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Enantioselective Halogenation of β-Oxo Esters Catalyzed by a Chiral Sulfoximine–Copper Complex

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A C_1-symmetric amino sulfoximine has been used as a chiral ligand in copper-catalyzed asymmetric halogenation reactions of β-oxo esters. Both the catalyst itself and the reaction conditions were optimized, and 26 fluorinated, chlorinated, and brominated products were obtained with enantioselectivities of up to 91 % *ee* in yields of up to 99 %.

Introduction

Sulfoximines, the monoaza analogues of sulfones, were discovered in the mid 1940s, and since then they have played an important role in various fields of chemistry. Initial research focused on their unusual structure and remarkable biological activity.[1] Derivatives with a stereogenic center at the sulfur atom have been used as chiral auxiliaries in asymmetric synthesis.[2] In the early 1990s we were the first to demonstrate the applicability of sulfoximines as chiral ligands,[3] and since then a wide variety of compounds with a sulfoximidoyl core have found application in asymmetric metal catalysis (Figure 1).[4] For example, β-hydroxy sulfoximines **1** have been used in nickel-catalyzed conjugate addition to chalcones, asymmetric 1,2-addition of diorganozinc reagents to aldehydes, enantioselective borane reduction of ketones and imine derivatives, and in the synthesis of asymmetric cyanohydrins.[3,5] C_2-symmetric bis(sulfoximines) **2** proved efficient ligands in highly enantioselective (hetero-)Diels–Alder and allylic alkylation reactions.[6] C_1-symmetric monosulfoximines of the type **3** have successfully been used in hetero-Diels–Alder reactions,[7] and the related N,N ligands **4** gave products with excellent stereoselectivities in Mukaiyama-type aldol reactions and its vinylogous analogue.[8,9] Further modification of the ligand structure led to C_1-symmetric oxazolinyl sulfoximines **5**, which have been used in Mukaiyama aldol and Henry reactions.[10] For iridium-catalyzed enantioselective hydrogenation of imines and enones sulfoximine-derived P,N ligands such as **6** have been used.[11] We now wondered if such sulfoximines could also be used in catalyzed asymmetric carbon–halogen bond-forming reactions.

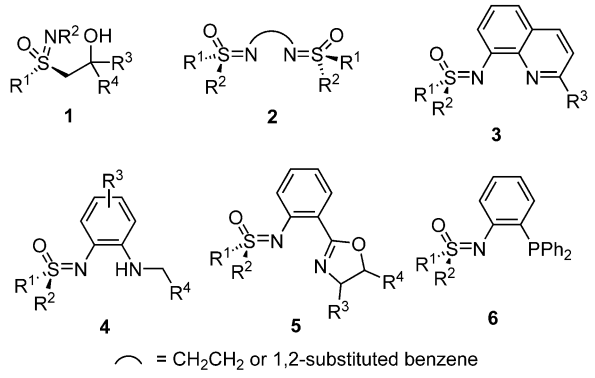

Figure 1. Sulfoximines **1**–**6** used as ligands in asymmetric metal catalysis.

Surprisingly, reports on catalyzed asymmetric halogenation reactions that provide products with high enantioselectivities in high yields are still comparatively rare despite the fact that C–X (X = F, Cl, Br, I) bonds are both valuable intermediates for further chemical transformations and important structural motifs in natural products.[12,13] Since the first catalytic enantioselective fluorination was reported by Togni and co-workers,[14] a number of related transformations have been described. Most of them rely on the use of enolizable carbonyl compounds, and catalytic systems for the asymmetric fluorination of nucleophiles such as β-oxo esters,[14a,15] β-oxo phosphonates,[15e,16] oxindoles,[17] malonates,[18] cyanoacetates,[19] and other acid derivatives[20] have been developed. Furthermore, aldehydes have recently been enantioselectively fluorinated by organocatalysis.[21] All the methods mentioned above have also been adopted for organocatalytic and metal-catalyzed asymmetric bromination and chlorination reactions.[16b,17b,22]

Herein we report on the general asymmetric carbon–halogen bond formation of both cyclic and acyclic β-oxo esters catalyzed by a sulfoximine–copper complex leading

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to brominated, chlorinated, and fluorinated products in high yields and with moderate to good enantioselectivities.[23]

