JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

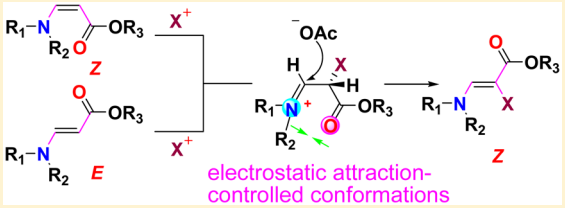
Stereoselective Chlorination and Bromination of Enamides and Enamines via an Electrostatic Attraction Effect Using (1,1-Diacetoxyiodo)benzene and a Halide Source

Linlin Xing and Chunbao Li*

Department of Chemistry, School of Science, Tianjin University, Tianjin 300072, China

Supporting Information

ABSTRACT: The direct chlorination and bromination of (*E*)-enamines and (*Z*)-enamides to the corresponding (*Z*)-configurated α-chloroenamines, α-bromoenamines, and α-chloroenamides have been realized using $NiCl_2·6H_2O$ or tetrabutyl ammonium bromide as a halide source and (1,1-diacetoxyiodo)benzene as an oxidant. The high stereoselective reactions which produce products with only (*Z*)-configurations can be attributed to the structure of the intermediates, the conformations of which are controlled by the electrostatic attractions between the positively charged nitrogen atoms and the oxygen atoms of the carbonyl group. This type of electrostatic effect has never been reported in olefin halogenations. For this reason, the three-membered bromonium ion is only a minor intermediate in the enamine bromination pathway. These methods open pathways to prepare α-chloroenamines and α-chloroenamides, which are not accessible via the currently used methods.



INTRODUCTION

Enamides[1−4] and enamines[5,6] have proved to be useful building blocks for complex nitrogen-containing compounds and substrates of various synthetic reactions such as the Porarov reaction, the Diels−Alder reaction, the Mannich reaction, metal-catalyzed regioselective functionalization, and halogenation. Among these products, halogenated enamides and enamines are important intermediates for the synthesis of heterocycles,[7] α-halo-β-amino acid derivatives,[8−10] and α-aryl-β-amino acid derivatives,[11−13] some of which are bioactive.[7,14] However, only a few procedures have been used in preparing α-chloroenamides.[15−18] In the NBS/DABCO procedure,[17] only succinimide substituted α-chloroenamide products were prepared. In the Pummerer reactions of sulfoxides,[18] the products were limited to tetrasubstituted α-chloroenamides. Currently enamides are available through the Wittig reaction[19] and Pd-catalyzed cross-coupling reaction of an amide and an acrylic ester.[20] However, there have been no reports on transforming disubstituted enamides to α-chlorinated trisubstituted enamides. (1,1-Diacetoxyiodo)benzene (PIDA)[21−25] is a commercially available and widely used oxidant in organic synthesis and capable to oxidize halide, which could possibly halogenate enamides and enamines. Herein, we report such a transformation, which used $NiCl_2·6H_2O$ as a chloride source and (1,1-diacetoxyiodo)benzene (PIDA) as an oxidant. These reactions are highly stereoselective. The direct transformations of enamines to α-chloro- and α-bromoenamines are also reported.

RESULTS AND DISCUSSION

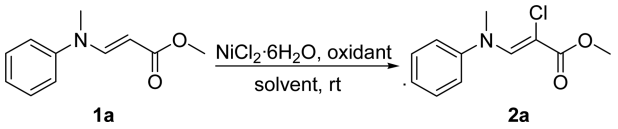
Initially, enamine **1a** was used as a model compound and treated with a series of oxidants and $NiCl_2·6H_2O$ in MeOH (Table 1). No reactions occurred with BQ, DDQ, $K_2S_2O_8$, TBHP, H_2O_2, and *m*-CPBA (Table 1, entries 2−7). The oxidation of **1a** with PIDA and $NiCl_2·6H_2O$ led to **2a** in 30% yield (Table 1, entry 1). Next, a series of solvents including MeCN, toluene, THF, DMF, DCE, and dioxane were screened and MeCN offered the best result (Table 1, entries 8−13). The employment of other solvents decreased the reaction yields to a large extent. The reaction conditions were further optimized by varying the amounts of PIDA between 0.5 and 1.3 equiv and $NiCl_2·6H_2O$ between 1.0 and 2.5 equiv (Table 1, entries 14−20). The optimized reaction conditions were 1.0 equiv of enamine, 1.2 equiv of PIDA, and 2.0 equiv of $NiCl_2·6H_2O$ in acetonitrile, which produce a yield of 64% (Table 1, entry 19).

Fifteen enamines were then subjected to the optimized conditions to produce the corresponding α-chloroenamines in good (Scheme 1, **2c**, **2f**), fair (Scheme 1, **2a**, **2b**, **2d**, **2e**, **2g**−**2n**), and low (Scheme 1, **2o**) yields. Enamines **1a**−**1n** are all aryl enamines, which are stable toward Lewis acid $NiCl_2$. However, alkyl enamine **1o** is not particularly stable toward $NiCl_2$, causing the low chlorination yield. All the chlorinations took 15 min regardless of the nature and position of the substituents on the aryl groups. The chlorination worked equally well when the alkyl group on the nitrogen atom was an ethyl group (Scheme 1, **2l**). The (*Z*)-configuration of the

Received: July 11, 2015
Published: September 30, 2015

DOI: 10.1021/acs.joc.5b01603
J. Org. Chem. 2015, 80, 10000−10008

Table 1. Optimization of Reaction Conditions[a]



entry	$NiCl_2·6H_2O$ (equiv)	oxidant (equiv)	solvent (5 mL)	yield (%)[b]
1	1.0	PIDA (1.0)	MeOH	30
2	1.0	BQ (1.0)	MeOH	NR[c]
3	1.0	DDQ (1.0)	MeOH	NR[c]
4	1.0	$K_2S_2O_8$ (1.0)	MeOH	NR[c]
5	1.0	TBHP (1.0)	MeOH	NR[c]
6	1.0	H_2O_2 (1.0)	MeOH	NR[c]
7	1.0	*m*-CPBA (1.0)	MeOH	trace
8	1.0	PIDA (1.0)	MeCN	46
9	1.0	PIDA (1.0)	toluene	trace
10	1.0	PIDA (1.0)	THF	22
11	1.0	PIDA (1.0)	DMF	20
12	1.0	PIDA (1.0)	DCE	trace
13	1.0	PIDA (1.0)	dioxane	34
14	1.5	PIDA (1.0)	MeCN	52
15	2.0	PIDA (1.0)	MeCN	55
16	2.5	PIDA (1.0)	MeCN	55
17	2.0	PIDA (0.5)	MeCN	23
18	2.0	PIDA (1.1)	MeCN	61
19	2.0	PIDA (1.2)	MeCN	64
20	2.0	PIDA (1.3)	MeCN	60

[a]Reaction conditions: rt, 15 min. [b]GC yield, except for entry 19 (isolated yield). [c]NR, no reaction.

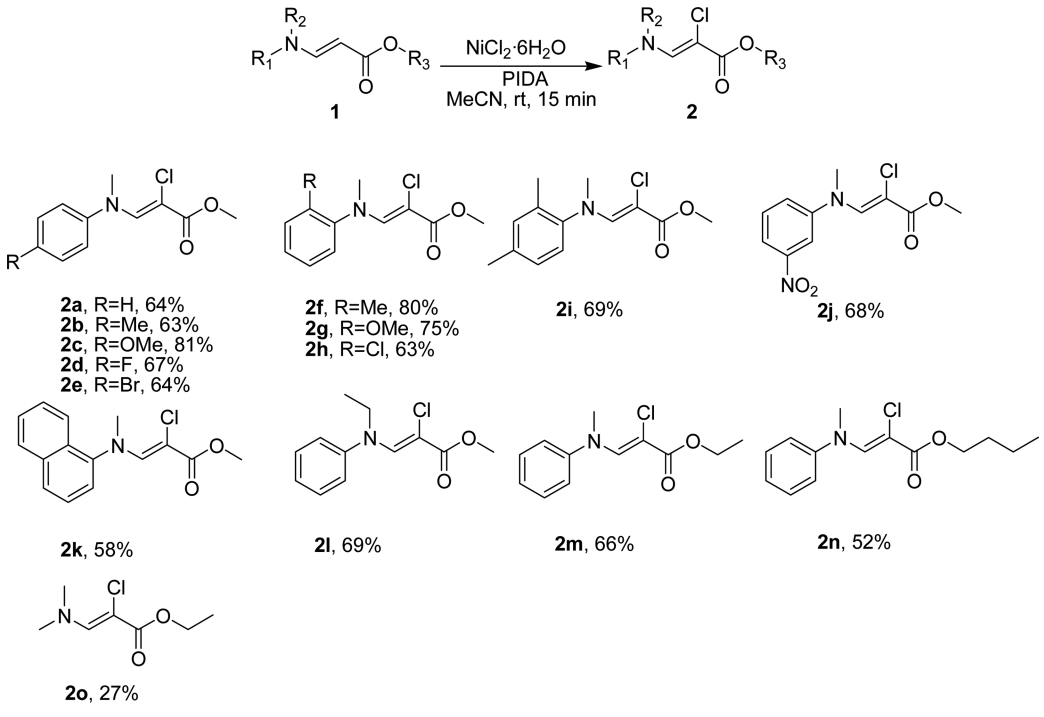
products was confirmed by NOE experiments on **2i** (Supporting Information, S38).

