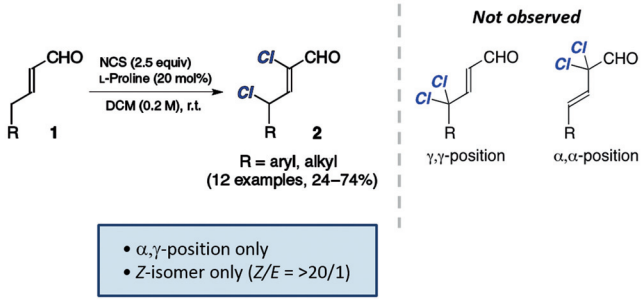
Synlett S. Arimitsu et al. Letter

Stereoselective Synthesis of 4-Substituted 2,4-Dichloro-2-butenals by α- and γ-Regioselective Double Chlorination of Dienamine Catalysis

Satoru Arimitsu*
Kazuto Terukina
Tatsuro Ishikawa

Department of Chemistry, Biology and Marine Science, University of the Ryukyus, 1 Senbaru, Nakagami, Nishihara, Okinawa 903-0213, Japan
arimitsu@sci.u-ryukyu.ac.jp



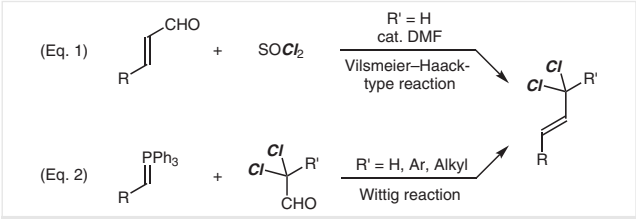
Received: 11.04.2018
Accepted after revision: 13.06.2018
Published online: 20.07.2018
DOI: 10.1055/s-0037-1609559; Art ID: st-2018-b0220-l

Abstract The L-proline-catalyzed reaction of enolizable α,β-unsaturated aldehydes with *N*-chlorosuccinimide (NCS) gave the corresponding 4-substituted 2,4-dichloro-2-butenals with moderate yields and excellent diastereoselectivities (*Z*/*E* = >20/1) through consecutive double chlorination at the α- and γ-positions of the dienamine intermediate. The corresponding 2,4-dichloro-2-butenals contain a multireactive 1,3-dichloro allylic unit useful for the construction of *Z*-vinyl chlorides; the chloride on the allylic position was replaced with mild nucleophiles such as MeOH and EtOH via an S_N2 substitution reaction, and its aldehyde moiety was used as a synthetic handle and transformed into an alcohol or a vinyl group. All products obtained after those synthetic manipulations maintained excellent diastereoselectivities (*Z*/*E* = >20/1).

Key words 2,4-dichloro-2-butenals, dienamine catalysis, chlorination, stereoselective, regioselective

Allylic halides have long been recognized as important chemicals in organic synthesis. For example, allylic fluorides can be found in many biologically active compounds,[1] therefore many regio- and stereoselective synthetic protocols have been developed so far.[2] In contrast, allylic chlorides have been prepared mainly as staring materials, and their versatile utility demonstrated either on classical S_N2- and/or S_N2'-type reactions with a wide range of nucleophiles or on advanced transition-metal chemistry, such as reactions through transition-metal π-allyl complexes.[3] However, many of those chemical transformations have been developed using allylic monochlorides, which permit only one functionalization due to one chloride moiety embedded in the structure.