Results and Discussion

To identify the best ligand structure for the metal-catalyzed asymmetric halogenation reactions ethyl 2-benzylacetoacetate (**7a**) was chosen as the test substrate, and chlorinations with copper catalysts were investigated first. Accordingly, an ethereal solution of β-oxo ester **7a** was treated with *N*-chlorosuccinimide (NCS, **8**) in the presence of a catalytic amount of a 1:1 mixture of $Cu(OTf)_2$ and a sulfoximine (10 mol-% each). After stirring at ambient temperature for 4 h, the product was isolated and analyzed spectroscopically. The enantiomer ratios were then determined by HPLC using a chiral stationary phase (CSP). Various sulfoximines (at least three examples of each substrate class depicted in Figure 1) were tested and representative results are shown in Table 1.

Chlorinated oxo ester **9a** was obtained in excellent yield (94–99%) in almost all cases. Only when *P*,*N*-sulfoximine **6a** was employed was the yield of **9a** moderate (66%), presumably due to a competitive chlorination of the phosphanyl substituent of the ligand reducing its metal-binding capability (Table 1, Entry 10). Most sulfoximine-based catalysts provided racemic products. Noteworthy exceptions were those with bis(sulfoximine) **2b**, which gave **9a** with 16% *ee* (Entry 4), and C_1-symmetric amino sulfoximines **4a** and **4b**, which led to the chlorinated product with 41 and 35% *ee*, respectively (Entries 6 and 7). Because monosulfoximine **4a** gave the best result it was employed in the subsequent studies.[24]

Because the reaction medium can strongly influence a catalyst by altering important parameters such as solubility, substrate/catalyst coordination, acidity, and polarity, the effect of the solvent was investigated next. Again, the chlorination of oxo ester **7a** with NCS (**8**) to give the product **9a** served as the test reaction. The results of this study are summarized in Table 2.

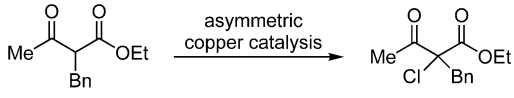
Table 2. Solvent effects in the copper-catalyzed asymmetric chlorination of oxo ester **7a** to give chlorinated product **9a**.[a]

Entry	Solvent	Yield [%]	*ee* [%][b]
1	CH_2Cl_2	98	16
2	$CHCl_3$	98	0
3	toluene	96	31
4	THF	99	19
5	1,4-dioxane	94	23
6[c]	CH_3CN	50	0
7[c]	CH_3OH	99	0
8	Et_2O	99	41

[a] Reaction conditions: $Cu(OTf)_2$ (10 mol-%), (*S*)-**4a** (10 mol-%), NCS (**8**; 1.2 equiv.), solvent (0.1 M), room temp., 4 h. [b] Determined by CSP-HPLC. [c] Reaction time: 18 h.

With the exception of the catalysis performed in acetonitrile (Table 2, Entry 6), all the reactions led to very high yields (94–99%) of the chlorinated oxo ester **9a** irrespective of the solvent. Very polar media (such as acetonitrile and methanol) hampered the catalysis, and the reaction time had to be extended (from 4 to 18 h). Under these conditions **9a** was obtained in 50 and 99% yields, respectively (Entries 6 and 7). Presumably, these solvents competed with the sulfoximine ligand in the coordination to the copper atom, leading to catalysts of low activity. This hypothesis was supported by the fact that in these reactions only racemic products were formed. Catalysis in dichloromethane or chloroform afforded **9a** in 98% yield (Entries 1 and 2), but the *ee* was low (up to 16%). Aromatic or weakly coordinating solvents such as toluene, THF, or 1,4-dioxane gave the chlorinated oxo ester **9a** with enantioselectivities in the range of 19–31% *ee* (Entries 3–5). The best result was obtained in the reaction performed in diethyl ether, which provided **9a** with 41% *ee* (in 99% yield; Entry 8).