Previously, chloroenamines have been prepared in high yields from the condensations of 2-chloroacetoacetate with aniline[26−28] or primary alkyl amines[29] and from the condensations of 2-formyl-2-chloroacetate sodium salt with the corresponding amine hydrochloride salts.[30] However, the products were only limited to primary amine-substituted olefins, which is different from the secondary amine-substituted olefins that were obtained in this work. Thus, this is the only viable method to prepare secondary amine-substituted α-chloroenamines.

Next, 11 (*Z*)-enamides were successfully transformed into the corresponding (*Z*)-α-chloroenamides using the same procedure (Scheme 2). The reactions were rapid (15 min) with yields ranging from 23% to 70%. The nature of the substituent on the aryl rings had only a minor influence on the product yields, but the position of the substituent greatly affected the yield. All the *ortho*-substituted aromatic enamides gave lower yields of the products (Scheme 2, **4e**−**4g** and **4i**). An X-ray analysis of **4b** was performed to determine the stereochemistry of **4** (Supporting Information, S39−S42). This type of primary amide-substituted α-chloroenamides cannot be synthesized by other currently available methods.

Bromination of enamines (Scheme 3, **1c**, **1d**, **1i**, **1l**, **1m**, **1g**) with TBAB and PIDA in MeCN offered the corresponding α-bromoenamines. The effect of the nature and position of the phenyl ring substituents on the reaction yields and rates was not obvious. All the yields were moderate (50−68%), and the reactions were all complete in 15 min. With the exception of **5c**, which bears a strong electron-donating *para*-MeO group, all the products were prepared stereoselectively in the (*Z*)-configurations. The stereochemistry of the compounds was confirmed by comparing the NMR data with those of known compounds.[11,31] The bromination of enamides using the same procedure ended in failure.

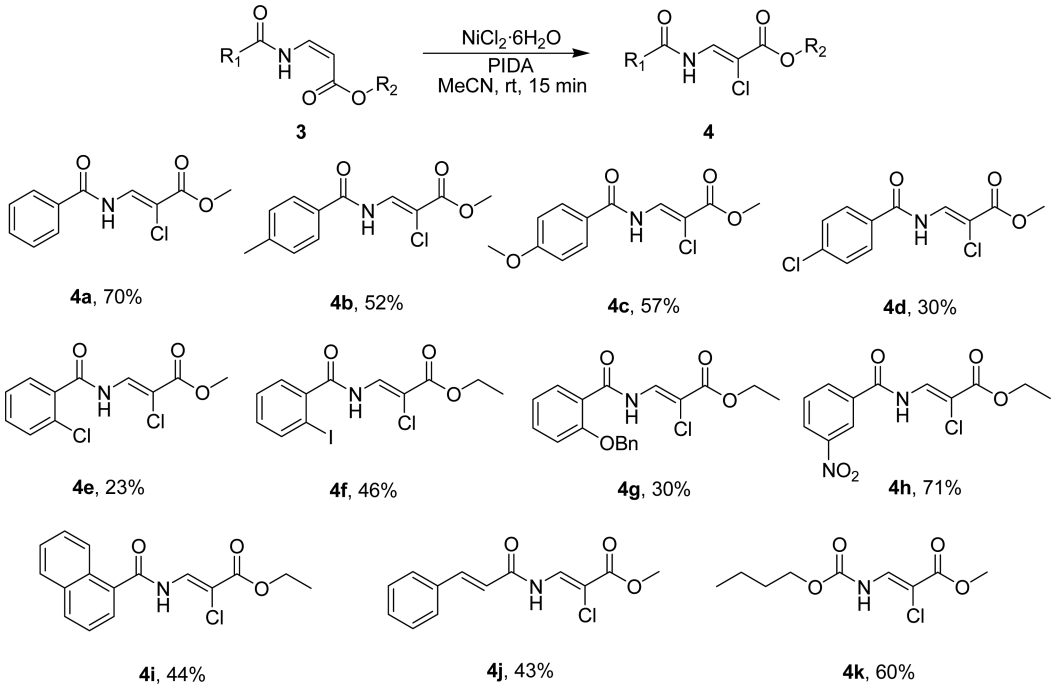
Scheme 1. Chlorination of Enamines[a]



[a]Reaction conditions: **1** (0.5 mmol), PIDA (0.6 mmol), $NiCl_2·6H_2O$ (1 mmol), MeCN (5 mL), rt, 15 min, isolated yields.

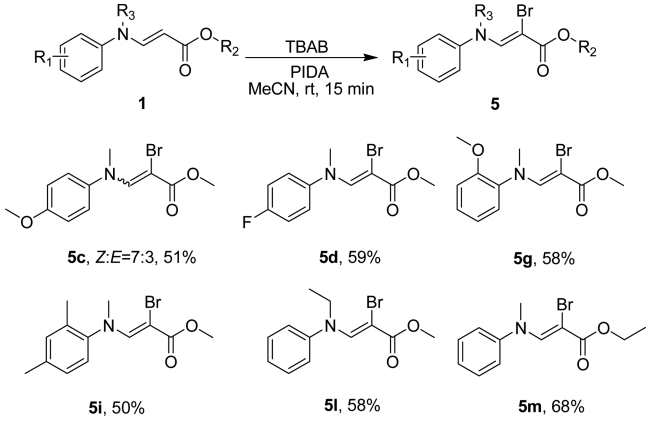
DOI: 10.1021/acs.joc.5b01603
J. Org. Chem. 2015, 80, 10000−10008

Scheme 2. Chlorination of Enamides[a]



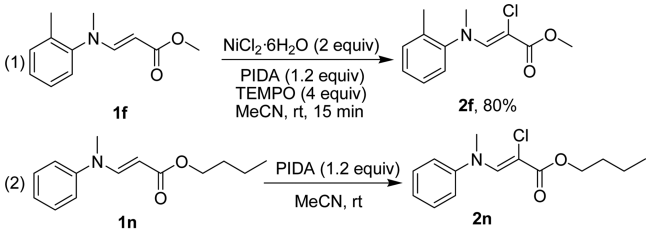
[a]Reaction conditions: **3** (0.5 mmol), PIDA (0.6 mmol), $NiCl_2·6H_2O$ (1 mmol), MeCN (5 mL), rt, 15 min, isolated yields.

Scheme 3. Bromination of Enamines[a]



[a]Reaction conditions: **1** (0.5 mmol), PIDA (0.6 mmol), TBAB (1 mmol), MeCN (5 mL), rt, 15 min, isolated yields.

Scheme 4. Mechanism Studies through Varying the Reaction Conditions[a]



conditions:	yield[a]
a: $ZnCl_2$ (2 equiv), 15 min	46%
b: $BnEt_3N^+Cl^-$ (4 equiv), 8 h	15%
c: $BnEt_3N^+Cl^-$ (4 equiv), $Ni(OAc)_2$ (1.2 equiv), 8 h	14%
d: $BnEt_3N^+Cl^-$ (4 equiv), HOAc (2.4 equiv), 8 h	33%
e: $BnEt_3N^+Cl^-$ (4 equiv), NaOAc (2.4 equiv), 8 h	6%
f : $BnEt_3N^+Cl^-$ (10 equiv), HOAc (2.4 equiv), 8 h	34%

[a]GCMS yield, except for condition "a" (isolated yield).

The current methods to construct brominated enamine skeletons include the reaction of 3,4-dihalo-2(5*H*) furan with amines,[32−34] the bromination of enamines with NBS,[35] the photolysis of isoxazol-5(2*H*)-ones in the presence of a bromide source ($BnEt_3N^+Br^-$ or Et_3NHBr),[36] and palladium-catalyzed aminohalogenation of alkenes oxidized by molecular oxygen.[11,31,37] The first method is limited to the production of furan skeletons, the next two produce a mixture of the two isomers, and the palladium-catalyzed coupling reaction produces primary amine-substituted or sulfoximine-substituted olefins. This method is stereoselective, convenient, and complementary to the known methods.

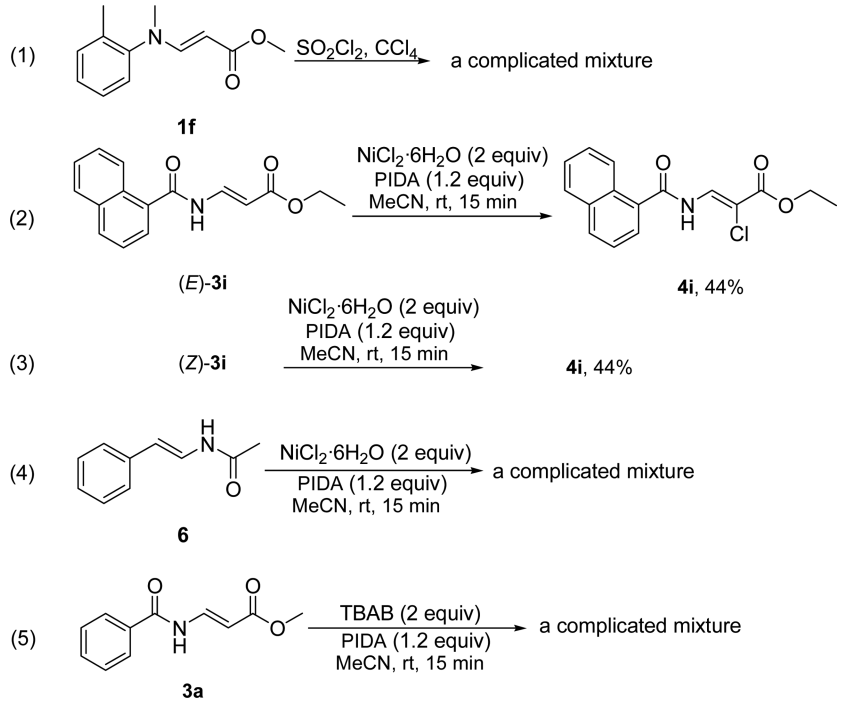
To gain insight into the halogenation mechanism, several control experiments were carried out (Scheme 4). A radical scavenger TEMPO was added to a mixture of **1f**, PIDA, and $NiCl_2·6H_2O$ in MeCN. The addition of TEMPO did not affect the reaction, which excludes the radical pathway (Scheme 4, reaction (1)).

