI), which is in conformity with **6a**.

Table 2. Substrate Scope of *N*-Boc-Aldimines 2 in the Vinylogous Mannich-Type Reaction with 1[a]



1 2, 2 equiv for aromatic, 4 equiv for aliphatic 3



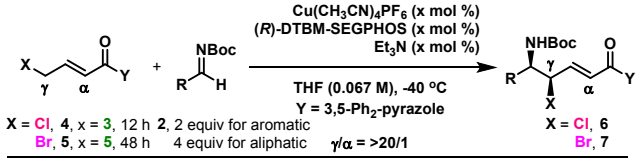
[a]**1**: 0.2 mmol, **2**: 0.4 mmol. Isolated yield reported. Regioselectivity and diastereoselectivity determined by ^1H NMR analysis of reaction crude mixture. Enantioselectivity determined by chiral-stationary-phase HPLC analysis. [b]Gram-scale reaction. [c]**1**: 0.2 mmol, **2**: 0.8 mmol. [d]γ:α = 6/1. [e]γ:α = 8/1. [f]γ:α = 3/1. [g]γ:α = 5/1.

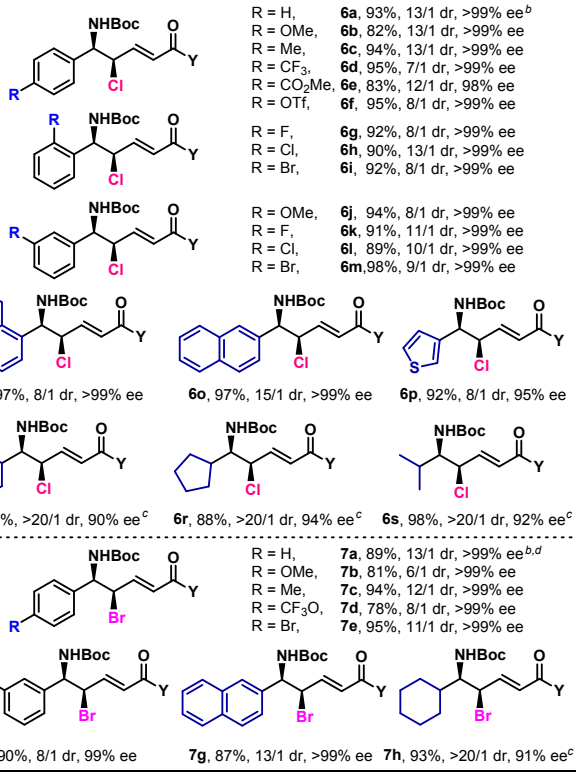
The present catalytic system was also suitable to γ-Cl and γ-Br-α,β-unsaturated compounds (**4** and **5**) (Table 3). As for chlorinated compound **4**, 3 mol % copper(I) complex and 3 mol % Et_3N were enough to catalyze the Mannich-type reaction of both aromatic aldimines and heteroaromatic aldimine. Both the yield and the enantioselectivity were generally excellent. However, the diastereoselectivity was moderate in some cases (**6d**, **6f**, **6g**, **6i**, **6j**, **6m**, **6n** and **6p**). Aliphatic aldimines exhibited lower reactivity as 10 mol % copper(I) complex and 10 mol % Cy_2NMe were required to achieve satisfactory results. Moreover, instead of (*R*)-DTBM-SEGPHOS, (*R*,R_p)-TANIAPHOS was employed due to its better performance at low temperature.[21a] As for brominated compound **5**, the same reaction tendency was observed. Although the diastereoselectivity was moderate in some cases, both regioselectivity and enantioselectivity were excellent. Even though allyl bromides are more useful synthetic intermediates, there are fewer reports in literature on the enantioselective construction of brominated chiral carbon centers containing a vinyl group.

The gram-scale reaction of **3a**, **6a** and **7a** proceeded smoothly to give constant results, highlighting the robustness of the present methodology. The two stereogenic carbon centers in **6a** were determined to be *R* and *R* by means of X-ray diffraction analysis (for details, see SI). The configurations of other vinylogous products (**3**,

6b-6p and **7a-7g**) were assigned by analogy. Since the ligand employed for the generation of **6q-6s** and **7h** was changed from (*R*)-DTBM-SEGPHOS to (R,R_p)-TANIAPHOS, the stereochemistry in these products required additional assignment. The X-ray crystallographic analysis of **7h** identified the absolute configurations of the two stereogenic carbon centers to be *R* and *R* (for details, see SI). Analogically, the absolute configurations of **6q-6s** were assigned tentatively.

Table 3. Substrate Scope of *N*-Boc-Aldimines 2 in the Vinylogous Mannich-Type Reaction with 4 and 5[a]

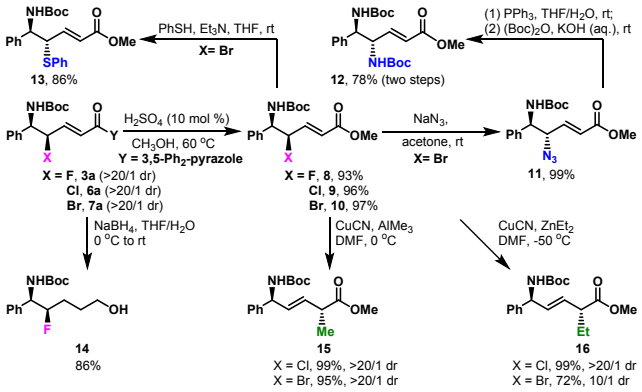




[a]**4**-**5**: 0.2 mmol, **2**: 0.4 mmol. Isolated yield reported. Regioselectivity and diastereoselectivity determined by ^{1}H NMR analysis of reaction crude mixture. Enantioselectivity determined by chiral-stationary-phase HPLC analysis. [b]Gram-scale reaction. [c]**4**-**5**: 0.2 mmol. **2**: 0.8 mmol. 3,5-Tol$_2$-pyrazole-amides (**4'** and **5'**) instead of 3,5-Ph$_2$-pyrazole-amides (**4** and **5**) used. 10 mol % $Cu(CH_3CN)_4PF_6$, 10 mol % (R,R_p)-TANIAPHOS and 10 mol % Cy_2NMe employed. 48 h. [d]3 mol % $Cu(CH_3CN)_4PF_6$, 3 mol % (*R*)-DTBM-SEGPHOS and 3 mol % Et_3N employed.