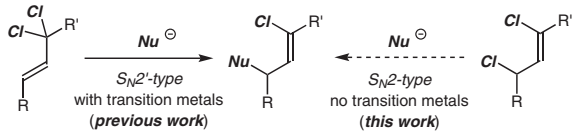
In principle, allylic dichlorides can be more functionalized than allylic monochlorides because the two chloride moieties can potentially be transformed in a tandem fashion. Recently, two independent research groups have developed methods for the preparation of *Z*-vinyl chlorides through S_N2' substitution reactions of allylic *gem*-dichlorides with organocuprates. The *Z*-vinyl chlorides obtained by those synthetic protocols can be used as synthetic building blocks toward various *Z*-olefinic compounds via consecutive coupling reactions or as chloroalkene dipeptide isosteres.[4] Known synthetic protocols toward allylic *gem*-dichlorides are summarized in Scheme 1. One method transforms α,β-unsaturated aldehydes into the corresponding allylic *gem*-dichlorides by the treatment with Vilsmeier–Haack-type reagents generated from thionyl chloride ($SOCl_2$) and a catalytic amount of *N*,*N*-dimethylformamide (DMF, Scheme 1, eq. 1).[5] An alternative method uses 1,1-dichloroacetaldehydes in Witting reaction, providing a wider range of substitution on R, such as aromatics and esters (Scheme 1, eq. 2).[6]



Scheme 1 Typical synthetic protocols for allylic *gem*-dichlorides

On the other hand, 1,3-dichloro allylic compounds can be considered as multitransformable reaction partners and synthetic equivalents of allylic *gem*-dichlorides.[7] In fact, 1,3-dihalopropenes (X = Cl, Br) tend to undergo transition-

metal-free S_N2-type substitution reactions with various nucleophiles.[8] However, this interesting synthetic transformation has been limited to a little variety of substrates on R and R′ due to the lack of robust and reliable preparation methods of 1,3-dichloro allylic compounds (Scheme 2, right).[8]



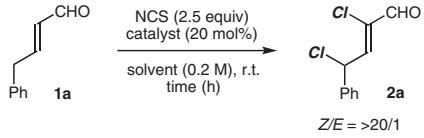
Scheme 2 Comparison of two reactions toward *Z*-vinyl chlorides

Recently, our group reported a highly stereoselective reaction of 2,2-difluoro-4,4-disubstituted 3-butenals using enolizable α,β-unsaturated aldehydes and *N*-fluorobenzenesulfonimide (NFSI) in the presence of L-proline as organocatalyst,[9] which can be applied in other halogenation reactions. In this context, herein, we wish to report the stereoselective organocatalytic synthesis of 2,4-dichloro-2-butenals in one step from enolizable α,β-unsaturated aldehydes. It is important to note that the control of the stereoselectivity and regioselectivity are challenging issues in this reaction.[10]

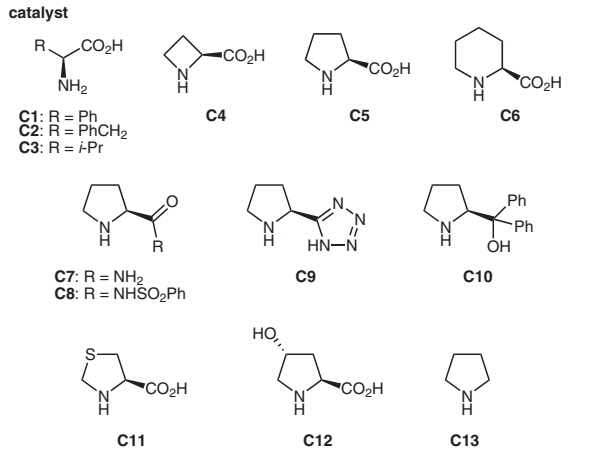
The initial investigation started with the screening of amine catalysts. Thus, the reaction of 4-phenyl-2-butenal (**1a**) and *N*-chlorosuccinimide (NCS) in dichloromethane (DCM) was conducted in the presence of various catalysts (20 mol%), such as primary and secondary amines. Primary amine catalysts did not promote the reaction at all, and only starting material **1a** was recovered (Table 1, entries 1–3). On the other hand, cyclic amino acid catalysts such as **C4**, **C5**, and **C6** led to complete conversions and provided the corresponding dichlorinated compound **2a** in moderate yields (Table 1, entries 4–6). Interestingly, the ring size of the catalyst significantly influences the reaction efficacy; the reactions with catalysts possessing either an azetidinyl or piperidinyl group required longer reaction time compared to the reaction using L-proline. Next, several proline-derived catalysts were investigated. Catalyst **C7**, which was reported as the best catalyst for a similar α-chlorination of simple aldehydes,[11] and similar proline-derived catalysts resulted in no reaction or very low yields of product despite the complete consumption of starting material **1a** (Table 1, entries 7–12). Interestingly, the reaction with pyrrolidine gave very low catalyst efficacy in comparison of the result using catalyst **C5** (Table 1, entries 5 and 13), and the importance of carboxylic acid of the catalyst **C5** in this reaction was proofed by this comparison.