Next, other chlorine sources were tested (Scheme 4, reaction (2)). Chlorination of **1n** using benzyltriethylammonium chloride instead of $NiCl_2·6H_2O$ as a chloride source made the reaction sluggish (reaction (2), condition b). Addition of $Ni(OAc)_2$ (reaction (2), condition c), a weaker Lewis acid than $NiCl_2·6H_2O$, to benzyltriethylammonium chloride, PIDA, and **1n** in MeCN gave a similar result to reaction (2), condition b. When $NiCl_2·6H_2O$ was replaced with $ZnCl_2$, the reaction was also rapid (reaction (2), condition a). These results suggest that acidic conditions are necessary to oxidize Cl^- to Cl^+ using PIDA.

Other variables were also tested. Raising the concentration of AcO^- by adding AcOH or AcONa did not accelerate the reactions, indicating that an attack of AcO^- on an intermediate is not a rate-determining step (reaction (2), conditions d, e).

DOI: 10.1021/acs.joc.5b01603
J. Org. Chem. 2015, 80, 10000−10008

Scheme 5. Mechanism Studies through Varying the Substrates



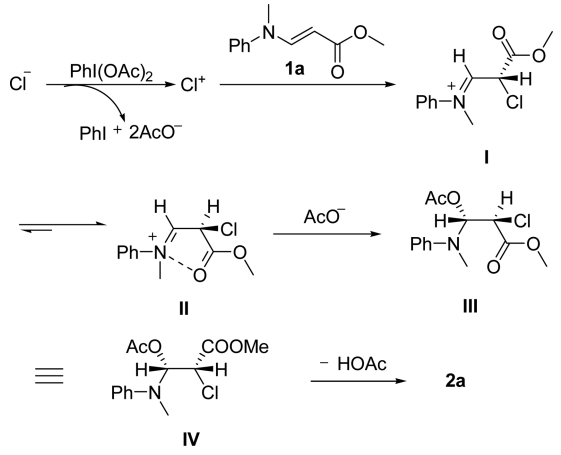
Increasing the amount of $BnEt_3N^+Cl^-$ to 10 equiv did not improve the reaction (reaction (2), conditions f vs d), which indicates that an attack of Cl^- on an intermediate is not a rate-determining step.

Addition of SO_2Cl_2 to the double bond is regarded as a convenient method for preparing dichlorides.[38] However, the reaction between SO_2Cl_2 and **1f** (Scheme 5, reaction (1)) yielded a complicated mixture, which indicates that dichloride is not the intermediate that leads to the desired (*Z*)-*α*-haloenamine. Another control experiment, the oxidation of (*E*)-ethyl 3-(1-naphthamido)acrylate ((*E*)-**3i**), produced the same product as that starting from the (*Z*)-isomer ((*Z*)-**3i**) (Scheme 5, reactions (2), (3)). This indicates that the same configuration-controlling intermediate is involved in the chlorinations of both (*E*)-**3i** and (*Z*)-**3i**. Probably for the same reason, oxidation of **6** and $NiCl_2·6H_2O$ with PIDA (Scheme 5, reaction (4)) yielded a complicated mixture.

On the basis of these experiments, the following mechanism is proposed (Scheme 6). The oxidation of chloride by PIDA generates a chloronium ion, which adds to the double bond of **1a** to form **I** and **II**. Conformation **II** dominates the equilibrium due to the attraction between the positively charged nitrogen atom and the electron-rich carbonyl oxygen atom. Addition of AcO^- from the less hindered side leads to **III**. An *anti*-elimination of AcOH produces (*Z*)-configurated *α*-chloroenamides, *α*-chloroenamines, and *α*-bromoenamines.

It is well-documented in the literature[39−42] and taught in both undergraduate[43] and graduate[44] courses that the three-membered bromonium ion is involved in the addition of bromine to olefins. However, this is not the primary mechanism here since all the products are (*Z*)-stereoisomers whether starting from (*E*)-enamines or (*Z*)-enamides. This is probably because the positive charge generated from the addition of bromonium ion to a C=C bond is better stabilized by delocalization onto the nitrogen atom than in the three-membered bromonium ion (Scheme 6, **I** and **II**). This allows

Scheme 6. Proposed Mechanism for the Halogenation of Enamine and Enamide Represented by the Chlorination of 1a

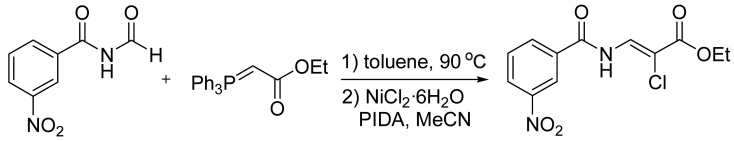


the stereoselective addition of acetate to the C=N bond from the direction opposite to the halogen atom. However, in the case of **5c** (*Z*: *E* = 7:3), the *para*-MeO group is feeding electrons into the *π*-system that is formed after the addition of bromide. This increases the electron density on the *π*-system, partially reducing the electrostatic attraction between oppositely charged groups and the stereoselectivity. In the cases of **5d**, **5i**, **5l**, and **5m** (without strong electron-donating groups), the stereoselectivities are high. In the case of **5g**, the *ortho*-MeO group reduces the conjugation between the ring and the enamine. In the meantime, the electron-rich anilino group of **5c** may stabilize the three-membered bromonium ion to some extent. The latter may account for the fact that the chlorination stereoselectivity for **2c** was higher than the bromination stereoselectivity for **5c**, since it is documented that the three-membered chloronium ion exists in a trace amount.[39,40] In the

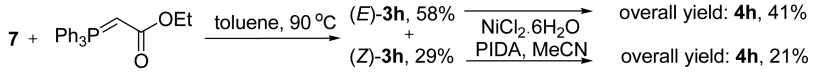
DOI: 10.1021/acs.joc.5b01603
J. Org. Chem. 2015, 80, 10000−10008

Scheme 7. Comparison of the Multipot and the One-Pot Synthesis Reactions

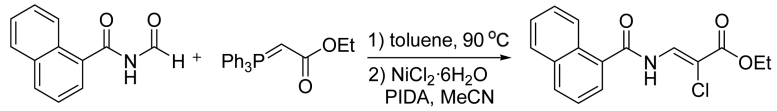
(1) One-pot Wittig reaction and chlorination of **7**



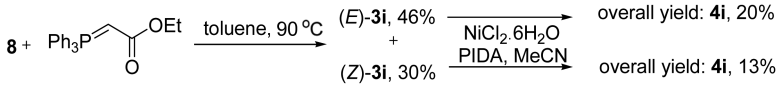
(2) Multi-pot Wittig reaction and chlorination of **7**



(3) One-pot Wittig reaction and chlorination of **8**



(4) Multi-pot Wittig reaction and chlorination of **8**



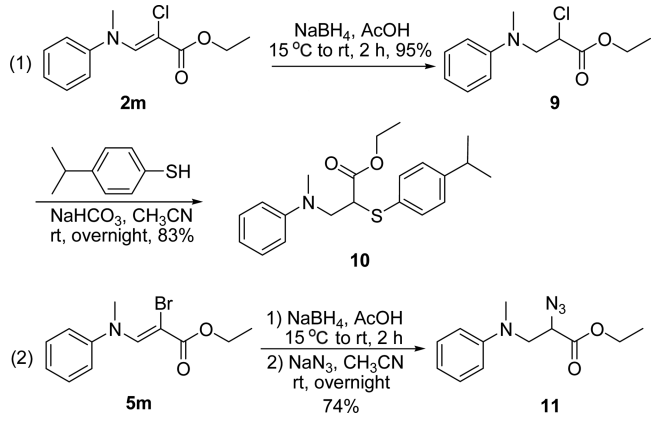
^{1}H NMR spectrum of crude **2a** (Supporting Information, S38), no signals for (*E*)-**2a** were detected. This may exclude the steric effect-dominated or three-membered chloronium ion-involved mechanism since halogenations via these two mechanisms would lead to stereoisomers in a detectable amount.