Table 1. Screening of sulfoximines **1**–**6** in the asymmetric chlorination of **7a**.[a]



7a **9a**

Entry	Sulfoximine	R^1	R^2	R^3	R^4	Yield [%]	*ee* [%][b]
1	(*S*,*S*)-**1a**	Ph	Me	*i*Pr	Ph	99	0
2	(*S*)-**1b**	Ph	Me	$(CH_2)_6$		99	0
3	(*S*,*S*)-**2a**[c]	Ph	Me	–	–	97	0
4	(*S*,*S*)-**2b**[d]	Ph	Me	–	–	96	16
5	(*R*)-**3a**	Me	2-$MeOC_6H_4$	H	–	99[e]	–2
6	(*S*)-**4a**	Ph	Me	H	2,4,6-$iPr_3C_6H_2$	99	41
7	(*S*)-**4b**	Ph	Me	H	2,4,6-$Me_3C_6H_2$	99	35
8	(*S*,1*R*,2*S*)-**5a**	Ph	Me	Me	Ph	99	6
9	(*S*,*S*)-**5b**	Ph	Me	*t*Bu	H	94	0
10	(*S*)-**6a**	Ph	Me	–	–	66	4

[a] Reaction conditions: $Cu(OTf)_2$ (10 mol-%), sulfoximine **1**–**6** (10 mol-%), NCS (**8**; 1.2 equiv.), Et_2O (0.1 M), room temp., 4 h. [b] Determined by CSP-HPLC. [c] Use of an ethylene-linked bis(sulfoximine). [d] Use of a bis(sulfoximine) with an *ortho*-disubstituted benzene linker. [e] Reaction carried out in DCM.

Besides $Cu(OTf)_2$ several other metal triflates were found to be catalytically active, affording **9a** in good to excellent yields (Table 3). Only the triflates of silver, tin, and bismuth (Entries 1, 5, and 10) were inapplicable, and even after prolonged reaction times (18 h) the product was obtained in low yields (27–39%). All the metal salts except iron and copper formed the racemic oxo ester **9a**. Interestingly, these two salts gave opposite enantiomers (Entries 11 and 12) with copper being superior in terms of enantioselectivity (41% *ee*).

Table 3. Variation of the metal source in the catalyzed asymmetric chlorination of **7a** with NCS (**8**) to give β-oxo ester **9a**.[a]

Entry	Metal source	Yield [%]	*ee* [%][b]
1[c]	AgOTf	27	0
2	LiOTf	86	0
3	$Mg(OTf)_2$	99	0
4	$Zn(OTf)_2$	98	3
5[c]	$Sn(OTf)_2$	39	0
6	$Sc(OTf)_3$	99	0
7	$Yb(OTf)_3$	99	0
8	$In(OTf)_3$	80	0
9	$Gd(OTf)_3$	80	0
10[c]	$Bi(OTf)_3$	29	0
11	$Fe(OTf)_2$	99	–12
12	$Cu(OTf)_2$	99	41
13[c]	$CuSO_4$	67	0
14[c]	$Cu(acac)_2$	69	4
15	$Cu(ClO_4)_2 \cdot 6H_2O$	99	21
16[d]	$Cu(BF_4)_2$	71	23
17[d]	$Cu(PF_6)_2$	79	0
18[d]	$Cu(SbF_6)_2$	93	6
19[d]	$Cu(ClO_4)_2$	96	15

[a] Reaction conditions: MX_n (10 mol-%), (*S*)-**4a** (10 mol-%), NCS (**8**; 1.2 equiv.), Et_2O (0.1 M), room temp., 4 h. [b] Determined by CSP-HPLC. [c] Reaction time: 18 h. [d] Prepared in situ from $CuCl_2$ (10 mol-%) and AgX (20 mol-%).

In previous studies it was shown that counterions are involved in the resulting sulfoximine–copper(II) complex,[25] and consequently their effect on the given catalysis (yielding **9a** from **7a**) was also studied in this work. Entries 12–19 of Table 3 reveal that their influence on both yield and enantioselectivity was significant with noncoordinating anions such as perchlorate, tetrafluoroborate, and triflate being the best. This trend is similar to that observed in previous studies by our group.[8b] Interestingly, the commercially available $Cu(ClO_4)_2$ hexahydrate gave better results (99% yield, 21% *ee*) than anhydrous $Cu(ClO_4)_2$ (96% yield, 15% *ee*), prepared in situ from $CuCl_2$ and $AgClO_4$ (Entry 15 vs. 19). $Cu(OTf)_2$ proved superior to all other ion combinations in this metal-salt screening process.