Next, other solvents of varying polarities were examined, however, DCM remained the best solvent among those tested (Table 1, entries 5 and 14–19). Other reaction parameters, such as chlorinating reagents or additives, did not im-

Table 1 Optimization of the Reaction Conditions



Z/*E* = >20/1



Entry	Catalyst	Solvent	Time (h)[a]	Yield of **2a** (%)[b]
1	**C1**	DCM	24	0
2	**C2**	DCM	24	0
3	**C3**	DCM	24	0
4	**C4**	DCM	96	56[c,d]
5	**C5**	DCM	14	56[c]
6	**C6**	DCM	69	45[c]
7	**C7**	DCM	24	14
8	**C8**	DCM	24	0
9	**C9**	DCM	80	38[c]
10	**C10**	DCM	24	0
11	**C11**	DCM	24	0
12	**C12**	DCM	24	0
13	**C13**	DCM	24	7[e]
14	**C5**	DCE	24	29
15	**C5**	$CHCl_3$	24	6
16	**C5**	MePh	24	7
17	**C5**	THF	24	25
18	**C5**	MeCN	6	32[c]
19	**C5**	DMF	9	0[c]

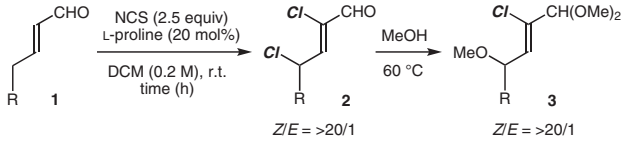
[a] The reaction time was determined by monitoring consumption of the starting material **1a** by TLC.
[b] The *Z*/*E* ratio and yield of product **2a** were determined by ^{1}H NMR spectroscopy of the crude reaction mixture using CH_2Br_2 as internal standard.
[c] No starting material **1a** remained.
[d] Vinyl chloride **3a** was isolated in 55%.
[e] Starting material **1a** was remained in 89%.

prove the yield of the reaction (see the Supporting Information for more details). It is important to mention that target compound **2a** was unstable, and any attempts to isolate the compound failed; therefore, the conversion into the more stable methoxylated product **3a** was carried out by treating compound **2a** with methanol, which allowed the isolation of the material.[12] This instability of compound **2a** might explain the low chemical yields observed in some of the reactions. Notably, all the reaction conditions resulted in excellent stereoselectivities (*Z*/*E* = >20/1) and gave only double-chlorinated product **2a** with exclusive chlorination at the α- and γ-positions. Moreover, neither α,α- nor γ,γ-dichlorinated products were observed in this reaction, which differs from a previous fluorination that gives only α,α-difluorinated products under similar conditions.[9]

After determining the optimal conditions, the substrate scope was investigated with regard to the substituent R of aldehyde **1** (Table 2). Generally, aromatic substituents bearing electron-withdrawing groups at the *para* position resulted in similar reaction outcomes as an unsubstituted phenyl group, and the corresponding products **2** and **3** were obtained in moderate yields (Table 2, entries 2–4). On the other hand, aromatics with electron-donating groups gave slightly better chemical yields regardless of the substitution pattern (Table 2, entries 5, 7, and 8), except for the reaction with aldehyde **1f** possessing a *p*-OMe-substituted phenyl ring; despite its total consumption after 24 h, the corresponding target **2f** was unstable and rapidly decomposed even under mild evaporation (Table 2, entry 6).[13] In the case of aliphatic substrates (Table 2, entries 10–12), the chlorination was slower than that of aromatic substrates, however, all chlorinated aldehydes were stable enough to be isolated by silica gel column chromatography; as a result, not only double-chlorinated products **2**, but also single-chlorinated products **2′** were isolated in similar yields, and both products showed excellent stereoselectivities (*Z*/*E* = >20/1) except for compound **2l′** (*Z*/*E* = 9.4/1, Figure 1). Unfortunately, all efforts to improve the yield of double-chlorinated compounds **2j–l**, such as increased reaction times, temperatures, or equivalents of NCS, failed; nevertheless, the formation of monochlorinated product **2′** is a strong evidence of the reaction mechanism pathway.