When we attempted to make α-bromoenamides that were analogous to the α-bromoenamines, only a complicated mixture was obtained (Scheme 5, reaction (5)). This is because the nitrogen atom in enamine is more electron-rich than that in enamide (Scheme 3, **5l**, vs Scheme 5, reaction (5)), and so the former stabilizes the positive charge better than the latter. Thus, in the case of enamides, the positive charge is more likely to be partially stabilized through the three-membered bromonium ion. Consequently, the lack of the electrostatic attraction led to the complicated mixture. Relevant examples of electrostatic attraction or repulsion are known to occur in substitution reactions involving multifunctionalized molecules[45] and in olefin epoxidations.[46] To the best of our knowledge, there have been no such reports with olefin halogenations.[47−50]

The stereoselective halogenation method was extended to the simplification of the synthesis of **4h** and **4i** (Scheme 7). In the case of **4h**, the conventional multipot reaction required both workup and purification of the Wittig products from **7** and ethyl triphenylphosphonoacetate to get (*E*)- and (*Z*)-**3h**. It was not easy to separate triphenylphosphine oxide and the Wittig products by chromatography. This was followed by chlorination of both (*E*)- and (*Z*)-**3h** separately, producing **4h** in 62% combined overall yield. In the simplified procedure, the Wittig reaction and chlorination were realized in one-pot avoiding workup and purification of the Wittig products and producing **4h** in 70% overall yield. This simplified procedure had benefits of saving two workup and two purification operations and improving the yield by 8%. A similar result was observed in the comparison reaction from **8** to **4i** (Scheme 7).

To further explore the utility of this synthetic method, chlorinated and brominated enamines (**2m**, **5m**) were transformed into three β-amino acid esters (Scheme 8). Reduction

Scheme 8. Selected Transformation of Enamines



of chlorinated enamine **2m** with $NaBH_4$ in AcOH leads to α-chloro-β-amino acid ester **9** in 95% yield, which was further transformed to α-mecapto-β-amino acid ester **10** in 83% yield. Brominated enamine **5m** was reduced with $NaBH_4$ and treated with sodium azide to produce α-azido-β-amino acid ester **11** in 74% overall yield. Although several methods are known to prepare these types of compounds,[51−57] these syntheses provide alternative methods, which compared favorably to most of the current procedures in terms of yield and operational convenience.

DOI: 10.1021/acs.joc.5b01603
J. Org. Chem. 2015, 80, 10000−10008

In conclusion, three types of halogenation methods including the direct chlorination of (*Z*)-enamides and the direct bromination and chlorination of (*E*)-enamines have been developed. The similar intermediates were deduced to exist in all three reactions, and their configurations were controlled by the electrostatic attraction effect, which is the primary mechanism of the stereoselective synthesis. This conclusion is supported by the results from the control experiments. The reactions were mild, fast, convenient, and highly stereoselective with good to moderate yields for most products. The α-chloroenamine and α-chloroenamide products are only accessible via the procedures reported herein.

EXPERIMENTAL SECTION

General Information. Commercially available reagents were used without further purification. The starting materials **1a−1o**,[58] **3a−3k**,[20] and PIDA[59] were prepared according to literature methods. ^{1}H NMR, ^{13}C NMR, and NOE spectra were recorded with a 400, 500, or 600 MHz spectrometer using TMS as an internal standard. Chemical shifts (δ) are reported relative to TMS (^{1}H) or $CDCl_3$ (^{13}C). Single crystal X-ray diffraction data for compound **4b** were collected on a diffractometer, using graphite-monochromatized Mo−Kα radiation (0.71073 Å). High-resolution mass spectra (HRMS) were recorded on a QTOF mass analyzer using electrospray ionization (ESI). Melting points were recorded with a micro melting point apparatus.

General Procedure for Chlorination of (*E*)-Enamines and (*Z*)-Enamides Using the Chlorination of 1a as an Example. To a solution of **1a** (0.5 mmol, 96 mg) in MeCN (5 mL) were added $NiCl_2 \cdot 6H_2O$ (1.0 mmol, 238 mg) and PIDA (0.6 mmol, 193 mg). The mixture was stirred at room temperature for 15 min (monitored by TLC). After completion, the reaction mixture was quenched with water (10 mL) and extracted with DCM (2 × 10 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and evaporated under vacuum. The residue was purified by preparative TLC (EtOAc:petroleum ether, 1:5) to yield **2a** (72 mg, 64%).

General Procedure for Bromination of (*E*)-Enamines Using the Bromination of 1c as an Example. To a solution of **1c** (0.5 mmol, 111 mg) in MeCN (5 mL) were added TBAB (1.0 mmol, 322 mg) and PIDA (0.6 mmol, 193 mg). The mixture was stirred at room temperature for 15 min (monitored by TLC). After completion, the reaction mixture was quenched with water (10 mL) and extracted with DCM (2 × 10 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and evaporated under vacuum. The residue was purified by preparative TLC (EtOAc:petroleum ether, 1:5) to yield **5c** (77 mg, 51%).

*(Z)-Methyl 2-Chloro-3-(methyl(phenyl)amino)acrylate (**2a**).* Enamine **1a** (96 mg, 0.50 mmol) was reacted according to the general procedure. After preparative TLC (EtOAc:petroleum ether, 1:5), α-chloroenamine **2a** was isolated as a yellow oil (72 mg, 64% yield); ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.90 (s, 1H), 7.36 (t, *J* = 7.2 Hz, 2H), 7.17 (t, *J* = 7.1 Hz, 1H), 7.13 (d, *J* = 7.4 Hz, 2H), 3.79 (s, 3H), 3.66 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$): δ 166.2, 147.0, 142.4, 129.3, 124.9, 121.0, 95.2, 52.4, 39.2; HRMS (ESI) *m*/*z*: $[M + Na]^+$ Calcd for $C_{11}H_{12}ClNO_2Na$ 248.0449, Found 248.0449.

*(Z)-Methyl 2-Chloro-3-(methyl(p-tolyl)amino)acrylate (**2b**).* Enamine **1b** (103 mg, 0.50 mmol) was reacted according to the general procedure. After preparative TLC (EtOAc:petroleum ether, 1:5), α-chloroenamine **2b** was isolated as a yellow oil (75 mg, 63% yield); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.88 (s, 1H), 7.18 (d, *J* = 8.2 Hz, 2H), 7.04 (d, *J* = 8.4 Hz, 2H), 3.80 (s, 3H), 3.66 (s, 3H), 2.36 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 166.2, 144.7, 142.7, 134.8, 129.8, 121.3, 94.2, 52.3, 39.6, 20.8; HRMS (ESI) *m*/*z*: $[M + Na]^+$ Calcd for $C_{12}H_{14}ClNO_2Na$ 262.0605, Found 262.0607.

*(Z)-Methyl 2-Chloro-3-((4-methoxyphenyl)(methyl)amino)acrylate (**2c**).* Enamine **1c** (111 mg, 0.50 mmol) was reacted according to the general procedure. After preparative TLC (EtOAc:petroleum ether, 1:5), α-chloroenamine **2c** was isolated as a yellow solid, (104 mg, 81% yield); mp 69−70 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.81 (s, 1H), 7.09 (d, *J* = 8.9 Hz, 2H), 6.89 (d, *J* = 8.9 Hz, 2H), 3.83 (s, 3H), 3.78 (s, 3H), 3.62 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 166.3, 157.3, 143.1, 140.3, 123.6, 114.3, 93.2, 55.5, 52.3, 40.9; HRMS (ESI) *m*/*z*: $[M + Na]^+$ Calcd for $C_{12}H_{14}ClNO_3Na$ 278.0554, Found 278.0559.

*(Z)-Methyl 2-Chloro-3-((4-fluorophenyl)(methyl)amino)acrylate (**2d**).* Enamine **1d** (105 mg, 0.50 mmol) was reacted according to the general procedure. After preparative TLC (EtOAc:petroleum ether, 1:5), α-chloroenamine **2d** was isolated as a yellow solid, (82 mg, 67% yield); mp 56−57 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.81 (s, 1H), 7.19−6.99 (m, 4H), 3.80 (s, 3H), 3.62 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 166.1, 160.1 (d, J_{CF} = 245.2 Hz), 142.9 (d, J_{CF} = 2.9 Hz), 142.6, 123.6 (d, J_{CF} = 8.3 Hz), 116.0 (d, J_{CF} = 22.8 Hz), 94.8, 52.4, 40.6; HRMS (ESI) *m*/*z*: $[M + Na]^+$ Calcd for $C_{11}H_{11}ClFNO_2Na$ 266.0360, Found 266.0356.

*(Z)-Methyl 2-Chloro-3-((4-bromophenyl)(methyl)amino)acrylate (**2e**).* Enamine **1e** (135 mg, 0.50 mmol) was reacted according to the general procedure. After preparative TLC (EtOAc:petroleum ether, 1:5), α-chloroenamine **2e** was isolated as a yellow solid, (97 mg, 64% yield); mp 58−60 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.83 (s, 1H), 7.54−7.41 (m, 2H), 7.11−6.73 (m, 2H), 3.80 (s, 3H), 3.61 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 165.8, 145.7, 141.8, 132.2, 122.4, 117.7, 96.7, 52.5, 39.4; HRMS (ESI) *m*/*z*: $[M + Na]^+$ Calcd for $C_{11}H_{11}BrClNO_2Na$ 325.9554, Found 325.9551.

*(Z)-Methyl 2-Chloro-3-(methyl(o-tolyl)amino)acrylate (**2f**).* Enamine **1f** (103 mg, 0.50 mmol) was reacted according to the general procedure. After preparative TLC (EtOAc:petroleum ether, 1:5), α-chloroenamine **2f** was isolated as a yellow oil (96 mg, 80% yield); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70 (s, 1H), 7.39−6.99 (m, 4H), 3.75 (s, 3H), 3.45 (s, 3H), 2.25 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 166.4, 144.0, 135.0, 130.9, 127.8, 126.9, 126.8, 91.3, 52.1, 17.7; HRMS (ESI) *m*/*z*: $[M + Na]^+$ Calcd for $C_{12}H_{14}ClNO_2Na$ 262.0605, Found 262.0611.