A brief screening of chlorine donors revealed that the halogenation reactions with NCS (**8**) gave the best results (Figure 2). The use of recrystallized **8** (from AcOH) had no positive effect on the enantioselectivity of the reaction. Although reagents **8**, **10**, and **12** bearing nitrogen–chlorine bonds gave rise to **9a** in excellent yields (90–99%), halogen donors **11** and **13** with carbon–chlorine bonds proved unsuitable.

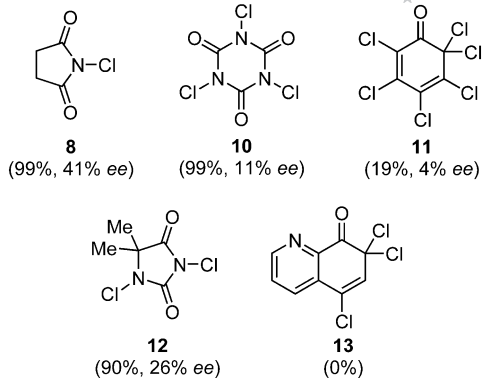


Figure 2. Chlorine donors used in the $Cu(OTf)_2$-catalyzed asymmetric halogenation of **7a** to give **9a**. Reaction conditions were as described in footnote [a] of Table 3 with $Cu(OTf)_2$ as MX_2; the numbers in parentheses refer to yields and *ee* values of **9a**.

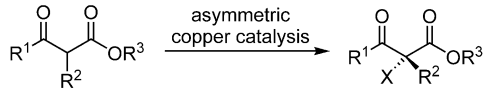
The fact that in successful reactions the yields were high but the enantioselectivities low suggested that uncatalyzed background reactions leading to racemic products were responsible for the reduced product *ee*s. This hypothesis, however, was disproved by a control experiment. In the absence of the sulfoximine–copper catalyst the chlorination reaction of oxo ester **7a** with **8** in Et_2O showed only traces of **9a** after 24 h.

Assuming that a decrease in temperature would have a positive effect on the enantioselectivity, the standard reaction of oxo ester **7a** with NCS (**8**) in the presence of a catalytic amount of $Cu(OTf)_2$/(*S*)-**4a** was carried out in Et_2O at –78 °C (with warming to room temp. over 16 h). Chlorinated **9a** was formed in excellent yield (99%) again, and the *ee* increased to 54%. Under these conditions the addition of 1 equiv. of hexafluoroisopropyl alcohol (HFIP) or 2,2,2-trifluoroethanol reduced the enantioselectivity to 51 and 43% *ee*, respectively, whereas the yields remained almost unaffected (99 and 96%). Both the yield and *ee* were lower when 1 equiv. of ethyldiisopropylamine (60% yield, 0% *ee*) or 2,6-lutidine (42% yield, 6% *ee*) was added.

The substrate scope of the enantioselective chlorination with NCS (**8**) was investigated next. Assuming analogous behavior in asymmetric bromination reactions with NBS (**14**) both halogenation reactions were performed in parallel (Table 4). In all cases $Cu(OTf)_2$/(*S*)-**4a** served as the catalyst, and the applicability of cyclic and acyclic β-oxo esters **7** was examined.

In general, both the chlorinated and brominated products **9** and **15** were obtained in very high yields (88–99%), and the enantioselectivity reached a value of 91% *ee* (for chlorinated product **9f**, Table 4, Entry 6). In the chlorination reactions both the acyclic (Entries 1–4) and cyclic (Entries 5–8) oxo esters **7** gave the corresponding products in moderate to good enantioselectivities. Among the acyclic substrates α-methyl-substituted oxo ester **9d** had the highest *ee* (73%), whereas **9b** with a phenyl group at the α position had only a 28% *ee* (Entries 4 and 2). For the cyclic oxo esters, six-membered-ring product **9f** gave the best result (91% *ee*, Entry 6). Oxo esters with five- and eight-mem-

Table 4. Catalytic enantioselective chlorination and bromination reactions of β-oxo esters **7a**–**i**.[a]