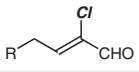
A plausible reaction mechanism is depicted in Scheme 3. First, dienamine intermediate **Int-A** forms from the reaction of aldehyde **1** and L-proline. According to previous DFT calculations of similar dienamine intermediates generated with pyrrolidinyl-derived secondary amine catalysts, the electron density of C_α and C_γ suggests similar reactivity at these carbon atoms.[14] However, all products observed in this reaction contain at least one chlorine substituent at the α-position, which might be induced by the 1,3-sigmatropic shift of a chlorine atom of *N*-chlorinated intermediate **Int-B**, formed by the reaction of **Int-A** and NCS, to the closer reactive center (C_α).[15] The second chlorination is also believed to undergo through a dienamine intermediate **Int-D**;[16] however, the reasons behind the second chlorination exclusively occurring at the γ-position are currently not clear (**Path A**, Scheme 3). On the other hand, hydrolysis of **Int-C** will produce α-monochlorinated homoallylic aldehyde, which will convert into vinyl chloride **2′**, as this type of aldehydes are known to isomerize rapidly into the more stable α,β-unsaturated aldehydes (**Path B**, Scheme 3).[17] The compound **2′** can be a precursor of dichlorinated compound **2**, however, the control experiment using isolated **2l′** under the standard chlorination conditions, treating with 2.5 equiv of NCS and catalytic amounts of L-proline (20 mol%) in DCM, showed no sign of compound **2l** after 24 h, confirmed by ^{1}H NMR spectroscopy.

Table 2 Substrate Scope



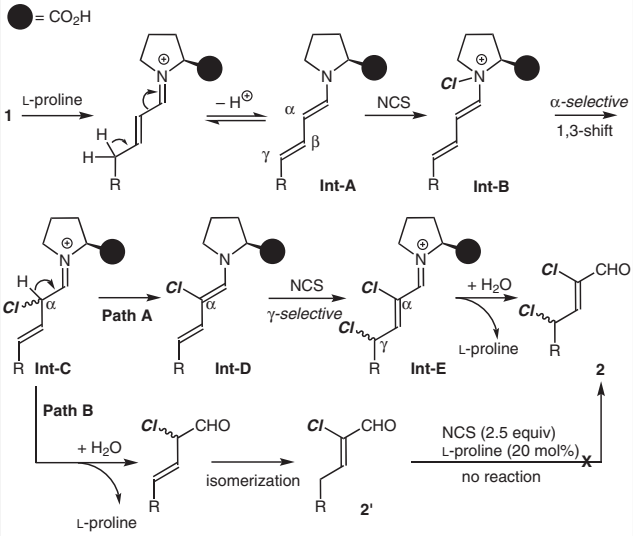
Entry	R	Time (h)[a]	*Z*/*E*[b]	Yield of **2** and **3** (%)[b,c]
1	**1a** C_6H_5	14	>20/1	**2a** 56, **3a** 55
2	**1b** 4-FC_6H_4	14	>20/1	**2b** 54, **3b** 53
3	**1c** 4-ClC_6H_4	20	>20/1	**2c** 68, **3c** 66
4	**1d** 4-BrC_6H_4	16	>20/1	**2d** 55, **3d** 52
5	**1e** 4-MeC_6H_4	15	>20/1	**2e** 66, **3e** 62
6	**1f** 4-$MeOC_6H_4$	24	–	**2f** 0
7	**1g** 3-MeC_6H_4	18	>20/1	**2g** 74, **3g** 72
8	**1h** 2-MeC_6H_4	14	>20/1	**2h** 62, **3h** 61
9	**1i** 1-naphthyl	16	>20/1	**2** 74, **3i** 72
10	**1j** $PhCH_2$	24	>20/1	**2j** 29[d]
11	**1k** $BnOCH_2$	24	>20/1	**2k** 24[d]
12	**1l** *n*-Hex	24	>20/1	**2l** 44[d]