*(Z)-Methyl 2-Chloro-3-((2-methoxyphenyl)(methyl)amino)-acrylate (**2g**).* Enamine **1g** (111 mg, 0.50 mmol) was reacted according to the general procedure. After preparative TLC (EtOAc:petroleum ether, 1:5), α-chloroenamine **2g** was isolated as a yellow oil (96 mg, 75% yield); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71 (s, 1H), 7.27 (td, *J* = 8.1, 1.6 Hz, 1H), 7.19−7.10 (m, 1H), 6.94 (t, *J* = 7.4 Hz, 2H), 3.85 (s, 3H), 3.74 (s, 3H), 3.46 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 166.5, 154.6, 144.5, 128.5, 127.6, 120.6, 111.8, 91.5, 55.7, 52.1, 43.4; HRMS (ESI) *m*/*z*: $[M + Na]^+$ Calcd for $C_{12}H_{14}ClNO_3Na$ 278.0554, Found 278.0560.

*(Z)-Methyl 2-Chloro-3-((2-chlorophenyl)(methyl)amino)acrylate (**2h**).* Enamine **1h** (113 mg, 0.50 mmol) was reacted according to the general procedure. After preparative TLC (EtOAc:petroleum ether, 1:5), α-chloroenamine **2h** was isolated as a yellow oil (82 mg, 63%); ^{1}H NMR (400 MHz, CDCl3): δ 7.69 (s, 1H), 7.52−7.36 (m, 1H), 7.36−7.13 (m, 3H), 3.76 (s, 3H), 3.46 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 166.1, 143.7, 132.2, 130.2, 128.9, 128.8, 127.5, 93.0, 77.4, 77.1, 76.7, 52.2, 44.1; HRMS (ESI) *m*/*z*: $[M + Na]^+$ Calcd for $C_{11}H_{11}Cl_2NO_2Na$ 282.0059, Found 282.0059.

*(Z)-Methyl 2-Chloro-3-((2,4-dimethylphenyl)(methyl)amino)-acrylate (**2i**).* Enamine **1i** (110 mg, 0.50 mmol) was reacted according to the general procedure. After preparative TLC (EtOAc:petroleum ether, 1:5), α-chloroenamine **2i** was isolated as a yellow solid, (88 mg, 69% yield); mp 75−77 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70 (s, 1H), 7.19−6.87 (m, 3H), 3.76 (s, 3H), 3.43 (s, 3H), 2.35 (s, 3H), 2.21 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 166.5, 144.2, 137.6, 134.7, 131.5, 127.4, 126.7, 91.0, 52.1, 21.0, 17.6; HRMS (ESI) *m*/*z*: $[M + Na]^+$ Calcd for $C_{13}H_{16}ClNO_2Na$ 276.0762, Found 276.0765.

*(Z)-Methyl 2-Chloro-3-(methyl(4-nitrophenyl)amino)acrylate (**2j**).* Enamine **1j** (118 mg, 0.50 mmol) was reacted according to the general procedure. After preparative TLC (EtOAc:petroleum ether, 1:5), α-chloroenamine **2j** was isolated as a yellow solid, (92 mg, 68% yield); mp 118−121 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.98 (ddd, *J* = 8.1, 2.0, 0.8 Hz, 1H), 7.94 (t, *J* = 2.2 Hz, 1H), 7.88 (s, 1H), 7.54 (t, *J* = 8.2 Hz, 1H), 7.40 (ddd, *J* = 8.2, 2.4, 0.7 Hz, 1H), 3.84 (s, 3H), 3.67 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 165.3, 148.8, 147.0, 140.9,

DOI: 10.1021/acs.joc.5b01603
J. Org. Chem. 2015, 80, 10000−10008

130.0, 125.7, 118.6, 114.5, 100.2, 52.8, 39.4; HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{11}H_{11}ClN_2O_4Na$ 293.0300, Found 293.0295.

*(Z)-Methyl 2-Chloro-3-(methyl(naphthalen-1-yl)amino)acrylate (**2k**).* Enamine **1k** (121 mg, 0.50 mmol) was reacted according to the general procedure. After preparative TLC (EtOAc:petroleum ether, 1:5), α-chloroenamine **2k** was isolated as a yellow oil (80 mg, 58% yield); ^1H NMR (400 MHz, $CDCl_3$): δ 7.89 (dt, J = 16.3, 8.5 Hz, 4H), 7.57 (dq, J = 6.7, 5.8 Hz, 2H), 7.48 (t, J = 7.7 Hz, 1H), 7.38 (d, J = 7.2 Hz, 1H), 3.75 (s, 3H), 3.66 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 166.4, 144.8, 134.4, 129.8, 128.6, 128.2, 127.1, 126.6, 125.5, 124.3, 122.6, 92.0, 52.2, 44.5; HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{15}H_{14}ClNO_2Na$ 298.0605, Found 298.0607.

*(Z)-Methyl 2-Chloro-3-(ethyl(phenyl)amino)acrylate (**2l**).* Enamine **1l** (103 mg, 0.50 mmol) was reacted according to the general procedure. After preparative TLC (EtOAc:petroleum ether, 1:5), α-chloroenamine **2l** was isolated as a yellow oil (83 mg, 69% yield); ^1H NMR (400 MHz, $CDCl_3$): δ 7.86 (s, 1H), 7.38 (t, J = 7.8 Hz, 2H), 7.22 (t, J = 7.4 Hz, 1H), 7.15 (d, J = 8.0 Hz, 2H), 4.05 (q, J = 7.1 Hz, 2H), 3.80 (s, 3H), 1.31 (t, J = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 166.3, 145.2, 142.0, 129.2, 125.5, 123.0, 93.9, 524, 47.3, 14.8; HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{12}H_{14}ClNO_2Na$ 262.0605, Found 262.0609.

*(Z)-Ethyl 2-Chloro-3-(methyl(phenyl)amino)acrylate (**2m**).* Enamine **1m** (103 mg, 0.50 mmol) was reacted according to the general procedure. After preparative TLC (EtOAc:petroleum ether, 1:5), α-chloroenamine **2m** was isolated as a yellow oil (79 mg, 66% yield); ^1H NMR (400 MHz, $CDCl_3$): δ 7.92 (s, 1H), 7.38 (dd, J = 8.3, 7.6 Hz, 2H), 7.19 (d, J = 7.4 Hz, 1H), 7.14 (d, J = 7.7 Hz, 2H), 4.27 (q, J = 7.1 Hz, 2H), 3.68 (s, 3H), 1.33 (t, J = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 165.6, 147.0, 142.2, 129.3, 124.7, 120.9, 95.9, 61.3, 39.1, 14.5; HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{12}H_{14}ClNO_2Na$ 262.0605, Found 262.0610.

*(Z)-Butyl 2-Chloro-3-(methyl(phenyl)amino)acrylate (**2n**).* Enamine **1n** (117 mg, 0.50 mmol) was reacted according to the general procedure. After preparative TLC (EtOAc:petroleum ether, 1:5), α-chloroenamine **2n** was isolated as a yellow oil (69 mg, 52% yield); ^1H NMR (400 MHz, $CDCl_3$): δ 7.91 (s, 1H), 7.38 (t, J = 7.9 Hz, 2H), 7.18 (d, J = 7.5 Hz, 1H), 7.13 (d, J = 8.3 Hz, 2H), 4.21 (t, J = 6.7 Hz, 2H), 3.67 (s, 3H), 1.75−1.60 (m, 2H), 1.55−1.36 (m, 2H), 0.97 (t, J = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 165.7, 147.0, 142.1, 129.3, 124.7, 120.8, 96.0, 65.2, 39.0, 30.9, 19.2, 13.8; HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{14}H_{18}ClNO_2Na$ 290.0918, Found 290.0921.

*(Z)-Methyl 2-Chloro-3-(dimethylamino)acrylate (**2o**).*[60] Enamine **1o** (72 mg, 0.50 mmol) was reacted according to the general procedure. After preparative TLC (EtOAc:petroleum ether, 1:5), α-chloroenamine **2o** was isolated as a yellow oil (22 mg, 27% yield); ^1H NMR (400 MHz, $CDCl_3$): δ 7.50 (s, 1H), 4.22 (q, J = 7.1 Hz, 2H), 3.18 (s, 6H), 1.31 (t, J = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 166.2, 145.3, 89.0, 60.7, 42.8, 14.5.

*(Z)-Methyl 3-Benzamido-2-chloroacrylate (**4a**).* Enamide **3a** (103 mg, 0.50 mmol) was reacted according to the general procedure. After preparative TLC (EtOAc:petroleum ether, 1:5), α-chloroenamide **4a** was isolated as a white solid (84 mg, 70% yield); mp 117−119 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 8.55 (d, J = 11.7 Hz, 1H), 8.34 (d, J = 11.2 Hz, 1H), 7.91 (d, J = 7.3 Hz, 2H), 7.66 (t, J = 7.4 Hz, 1H), 7.55 (t, J = 7.6 Hz, 2H), 3.89 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 164.0, 163.0, 133.3, 132.0, 131.8, 129.1, 127.6, 106.2, 52.9; HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{11}H_{10}ClNO_3Na$ 262.0241, Found 262.0243.