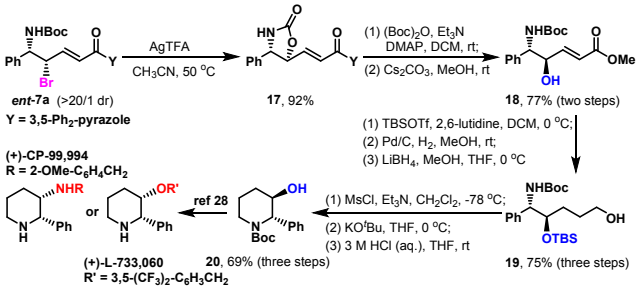
The transformations of vinylogous products were presented in Scheme 2. The alcoholysis of **3a**, **6a** and **7a** afforded esters **8**, **9** and **10** in excellent yields. S_N2 reaction of **10** with NaN_3 led to **11** in 99% yield. The Staudinger reduction of azide group in **11** and the subsequent protection of newly generated amine with $(Boc)_2O$ led to chiral diamine derivative **12** in 78% yield for two steps. Moreover, S_N2 reaction of **10** with PhSH generated thioether **13** in 86% yield. The full reduction of **3a** was achieved to furnish **14** in 86% yield. The reported conditions for the S_N2' substitution of allyl halides promoted by copper(I) salt were slightly modified.[24] In the presence of CuCN, the reactions of **9** and **10** with $AlMe_3$ were set up in DMF at 0 °C, which afforded **15** in excellent yields with >20/1 dr. The reaction of **9** with $ZnEt_2$ in DMF at -50 °C proceeded in excellent results while the reaction of **10** with $ZnEt_2$ provided **16** in 72% yield with 10/1 dr. The newly generated stereogenic center in **15** was determined to be *R* by further transformation (For details, see SI) and the one in **16** was assigned to be *R* tentatively by analogy.

Scheme 2. Transformations of Vinylogous Products



Structure elaboration of the optically enriched vinylogous product ***ent*-7a** opens a pathway for further transformations to chiral 2,3-disubstituted piperidines with β-hydroxyl or β-amino functional groups (Scheme 3), which are common subunits in numerous natural products, as well as in pharmaceutically active compounds.[25] For example, (+)-L-733,060[26] and (+)-CP-99,994[27] are potent and selective nerokinin-1 substance P receptor antagonists, both of which can be accessed from a common intermediate **20** according to reported procedures.[28] The silver-mediated intramolecular substitution of ***ent*-7a** proceeded smoothly to give intermediate **17** in 92% yield, which afforded **18** in 77% yield for two steps through the protection with $(Boc)_2O$ and the following opening of the oxazolidin-2-one moiety. TBS-protection of the secondary alcohol and fully reduction of the α,β-unsaturated moiety gave **19** in 75% yield for three steps. Then, cyclization and removal of the TBS group led to the common intermediate **20** in 69% yield for three steps.

Scheme 3. Synthetic Application of Vinylogous Product *ent*-7a



In summary, by introducing a halogen (F, Cl or Br) at the γ-position of α,β-unsaturated *N*-acylpyrazole, we achieved a copper(I)-catalyzed direct catalytic asymmetric vinylogous Mannich-type reaction for the first time, which constructed a series of halogenated chiral stereogenic carbon centers in high enantioselectivity. The reaction showed advantages, such as mild reaction conditions, broad substrate scope, good tolerance of functional groups, and good to excellent regio- and stereoselectivity. The produced chiral allyl bromide was successfully employed as a chiral electrophile in common S_N2 reaction and copper-catalyzed S_N2' reaction. Moreover, the present methodology was applied to the synthesis of a common intermediate towards the synthesis of two chiral piperidine pharmaceuticals. Further efforts regarding the expansion of the present methodology and its application in the synthesis of bioactive natural products are in progress.

ASSOCIATED CONTENT

Supporting Information

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

Crystallographic data for **3b**, **6a** and **7h** (CIF)

Experimental procedures, characterizations and analytical data of new compounds, X-ray diffraction data for **3b**, **6a** and **7h**, and spectra of NMR and HPLC for new compounds (PDF)

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Notes

The authors declare no competing financial interests.

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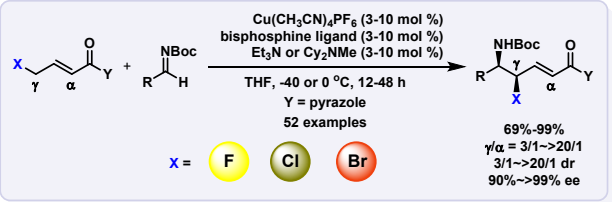
Cu(CH3CN)4PF6 (3-10 mol %)
bisphosphine ligand (3-10 mol %)
Et3N or Cy2NMe (3-10 mol %)
THF, -40 or 0 °C, 12-48 h
Y = pyrazole
52 examples
x =
F
Cl
Br
69%-99%
γ/α = 3/1~>20/1
3/1~>20/1 dr
90%~>99% ee