[a] The reaction time was determined by monitoring consumption of the starting material **1** by TLC.
[b] The *Z*/*E* ratio and yield of product **2** were determined by ^{1}H NMR spectroscopy of the crude reaction mixture using CH_2Br_2 as internal standard.
[c] Isolated yield of vinyl chlorides **3** is given.
[d] Vinyl chlorides **2j′**, **2k′**, and **2l′** were isolated, respectively.

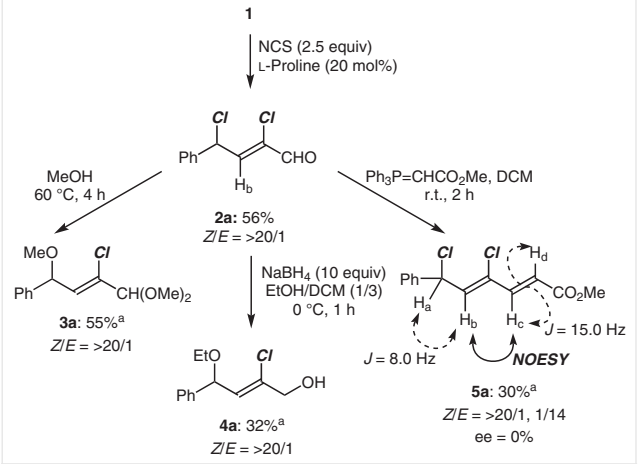


2j′: 27%, *Z*/*E* = >20/1
2k′: 34%, *Z*/*E* = >20/1
2l′: 22%, *Z*/*E* = 9.4/1

Figure 1



Scheme 3 Plausible reaction mechanism



Scheme 4 Synthetic applications of **2a** and confirmation of its stereochemistry. [a] The yield was calculated in two steps.

Initially, methoxylation was conducted in order to transform unstable compound **2** into more stable compound **3**, however, this transformation is a good demonstration of a synthetic application of compound **2** as 1,3-dichloro allylic electrophile; all dichlorinated aldehydes **2** undergo methoxylation through an S_N2-type substitution maintaining good *Z*/*E* selectivity (*Z*/*E* = >20/1) and acetal conversion of the aldehyde functionality to produce compounds **3**; S_N2' substitution was not observed for any substrate. The stereo- and regiochemistry were unambiguously determined by 2D NMR analyses for compound **3a**. Moreover, the aldehyde moiety of compound **2a** is a useful synthetic handle, and thus, it was readily reduced to alcohol **4a** using $NaBH_4$ or coupled with a Wittig reagent to give extended 1,4-diene **5a** as shown in Scheme 4. Due to its unstable nature the stereochemistry of compound **2** was indirectly determined by analyzing the Wittig product **5a** by 2D NMR spectroscopy; NOESY correlations observed between proton H_b and H_c clearly indicate the stereochemistry of compound **5a** as depicted in Scheme 4. Proton H_c originates from the aldehyde proton, therefore the aldehyde group of compound **2a** and H_b are located on the same side of the vinyl group. The stereoconfiguration of all products **2** and **3** was determined by comparison of the chemical shifts and coupling constants with those of **2a** and **3a**. Additionally, compounds **2** possess a chiral center at the γ-position, which could potentially be enantiomeric due to the use of L-proline, however, compound **5a** was found to be racemic (ee = 0%).