*(Z)-Methyl 2-Chloro-3-(4-methylbenzamido)acrylate (**4b**).* Enamide **3b** (110 mg, 0.50 mmol) was reacted according to the general procedure. After preparative TLC (EtOAc:petroleum ether, 1:5), α-chloroenamide **4b** was isolated as a white solid (66 mg, 52% yield); mp 127−128 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 8.55 (d, J = 11.8 Hz, 1H), 8.31 (d, J = 11.4 Hz, 1H), 7.81 (d, J = 8.2 Hz, 2H), 7.35 (d, J = 8.0 Hz, 2H), 3.89 (s, 3H), 2.47 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 163.9, 163.1, 144.3, 132.2, 129.8, 128.9, 127.6, 105.9, 52.9, 21.7; HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{12}H_{12}ClNO_3Na$ 276.0398, Found 276.0401.

*(Z)-Methyl 2-Chloro-3-(4-methoxybenzamido)acrylate (**4c**).* Enamide **3c** (118 mg, 0.50 mmol) was reacted according to the general procedure. After preparative TLC (EtOAc:petroleum ether, 1:5), α-chloroenamide **4c** was isolated as a white solid (77 mg, 57% yield); mp 126−128 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 8.55 (d, J = 11.8 Hz, 1H), 8.27 (d, J = 10.9 Hz, 1H), 7.88 (d, J = 8.8 Hz, 2H), 7.02 (d, J = 8.8 Hz, 2H), 3.91 (s, 3H), 3.88 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 163.7, 163.3, 163.2, 132.3, 129.7, 123.9, 114.3, 105.6, 55.6, 52.8; HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{12}H_{12}ClNO_4Na$ 292.0347, Found 292.0349.

*(Z)-Methyl 2-Chloro-3-(4-chlorobenzamido)acrylate (**4d**).* Enamide **3d** (120 mg, 0.50 mmol) was reacted according to the general procedure. After preparative TLC (EtOAc:petroleum ether, 1:5), α-chloroenamide **4d** was isolated as a white solid (42 mg, 30% yield); mp 109−110 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 8.52 (d, J = 11.7 Hz, 1H), 8.27 (d, J = 10.9 Hz, 1H), 7.85 (d, J = 8.6 Hz, 2H), 7.53 (d, J = 8.6 Hz, 2H), 3.89 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 163.0, 162.9, 139.9, 131.8, 130.2, 129.5, 129.0, 106.7, 53.0; HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{11}H_9Cl_2NO_3Na$ 295.9857, Found 295.9856.

*(Z)-Methyl 2-Chloro-3-(2-chlorobenzamido)acrylate (**4e**).* Enamide **3e** (120 mg, 0.50 mmol) was reacted according to the general procedure. After preparative TLC (EtOAc:petroleum ether, 1:5), α-chloroenamide **4e** was isolated as white solid (32 mg, 23% yield); mp 97−99 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 8.86 (d, J = 10.5 Hz, 1H), 8.53 (d, J = 11.6 Hz, 1H), 7.92 (d, J = 7.6 Hz, 1H), 7.51 (d, J = 4.0 Hz, 2H), 7.48−7.38 (m, 1H), 3.88 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 163.1, 163.0, 133.2, 131.8, 131.6, 131.1, 131.0, 127.6, 107.0, 53.0; HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{11}H_9Cl_2NO_3Na$ 295.9857, Found 295.9856.

*(Z)-Ethyl 2-Chloro-3-(2-iodobenzamido)acrylate (**4f**).* Enamide **3f** (173 mg, 0.50 mmol) was reacted according to the general procedure. After preparative TLC (EtOAc:petroleum ether, 1:5), α-chloroenamide **4f** was isolated as white solid (87 mg, 46% yield); mp 97−98 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 8.48 (d, J = 11.7 Hz, 1H), 8.12 (d, J = 10.9 Hz, 1H), 7.97 (d, J = 8.0 Hz, 1H), 7.55 (d, J = 7.5 Hz, 1H), 7.49 (t, J = 7.5 Hz, 1H), 7.23 (td, J = 7.9, 1.7 Hz, 1H), 4.33 (q, J = 7.1 Hz, 2H), 1.37 (t, J = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 165.8, 162.4, 140.7, 139.1, 132.7, 131.0, 129.2, 128.5, 107.7, 92.2, 62.2, 14.3; HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{12}H_{11}ClINO_3Na$ 401.9364, Found 401.9375.

*(Z)-Ethyl 3-(2-(Benzyloxy)benzamido)-2-chloroacrylate (**4g**).* Enamide **3g** (163 mg, 0.50 mmol) was reacted according to the general procedure. After preparative TLC (EtOAc:petroleum ether, 1:5), α-chloroenamide **4g** was isolated as white solid (54 mg, 30% yield); mp 143−144 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 10.26 (d, J = 11.3 Hz, 1H), 8.52 (d, J = 11.6 Hz, 1H), 8.31 (dd, J = 8.0, 1.7 Hz, 1H), 7.62−7.54 (m, 1H), 7.54−7.47 (m, 2H), 7.47−7.42 (m, 3H), 7.17 (t, J = 7.6 Hz, 2H), 5.26 (s, 2H), 4.27 (q, J = 7.1 Hz, 2H), 1.33 (t, J = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 163.0, 162.9, 157.5, 134.7, 134.4, 133.3, 132.3, 129.4, 129.2, 129.1, 121.9, 119.3, 112.8, 106.1, 72.0, 61.8, 14.3; HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{19}H_{18}ClNO_4Na$ 382.0817, Found 382.0819.

*(Z)-Ethyl 2-Chloro-3-(3-nitrobenzamido)acrylate (**4h**).* Enamide **3h** (132 mg, 0.50 mmol) was reacted according to the general procedure. After preparative TLC (EtOAc:petroleum ether, 1:5), α-chloroenamide **4h** was isolated as a white solid (106 mg, 71% yield); mp 142−145 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 8.73 (s, 1H), 8.47 (s, 3H), 8.25 (d, J = 7.8 Hz, 1H), 7.77 (t, J = 8.0 Hz, 1H), 4.32 (q, J = 7.1 Hz, 2H), 1.36 (t, J = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 162.3, 162.1, 148.5, 133.6, 133.3, 131.1, 130.4, 127.6, 122.7, 108.1, 77.4, 77.1, 76.8, 62.4, 14.3; HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{12}H_{11}ClN_2O_5Na$ 321.0249, Found 321.0228.

*(Z)-Ethyl 2-Chloro-3-(1-naphthamido)acrylate (**4i**).* Enamide **3i** (135 mg, 0.50 mmol) was reacted according to the general procedure. After preparative TLC (EtOAc:petroleum ether, 1:5), α-chloroenamide **4i** was isolated as a white solid (67 mg, 44% yield); mp 93−96 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 8.62 (d, J = 11.5 Hz, 1H), 8.40 (d, J = 8.1 Hz, 1H), 8.23 (d, J = 11.6 Hz, 1H), 8.06 (d, J = 8.3 Hz, 1H), 8.01−7.86 (m, 1H), 7.79 (d, J = 7.0 Hz, 1H), 7.69−7.58 (m, 2H), 7.55 (dd, J = 8.0, 7.4 Hz, 1H), 4.35 (q, J = 7.1 Hz, 2H), 1.39 (t, J

DOI: 10.1021/acs.joc.5b01603
J. Org. Chem. 2015, 80, 10000−10008

= 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 166.0, 162.6, 133.9, 132.7, 131.6, 131.1, 130.2, 128.7, 128.0, 127.0, 126.1, 124.9, 124.6, 106.8, 62.1, 14.3; HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{16}H_{14}ClNO_3Na$ 326.0554, Found 326.0575.

*(Z)-Ethyl 2-Chloro-3-((E)-3-phenylacrylamido)acrylate (**4j**).* Enamide **3j** (116 mg, 0.50 mmol) was reacted according to the general procedure. After preparative TLC (EtOAc:petroleum ether, 1:5), α-chloroenamide **4j** was isolated as a white solid (60 mg, 43% yield); mp 82−84 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.48 (d, J = 11.9 Hz, 1H), 7.95 (d, J = 11.9 Hz, 1H), 7.86 (d, J = 15.6 Hz, 1H), 7.57 (dd, J = 7.0, 2.2 Hz, 2H), 7.42 (dd, J = 5.1, 1.7 Hz, 3H), 6.62 (d, J = 15.6 Hz, 1H), 3.85 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 163.2, 163.0, 145.9, 133.9, 132.0, 130.9, 129.1, 128.4, 117.9, 105.6, 52.9; HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{13}H_{12}ClNO_3Na$ 288.0398, Found 288.0390.

*(Z)-Methyl 3-(Butoxycarbonylamino)-2-chloroacrylate (**4k**).* Enamide **3k** (101 mg, 0.50 mmol) was reacted according to the general procedure. After preparative TLC (EtOAc:petroleum ether, 1:5), α-chloroenamide **4k** was isolated as a colorless oil (71 mg, 70% yield); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.11 (d, J = 11.8 Hz, 1H), 7.08 (d, J = 7.7 Hz, 1H), 4.24 (t, J = 6.6 Hz, 2H), 3.83 (s, 3H), 1.81−1.53 (m, 2H), 1.53−1.32 (m, 2H), 0.96 (t, J = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 163.1, 152.4, 133.7, 103.5, 66.9, 52.7, 30.7, 18.9, 13.6; HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_9H_{14}ClNO_4Na$ 258.0504, Found 258.0508.