7a–i **9a–i**: X = Cl **15a–h**: X = Br

Entry	7	R^1	R^2	R^3	9	Yield [%]	*ee*[b,c] [%]	15	Yield [%]	*ee*[b,c] [%]
1	**a**	Me	Bn	Et	**a**	99	54	**a**	98	48
2	**b**	Me	Ph	Et	**b**	97	28 (*R*)	**b**	99	39 (*R*)
3	**c**	Me	Et	Et	**c**	96	59	**c**	97	73
4	**d**	Me	Me	Et	**d**	96	73 (*R*)	**d**	95	n.d.[d]
5	**e**	$(CH_2)_3$		Et	**e**	98	39 (*R*)	**5e**	99	0
6	**f**	$(CH_2)_4$		Et	**f**	99	91 (*R*)	**f**	99	42 (*R*)
7	**g**	$(CH_2)_6$		Et	**g**	88	57	**g**	91	25
8	**h**	$(CH_2)_3$		Me	**h**	88	36	–	–	–
9	**i**	Me	$(CH_2)_2$		**i**	92	24	**h**	90	0

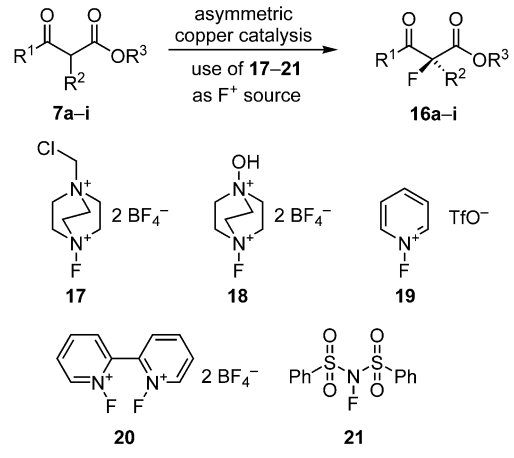
[a] Reaction conditions: $Cu(OTf)_2$ (10 mol-%), (*S*)-**4a** (10 mol-%), NCS (**8**) or NBS (**14**) (1.2 equiv.), Et_2O (0.1 M), –78 °C to room temp. 16 h. [b] Determined by CSP-HPLC or GC. [c] The absolute configurations given in parentheses were determined by comparison of the optical rotation values with those reported in the literature. [d] Not determined; no separation conditions could be found on HPLC or GC.

bered rings gave products with considerably lower *ee* (39% for **9e** and 57% for **9g**, Entries 5 and 7). Changing from an ethyl to a methyl ester had no significant influence on the stereoselectivity (39% for **9e** vs. 36% for **9h**), but led to a lower yield (98% vs. 88%, Entries 5 and 8). The ester functionality could also be located inside the ring (Entry 9); acetyl butyrolactone (**7i**) afforded chlorinated product **9i** in a very good yield (92%), albeit with a low *ee* (24%).

The enantioselective bromination reactions also gave the corresponding products **15** in high yields, but in most cases, the enantioselectivities were lower than in the analogous chlorination reactions. The only exceptions were observed for the halogenation reactions of **7b** and **7c**, which gave the corresponding brominated oxo esters **15b** and **15c**, respectively, with higher *ee*s (Entries 2 and 3). In the bromination reactions of cyclic oxo esters **7e** and **7h** the products **15e** and **15h** were obtained as racemates, albeit in high yields (Entries 5 and 9).

To extend the scope of the reaction further, enantioselective fluorination reactions catalyzed by $Cu(OTf)_2$/(*S*)-**4a** were investigated. As the optimization of the chlorination reactions had revealed that the enantioselectivity strongly depended on the halogen source, the five commercially available electrophilic fluorination agents **17**–**21** were examined. Again, oxo ester **7a** served as the initial test substrate. Only *N*-fluorobenzenesulfonimide (NFSI, **21**) could successfully be used under the previously optimized reaction conditions, affording fluorinated product **16a** with 58% *ee* in 83% yield (Table 5, Entry 1). All the other electrophilic fluorine donors **17**–**20** showed no conversion, and unhalogenated oxo ester **7a** was fully recovered. These results can be rationalized by the poor solubility of the fluorinating agents of the type $R_3N^+F^-$ (**17**–**20**) in most organic solvents. Whereas "neutral" NFSI (**21**) is fairly soluble in Et_2O, mono- or dicationic species, **17**–**20** require aprotic, dipolar solvents such as CH_3CN, DMF, or CH_3NO_2 for dissolution.[26] These, however, are inadequate due to their high boiling points, which prevents a clean separation from volatile products (for details see the Experimental Section). Table 5 summarizes the results obtained from the fluorination of oxo esters **7a**–**i** with NFSI (**21**).