In summary, a highly stereoselective synthesis of 2,4-dichloro-2-butenals **2** was achieved with excellent diastereoselectivities (*Z*/*E* = >20/1) using readily accessible α,β-unsaturated aldehyde **1** and NCS in the presence of catalytic amounts of L-proline (20 mol%) as organocatalyst.[12] Additionally, the synthetic application of 2,4-dichloro-2-butenals **2** has been demonstrated; only S_N2 substitution reaction progressed on the allylic chloride position even with mild nucleophiles, such as alcohols like MeOH and EtOH, and the aldehyde moiety could be transformed to its alcohol by $NaBH_4$ reduction or to a vinyl group by Wittig reaction with retention of the diastereoselectivity (*Z*/*E* = >20/1). Thus, this reaction is the first reported double nucleophilic reaction on the α- and γ-positions of a dienamine catalysis to date and represents a new method for the preparation of widely substituted 1,3-dichloro allylic compounds and *Z*-vinyl chlorides.

Funding Information

Part of this research was financially supported by MEXT/JSPS KAKENHI, Grant No. JP17K14451.

Acknowledgment

The authors thank Prof. Konno Tsutomu at Kyoto Institute of Technology for assistance with HRMS.

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1609559.

References and Notes

(1) Wang, J.; Sánchez-Roselló, M.; Aceña, J. L.; del Pozo, C.; Sorochinsky, A. E.; Fustero, S.; Soloshonok, V. A.; Liu, H. *Chem. Rev.* **2014**, *114*, 2432.
(2) (a) Hollingworth, C.; Gouverneur, V. *Chem. Commun.* **2012**, *48*, 2929. (b) Pacheco, M. C.; Purser, S.; Gouverneur, V. *Chem. Rev.* **2008**, *108*, 1943.
(3) For a recent review, see: Cherney, A. H.; Kadunce, N. T.; Reisman, S. E. *Chem. Rev.* **2015**, *115*, 9587.
(4) (a) Giannerini, M.; Fañanás-Mastral, M.; Feringa, B. L. *J. Am. Chem. Soc.* **2012**, *134*, 4108. (b) Kobayakawa, T.; Tamamura, H. *Tetrahedron* **2017**, *73*, 4464; and references cited therein.
(5) Newman, M. S.; Sujeeth, P. K. *J. Org. Chem.* **1978**, *43*, 4367.
(6) (a) Narumi, T.; Kobayakawa, T.; Aikawa, H.; Seike, S.; Tamamura, H. *Org. Lett.* **2012**, *14*, 4490. (b) Courtheyn, D.; Verhé, R.; De Kimpe, N.; De Buyck, L.; Schamp, N. *J. Org. Chem.* **1981**, *46*, 3226; and references cited therein.
(7) (a) Masuyama, Y.; Ito, A.; Kurusu, Y. *Chem. Commun.* **1998**, 315. (b) Kakiya, H.; Inoue, R.; Shinokubo, H.; Oshima, K. *Chem. Lett.* **1998**, *27*, 73. (c) Guijarro, A.; Yus, M. *Tetrahedron* **1994**, *50*, 13269. (d) Chan, T.-H.; Li, C.-J. *Organometallics* **1990**, *9*, 2649. (e) Souppe, J.; Danon, L.; Namy, J. L.; Kagan, H. B. J. *Organomet. Chem.* **1983**, *250*, 227.
(8) (a) Chen, H. G.; Gage, J. L.; Barrett, S. D.; Knochel, P. *Tetrahedron Lett.* **1990**, *31*, 1829. (b) Gawley, R. E.; Termine, E. J. *J. Org. Chem.* **1984**, *49*, 1946. (c) Schuda, P. F.; Heimann, M. R. *J. Org. Chem.* **1982**, *47*, 2484. (d) Nishiyama, H.; Narimatsu, S.; Itoh, K. *Tetrahedron Lett.* **1981**, *22*, 5289.
(9) Arimitsu, S.; Nakasone, M. *J. Org. Chem.* **2016**, *81*, 6707.
(10) For a recent review, see: Marcos, V.; Alemán, J. *Chem. Soc. Rev.* **2016**, *45*, 6812.
(11) (a) Kang, B.; Britton, R. *Org. Lett.* **2007**, *9*, 5083. (b) Halland, N.; Braunton, A.; Bachmann, S.; Marigo, M.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2004**, *126*, 4790.