*(Z,E)-Methyl 2-Bromo-3-((4-methoxyphenyl)(methyl)amino)acrylate (**5c**).* Enamine **1c** (111 mg, 0.50 mmol) was reacted according to the general procedure. After preparative TLC (EtOAc:petroleum ether, 1:5), α-bromoenamine **5c** was isolated as a yellow solid, (77 mg, 51% yield); mp 56−57 °C; ^{1}H NMR (400 MHz, $CDCl_3$) (Z:E = 7:3): δ 8.07/7.81 (s, 1H), 7.09 (d, J = 8.9 Hz, 2H), 6.89 (d, J = 8.9 Hz, 2H), 3.82 (s, 3H), 3.78 (s, 3H), 3.62/3.61 (s, 3H); ^{13}C NMR (*Z*-isomer) (101 MHz, CDCl3): δ 166.3, 157.5, 146.0, 143.1, 139.8, 124.3, 114.3, 80.7, 77.4, 77.1, 76.7, 55.5, 52.5, 41.7; HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{12}H_{14}BrNO_3Na$ 322.0049, Found 322.0049.

*(Z)-Methyl 2-Bromo-3-((4-fluorophenyl)(methyl)amino)acrylate (**5d**).* Enamine **1d** (105 mg, 0.50 mmol) was reacted according to the general procedure. After preparative TLC (EtOAc:petroleum ether, 1:5), α-bromoenamine **5d** was isolated as a yellow solid, (85 mg, 59% yield); mp 49−50 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.07 (s, 1H), 7.10 (m, 4H), 3.78 (s, 3H), 3.61 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 166.0, 160.3 (d, J_{CF} = 245.5 Hz), 145.5, 142.5 (d, J_{CF} = 2.8 Hz), 124.3 (d, J_{CF} = 8.3 Hz), 116.0 (d, J_{CF} = 22.8 Hz), 82.4, 52.7, 41.5; HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{11}H_{11}BrFNO_2Na$ 309.9849, Found 309.9854.

*(Z)-Methyl 2-Bromo-3-((2-methoxyphenyl)(methyl)amino)acrylate (**5g**).* Enamine **1g** (111 mg, 0.50 mmol) was reacted according to the general procedure. After preparative TLC (EtOAc:petroleum ether, 1:5), α-bromoenamine **5g** was isolated as a yellow oil (87 mg, 58% yield); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.98 (s, 1H), 7.29 (ddd, J = 7.9, 6.1, 1.6 Hz, 1H), 7.16 (dd, J = 7.6, 1.5 Hz, 1H), 6.95 (m, 2H), 3.87 (s, 3H), 3.76 (s, 3H), 3.46 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 166.4, 155.0, 147.0, 128.7, 128.1, 120.6, 111.8, 78.9, 55.7, 52.3, 44.3; HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{12}H_{14}BrNO_3Na$ 322.0049, Found 322.0053.

*(Z)-Methyl 2-Bromo-3-((2,4-dimethylphenyl)(methyl)amino)acrylate (**5i**).* Enamine **1i** (110 mg, 0.50 mmol) was reacted according to the general procedure. After preparative TLC (EtOAc:petroleum ether, 1:5), α-bromoenamine **5i** was isolated as a yellow solid, (75 mg, 50% yield); mp 68−70 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.97 (s, 1H), 7.03 (m, 3H), 3.75 (s, 3H), 3.41 (s, 3H), 2.34 (s, 3H), 2.19 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 166.4, 146.6, 137.8, 135.1, 131.4, 127.4, 127.1, 78.2, 52.3, 21.1, 17.7; HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{13}H_{16}BrNO_2Na$ 320.0257, Found 320.0257.

*(Z)-Methyl 2-Bromo-3-(ethyl(phenyl)amino)acrylate (**5l**).* Enamine **1l** (103 mg, 0.50 mmol) was reacted according to the general procedure. After preparative TLC (EtOAc:petroleum ether, 1:5), α-bromoenamine **5l** was isolated as a yellow oil (82 mg, 58% yield); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.12 (s, 1H), 7.37 (td, J = 7.6, 1.9 Hz, 2H), 7.23 (dd, J = 10.6, 4.2 Hz, 1H), 7.15 (dd, J = 8.4, 1.0 Hz, 2H), 4.02 (q, J = 7.1 Hz, 2H), 3.78 (s, 3H), 1.29 (t, J = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 166.2, 144.9, 144.8, 129.2, 125.8, 123.9, 81.7, 52.6, 48.0, 14.7; HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{12}H_{14}BrNO_2Na$ 306.0100, Found 306.0107.

*(Z)-Ethyl 2-Bromo-3-(methyl(phenyl)amino)acrylate (**5m**).* Enamine **1m** (103 mg, 0.50 mmol) was reacted according to the general procedure. After preparative TLC (EtOAc:petroleum ether, 1:5), α-bromoenamine **5m** was isolated as a yellow oil (97 mg, 68% yield); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.18 (s, 1H), 7.38 (m, 2H), 7.19 (t, J = 7.4, 1H), 7.17−7.11 (m, 2H), 4.26 (q, J = 7.1 Hz, 2H), 3.67 (s, 3H), 1.33 (t, J = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 165.5, 146.8, 145.1, 129.3, 124.9, 121.4, 83.9, 61.5, 39.7, 14.5; HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{12}H_{14}BrNO_2Na$ 306.0100, Found 306.0104.

Preparation of Ethyl 2-Chloro-3-(methyl(phenyl)amino)-propionate (9). To a solution of **2m** (0.5 mmol, 120 mg) in HOAc (2 mL) was added $NaBH_4$ (1.5 mmol, 57 mg) portionwise at 15 °C. Then, the mixture was stirred at room temperature for 2 h (monitored by TLC). After completion, the reaction mixture was quenched with ice water (5 mL), neutralized with saturated $NaHCO_3$ (aq), and extracted with DCM (2 × 5 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under vacuum to yield pure **9** as a yellow oil (115 mg, 95%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35−7.25 (m, 2H), 6.96−6.69 (m, 3H), 4.53 (dd, J = 8.0, 6.2 Hz, 1H), 4.29−4.16 (m, 2H), 4.06 (dd, J = 15.1, 8.0 Hz, 1H), 3.77 (dd, J = 15.1, 6.1 Hz, 1H), 3.06 (s, 3H), 1.30 (t, J = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 169.1, 148.0, 129.4, 117.5, 112.3, 62.3, 56.8, 53.3, 39.4, 14.0; HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{12}H_{17}ClNO_2$ 242.0942, Found 242.0943.

Preparation of Ethyl 2-(4-Isopropyl)phenylthio-3-(methyl-(phenyl)amino)propionate (10). Ethyl 2-chloro-3-(methyl-(phenyl)amino)propionate (**9**, 0.48 mmol, 115 mg) was dissolved in CH_3CN (2 mL), to which were added 4-isopropylphenylthiol (1.16 mmol, 176 mg) and $NaHCO_3$ (2.88 mmol, 242 mg). Then, the mixture was stirred at room temperature overnight (monitored by TLC). After completion, the reaction mixture was concentrated under vacuum. The residue was purified by preparative TLC (EtOAc:petroleum ether, 1:25) to yield **10** as a colorless oil (142 mg, 83%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47 (d, J = 8.2 Hz, 2H), 7.23 (dt, J = 7.3, 3.9 Hz, 4H), 6.75 (t, J = 7.3 Hz, 1H), 6.64 (d, J = 8.1 Hz, 2H), 4.18−4.06 (m, 2H), 3.97−3.82 (m, 2H), 3.74 (dd, J = 14.4, 4.2 Hz, 1H), 3.02−2.82 (m, 4H), 1.29 (d, J = 6.9 Hz, 6H), 1.19 (t, J = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 171.6, 149.6, 148.4, 134.1, 129.2, 127.3, 116.9, 112.3, 61.4, 54.9, 48.9, 39.1, 33.9, 23.91, 23.89, 14.0; HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{21}H_{27}NO_2SNa$ 380.1655, Found 380.1658.

Preparation of Ethyl 2-Azido-3-(methyl(phenyl)amino)-propionate (11). To a solution of **5m** (0.5 mmol, 142 mg) in HOAc (2 mL) was added $NaBH_4$ (1.5 mmol, 57 mg) portionwise at 15 °C. Then, the mixture was stirred at room temperature for 2 h (monitored by TLC). After completion, the reaction mixture was quenched with ice water (5 mL), neutralized with saturated $NaHCO_3$ (aq), and extracted with DCM (2 × 5 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under vacuum. The residue was dissolved in CH_3CN (2 mL), to which was added NaN_3 (1.0 mmol, 65 mg). Then, the mixture was stirred at room temperature overnight (monitored by TLC). After completion, the reaction mixture was concentrated under vacuum. The residue was purified by preparative TLC (EtOAc:petroleum ether, 1:30) to yield **11** as a colorless oil (92 mg, 74%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34−7.26 (m, 2H), 6.88−6.74 (m, 3H), 4.40−4.17 (m, 2H), 3.98 (dd, J = 15.2, 4.8 Hz, 1H), 3.58 (dd, J = 15.2, 8.2 Hz, 1H), 3.07 (s, 3H), 1.35 (t, J = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 169.3, 148.1, 129.4, 117.4, 112.4, 62.1, 60.4, 54.4, 39.4, 14.2; HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{12}H_{17}N_4O_2$ 249.1346, Found 249.1349.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b01603.

DOI: 10.1021/acs.joc.5b01603
J. Org. Chem. 2015, 80, 10000−10008

X-ray crystallographic data for **4b** (CIF)
Copies of ^{1}H NMR and ^{13}C NMR spectra and NOE spectrum for **2i**. X-ray crystallographic analysis for **4b** (PDF)

AUTHOR INFORMATION

Corresponding Author

*E-mail: lichunbao@tju.edu.cn. Fax: (+86) 2227403475.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

Dedicated to Prof. Jun Zhou on the occasion of his 83rd birthday.