Table 5. Catalytic enantioselective fluorination of β-oxo esters **7a**–**i**.[a]



Entry	β-Oxo ester	R^1	R^2	R^3	Product	Yield [%]	*ee*[b,c] [%]
1	**7a**	Me	Bn	Et	**16a**	83	58
2	**7b**	Me	Ph	Et	**16b**	88	42
3	**7c**	Me	Et	Et	**16c**	66	68
4	**7d**	Me	Me	Et	**16d**	49	63 (*S*)
5	**7e**	$(CH_2)_3$		Et	**16e**	99	74 (*S*)
6	**7f**	$(CH_2)_4$		Et	**16f**	92	71
7	**7g**	$(CH_2)_6$		Et	**16g**	96	73
8	**7h**	$(CH_2)_3$		Me	**16h**	99	74
9	**7i**	Me	$(CH_2)_2$		**16i**	99	39

[a] Reaction conditions: $Cu(OTf)_2$ (10 mol-%), (*S*)-**4a** (10 mol-%), NFSI (**21**) (1.2 equiv.), Et_2O (0.1 M), –78 °C to room temp., 16 h. [b] Determined by CSP-HPLC or GC. [c] The absolute configurations given in parentheses were determined by comparison of the optical rotation values with those reported in the literature.

Most of the fluorinated oxo esters **16** were obtained in excellent yields ranging from 83 to 99% (Entries 1, 2, and 5–9). Only the acyclic substrates **7c** and **7d**, bearing an ethyl and a methyl substituent at the α position, respectively (Entries 3 and 4), gave the corresponding products in lower yields (66 and 49%, respectively). Compared with the chlorination and bromination reactions, in which such a decrease in yield did not occur, this observation was surprising. Note that the enantioselectivities were generally higher in the fluorination reactions (39–74% *ee*) than in the analogous chlorination and bromination reactions. Overall, the trend with respect to the product *ee* was fluorination > chlorination > bromination.

Recently, Shibatomi et al. reported that the slow addition of a solution of **21** to a mixture of β-oxo esters and an $Ni(ClO_4)_2$/*N*,*N*,*N*-tridentate ligand complex (instead of simultaneously mixing all the reagents) resulted in a significantly improved enantioselectivity.[15h] When this protocol was applied in this work and **21** was slowly added (by syringe pump over 5 h) to a mixture of **7a** and $Cu(OTf)_2$/(*S*)-**4a** the *ee* of the resulting product **9a** remained unaffected.

Conclusions

We have developed a general protocol for the enantioselective halogenation of β-oxo esters. All three chlorination, bromination, and fluorination reactions proceeded well with the latter giving the best results. Starting from both cyclic and acyclic substrates the corresponding products were formed with moderate to good enantioselectivities (up to 91% *ee*) in excellent yields.[27] The catalyst was prepared in situ from $Cu(OTf)_2$ and a commercially available amino sulfoximine [(*S*)-**4a**]. An extension of the method to the use of other nucleophiles is now envisaged.

Experimental Section

General Procedure for the Copper-Catalyzed Bromination, Chlorination, or Fluorination Reactions of β-Oxo Esters: A dry Schlenk tube was charged with $Cu(OTf)_2$ (0.020 mmol, 0.10 equiv.) and sulfoximine (*S*)-**4a** (0.020 mmol, 0.10 equiv.) under Ar. Dry Et_2O (2.0 mL, 0.1 M) was added, and the green solution was stirred at room temp. for 30 min. Subsequently, oxo ester **7** (0.20 mmol) was added and stirring of the reaction mixture was continued at room temp. for an additional 5 min. The solution was then cooled to –78 °C, and halogen donor **8**, **14**, or **21** (0.24 mmol, 1.2 equiv.) was added. Stirring was continued for 16 h while the suspension warmed to room temp. Direct column chromatography of the now brownish reaction mixture afforded pure products. Depending on their volatility the products were dried at ambient temperature under high vacuum or at 40 °C in a rotary evaporator under reduced pressure.

Supporting Information (see footnote on the first page of this article): General Procedures for the halogenation reaction and characterization data for compounds **9a**–**i**, **15a**–**h**, and **16a**–**i**.

Acknowledgments

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