(12) **General Experimental Procedure for Dichlorinated Compound 2 and Methoxylated Compound 3**
To the solution of α,β-unsaturated aldehyde **1** (0.1 mmol) in DCM (0.5 mL, 0.2 M) was added L-proline (20 mol%) at room temperature, and the reaction was replaced into the ice bath. Next, NCS (2.5 equiv) was added into a solution at 0 °C, and the reaction was purged with argon gas, then the whole reaction mixture was stirred for 30 min at 0 °C. After 30 min, the reaction was removed from the ice bath and stirred at room temperature until TLC revealed that starting material **1** was totally consumed. *Note*: *The reaction flask was shielded from the light by an aluminum foil during the reaction.* The reaction was quenched by aq sat. $NaHCO_3$ and extracted by EtOAc (3 × 20 mL). Then, the whole organic layer was washed by brine and dried over $MgSO_4$. The organic solution was filtered and concentrated by the rotary evaporator. NMR yield of the compound **2** was determined by ^{1}H NMR spectroscopy after drying the reaction mixture by a high vacuum pump using CH_2Br_2 as an internal standard. Next, the mixture of compound **2** was diluted in methanol (0.1 M), and the whole reaction mixture was heated at 60 °C until compound **2** was totally consumed (monitored by TLC). The reaction was quenched by water and extracted by Et_2O (3 × 20 mL). Then, the whole organic layer was washed with brine and dried over $MgSO_4$. The organic solution was filtered and concentrated by the rotary evaporator. The residue was purified by a silica gel flash chromatography.
Compound **3a**: Purification by flash chromatography (SiO_2, hexane/Et_2O = 15:1) afforded **3a** (14.1 mg, 0.055 mmol, 55% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.27 (3 H, s), 3.33 (3 H, s), 3.36 (3 H, s), 4.74 (1 H, s), 5.22 (1 H, d, *J* = 8.5 Hz), 6.23 (1 H, dd, *J* = 8.5, 0.6 Hz), 7.26–7.30 (1 H, m), 7.32–7.40 (4 H, m). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 53.07, 53.14, 56.5, 79.5, 102.4, 126.5, 127.9, 128.6, 130.6, 131.4, 140.1. HRMS: *m/z* calcd for $C_{13}H_{16}ClO_3^+$: 255.0782 $[M - H]^+$; found: 255.0782 $[M - H]^+$.
(13) Analysis of the reaction mixture with TLC showed a promising spot of the target compound **2f** in a similar outcome to the rest of reactions.
(14) Bertelsen, S.; Marigo, M.; Brandes, S.; Dinér, P.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2006**, *128*, 12973.
(15) (a) Marquez, C. A.; Fabbretti, F.; Metzger, J. O. *Angew. Chem. Int. Ed.* **2007**, *46*, 6915. (b) Halland, N.; Alstrup Lie, M.; Kjærsgaard, A.; Marigo, M.; Schiøtt, B.; Jørgensen, K. A. *Chem. Eur. J.* **2005**, *11*, 7083.
(16) The reaction using aldehyde **1a** and 1.0 equiv of NCS, instead of 2.5 equiv, showed that dichlorinated compound **2a** was formed as the sole product in 20% with remaining starting material **1a** in 58% based on ^{1}H NMR analysis, moreover no other products such as monochlorinated products were observed. This control experiment indicates that the second chlorination is faster than the first one.
(17) Pace, V.; Castoldi, L.; Mazzeo, E.; Rui, M.; Langer, T.; Holzer, W. *Angew. Chem. Int. Ed.* **2007**, *56*, 12677; and references cited therein.