REFERENCES

(1) Carbery, D. R. *Org. Biomol. Chem.* **2008**, *6*, 3455.
(2) Gigant, N.; Chausset-Boissarie, L.; Gillaizeau, I. *Chem. - Eur. J.* **2014**, *20*, 7548.
(3) Bernadat, G.; Masson, G. *Synlett* **2014**, *25*, 2842.
(4) Courant, T.; Dagousset, G.; Masson, G. *Synthesis* **2015**, *47*, 1799.
(5) Palmieri, G.; Cimarelli, C. *ARKIVOC* **2006**, *6*, 104.
(6) Negri, G.; Kascheres, C.; Kascheres, A. J. *J. Heterocycl. Chem.* **2004**, *41*, 461.
(7) Henry, G. D. *Tetrahedron* **2004**, *60*, 6043.
(8) Bruneau, C.; Renaud, J. L.; Jerphagnon, T. *Coord. Chem. Rev.* **2008**, *252*, 532.
(9) Kiss, L.; Cherepanova, M.; Fülöp, F. *Tetrahedron* **2015**, *71*, 2049.
(10) Zhu, H.; Jiang, X.; Li, X.; Hou, C.; Jiang, Y.; Hou, K.; Wang, R.; Li, Y. *ChemCatChem* **2013**, *5*, 2187.
(11) Ji, X. C.; Huang, H. W.; Wu, W. Q.; Jiang, H. F. *J. Am. Chem. Soc.* **2013**, *135*, 5286.
(12) Suzuki, A. *Angew. Chem., Int. Ed.* **2011**, *50*, 6722.
(13) Heravi, M. M.; Hashemi, E. *Tetrahedron* **2012**, *68*, 9145.
(14) Liu, W. X.; Wang, R. *Med. Res. Rev.* **2012**, *32*, 536.
(15) Shrestha-Dawadi, P. B.; Lugtenburg, J. *Eur. J. Org. Chem.* **2003**, *2003*, 4654.
(16) Abell, A. D.; Oldham, M. D.; Taylor, J. M. *J. Org. Chem.* **1995**, *60*, 1214.
(17) Lone, A. M.; Bhat, B. A. *Org. Biomol. Chem.* **2014**, *12*, 242.
(18) Džambaski, Z.; Toljić, Đ.; Bondžić, B.; Marković, R.; Baranac-Stojanović, M. *Tetrahedron* **2013**, *69*, 9819.
(19) Villa, M.; Targett, S. M.; Barnes, J. C.; Whittingham, W. G.; Marquez, R. *Org. Lett.* **2007**, *9*, 1631.
(20) Panda, N.; Jena, A. K.; Raghavender, M. *ACS Catal.* **2012**, *2*, 539.
(21) Meng, X.; Fang, Z.; Barry, B. D.; Liao, P.; Bi, X. *Chin. Sci. Bull.* **2012**, *57*, 2361.
(22) Liu, G. Q.; Li, Y. M. *J. Org. Chem.* **2014**, *79*, 10094.
(23) Pan, Z. L.; Sun, X. M.; Liang, Y. M. *Huaxue Shiji* **2007**, *29*, 85.
(24) Dohi, T. *Yakugaku Zasshi* **2006**, *126*, 757.
(25) Zhdankin, V. V. Hypervalent Iodine Reagents in Organic Synthesis. In *Hypervalent Iodine Chemistry: Preparation, Structure and Synthetic Applications of Polyvalent Iodine Compounds*, 1st ed.; John Wiley & Sons: Chichester, U.K., 2014; pp 145−307.
(26) Rajitha, B.; Reddy, P. N.; Kumar, B. S.; Srinivasulu, N.; Reddy, Y. *J. Chem. Res.* **2005**, *2005*, 535.
(27) Bartoli, G.; Bosco, M.; Locatelli, M.; Marcantoni, E.; Melchiorre, P.; Sambri, L. *Synlett* **2004**, 0239.
(28) Schultz, A. G.; Hagmann, W. K. *J. Org. Chem.* **1978**, *43*, 3391.
(29) Xin, D.; Burgess, K. *Org. Lett.* **2014**, *16*, 2108.
(30) Guseinov, F. I.; Yudina, N. A.; Burangulova, R. N.; Ryzhikova, T. Ya.; Valiullina, R. Zh. *Chem. Heterocycl. Compd.* **2002**, *38*, 496.
(31) Ji, X. C.; Huang, H. W.; Xiong, W. F.; Huang, K. B.; Wu, W. Q.; Jiang, H. F. *J. Org. Chem.* **2014**, *79*, 7005.
(32) Xue, F. L.; Li, J. X.; Wang, Z. Y.; Xiong, J. F.; Li, D. *Res. Chem. Intermed.* **2013**, *39*, 1153.
(33) Hachihama, Y.; Shono, T.; Ikeda, S. *J. Org. Chem.* **1964**, *29*, 1371.
(34) Tan, Y. H.; Li, J. X.; Xue, F. L.; Qi, J.; Wang, Z. Y. *Tetrahedron* **2012**, *68*, 2827.
(35) Bellur, E.; Langer, P. *Eur. J. Org. Chem.* **2005**, *2005*, 4815.
(36) Ang, K. H.; Prager, R. H.; Williams, C. M. *Aust. J. Chem.* **1995**, *48*, 567.
(37) Chen, X. Y.; Bohmann, R. A.; Wang, L.; Dong, S.; Räuber, C.; Bolm, C. *Chem. - Eur. J.* **2015**, *21*, 10330.
(38) Easton, C. J.; Hay, M. P.; Love, S. G. *J. Chem. Soc., Perkin Trans. 1* **1988**, *2*, 265.
(39) Olah, G. A.; Bollinger, J. M.; Brinich, J. *J. Am. Chem. Soc.* **1968**, *90*, 2587.
(40) Olah, G. A.; Schilling, P.; Westerman, P. W.; Lin, H. C. *J. Am. Chem. Soc.* **1974**, *96*, 3581.
(41) Rolston, J. H.; Yates, K. *J. Am. Chem. Soc.* **1969**, *91*, 1469.
(42) Strating, J.; Wieringa, J. H.; Wynberg, H. *J. Chem. Soc. D* **1969**, 907.
(43) Solomons, T. Alkenes and Alkynes II. Addition Reactions. In *Organic Chemistry*, 5th ed.; John Wiley & Sons: New York, 1992; pp 354−359.
(44) Carey, F. A.; Sundberg, R. J. Polar Addition and Elimination Reactions. In *Advanced Organic Chemistry, Part A: Structure and Mechanisms*, 4th ed.; Kluwer Academic/Plenum Publishers: New York, 2000; pp 361−369.
(45) Yang, M. T.; Woerpel, K. A. *J. Org. Chem.* **2009**, *74*, 545.
(46) Dryuk, V. G.; Kartsev, V. G. *Russ. Chem. Rev.* **1999**, *68*, 183.
(47) Cheng, Y. A.; Yu, W. Z.; Yeung, Y. Y. *Org. Biomol. Chem.* **2014**, *12*, 2333.
(48) Herges, R. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 51.
(49) Denmark, S. E.; Kuester, W. E.; Burk, M. T. *Angew. Chem., Int. Ed.* **2012**, *51*, 10938.
(50) Carey, F. A.; Sundberg, R. J. Polar Electrophlic Addition to Carbon-carbon Multiple Bonds. In *Advanced Organic Chemistry, Part B: Reactions and Synthesis*, 4th ed.; Kluwer Academic/Plenum Publishers: New York, 2001; pp 200−209.
(51) Zhang, Y. M.; Fan, X.; Xiang, B.; Chakravarty, D.; Scannevin, R.; Burke, S.; Karnachi, P.; Rhodes, K.; Jackson, P. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 3096.
(52) Kim, Y.; Ha, H. J.; Yun, S. Y.; Lee, W. K. *Chem. Commun.* **2008**, 4363.
(53) Couturier, C.; Blanchet, J.; Schlama, T.; Zhu, J. *Org. Lett.* **2006**, *8*, 2183.
(54) Kapras, V.; Pohl, R.; Cisarova, I.; Jahn, U. *Org. Lett.* **2014**, *16*, 1088.
(55) Hase, T. A.; Kukkola, P. *Synth. Commun.* **1980**, *10*, 451.
(56) Kim, Y.; Ha, H. J.; Yun, H.; Lee, B. K.; Lee, W. K. *Tetrahedron* **2006**, *62*, 8844.
(57) Candela-Lena, J. I.; Davies, S. G.; Roberts, P. M.; Roux, B.; Russell, A. J.; Sánchez-Fernández, E. M.; Smith, A. D. *Tetrahedron: Asymmetry* **2006**, *17*, 1135.
(58) Zhao, M. N.; Lian, X. L.; Ren, Z. H.; Wang, Y. Y.; Guan, Z. H. *RSC Adv.* **2014**, *4*, 62042.
(59) Bogdan, A. R.; Poe, S. L.; Kubis, D. C.; Broadwater, S. J.; McQuade, D. T. *Angew. Chem., Int. Ed.* **2009**, *48*, 8547.
(60) Le Menn, J. C.; Sarrazin, J.; Tallec, A. *Electrochim. Acta* **1991**, *36*, 819.

DOI: 10.1021/acs.joc.5b01603
J. Org. Chem. 2015, 80, 10000−10008