Note

Asymmetric Chlorination of *β*-Keto Esters Using Diaminomethylenemalononitrile Organocatalyst

Takaaki Sakai, Shin-ichi Hirashima, Kosuke Nakashima, Chie Maeda, Akihiro Yoshida, Yuji Koseki, and Tsuyoshi Miura*

Tokyo University of Pharmacy and Life Sciences; 1432–1 Horinouchi, Hachioji, Tokyo 192–0392, Japan.
Received September 8, 2016; accepted September 23, 2016

Diaminomethylenemalononitrile organocatalysts promote the asymmetric chlorination of simple cyclic *β*-keto esters such as methyl, ethyl, and benzyl esters of 1-oxo-2,3-dihydro-1*H*-indene-2-carboxylic acid. This affords the corresponding chiral *α*-chlorinated carbonyl products in excellent yields with high enantioselectivities.

Key words organocatalyst; asymmetric chlorination; *β*-keto ester

Chiral *α*-chlorinated carbonyl compounds are valuable building blocks in the production of various biologically active compounds.[1–5] To synthesize enantiomerically enriched *α*-chlorinated carbonyl compounds, direct chlorination of carbonyl compounds using a chlorine source, such as *N*-chlorosuccinimide (NCS), is a reliable method. Several research groups have reported on the asymmetric chlorination of *β*-keto esters using metal catalysts.[6–17] Organocatalysis, meanwhile, has received considerable attention in the area of organic synthesis because, in comparison to reactions involving metal catalysts, it is an environmentally benign method. Synthetic methods for producing *α*-chlorinated compounds from *β*-keto esters using organocatalysts have also been developed.[18–24] Although chiral *α*-chlorinated *β*-keto esters are valuable synthetic intermediates, their preparation using organocatalysts and NCS with high enantioselectivity (>80% enantiomeric excess (ee)) has rarely been reported upon.[19–21] Several methods for the synthesis of chiral *α*-chlorinated *β*-keto esters require high catalyst loading (>5 mol%), a complex chlorine source, and bulky ester units such as the *t*-butyl and adamantyl groups. The highly stereoselective (>80% ee) *α*-chlorination of simple esters of 1-oxo-2,3-dihydro-1*H*-indene-2-carboxylic acid, such as methyl, ethyl, and benzyl esters (**6a**–**c**), is very rare.[12,18] Among the various chlorine sources, NCS is one of the best reagents because of its simple structure and low cost. The *α*-chlorination of a simple cyclic *β*-keto ester with NCS, in the presence of an organocatalyst (*ca.* 1 mol%), is therefore highly desirable, and it is one of the most challenging research topics.

Recently, we reported on some asymmetric reactions using organocatalysts bearing diaminomethylenemalononitrile (DMM) or diaminomethyleneindenedione (DMI) motifs.[25–32] In order to further demonstrate the value of DMM organocatalysts, we attempted to apply them to the asymmetric *α*-chlorination of simple cyclic *β*-keto esters.

Results and Discussion

We examined organocatalysts **1**–**5** (Fig. 1) for an enantioselective *α*-chlorination of *β*-keto ester **6a**, as shown in Table 1. DMM organocatalysts **1**–**3** with tertiary or secondary amine groups provided the desired product **7a** in excellent yields with low enantioselectivities (entries 1–3). Organocatalyst **4**, which bears a chiral primary amine group, accelerates the *α*-chlorination of **6a** and gives **7a** with good enantioselectivity

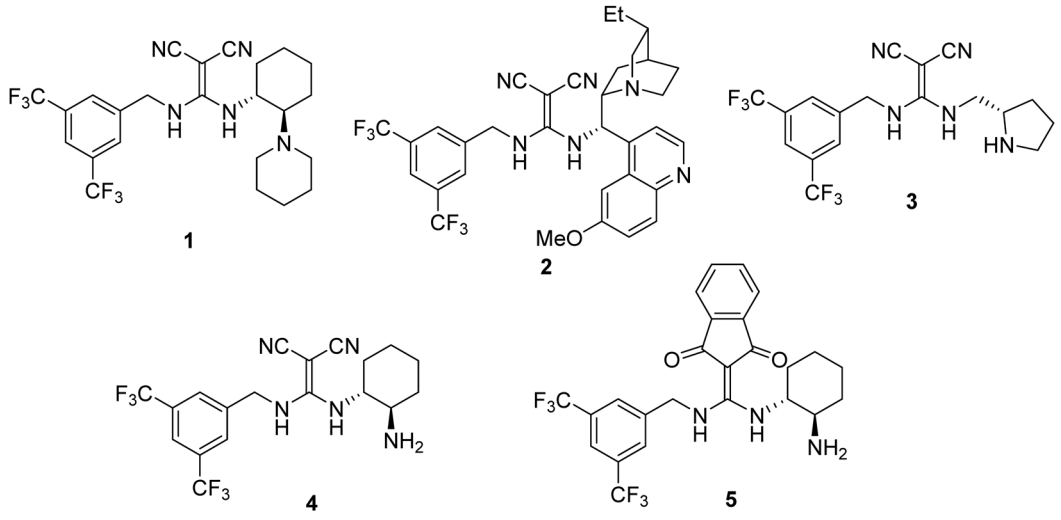


Fig. 1. Structure of Organocatalysts

* To whom correspondence should be addressed. e-mail: tmiura@toyaku.ac.jp

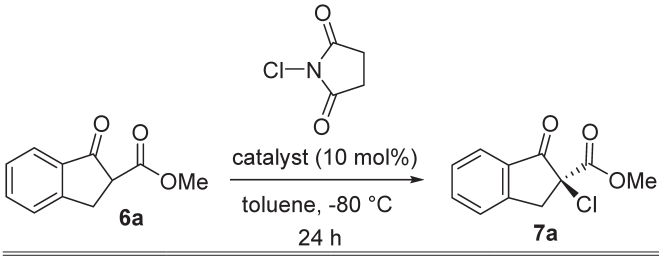
(entry 4). DMI organocatalyst **5** is a poor choice for asymmetric α-chlorination (entry 5). Owing to these results, we decided to further study its reaction conditions using catalyst **4** because we found that catalyst **4** provided the best results.

Various reaction conditions were examined for the asymmetric α-chlorination of **6a** using catalyst **4**, as shown in Table 2. Among the reaction solvents examined at 0°C, toluene was found to be the most suitable solvent (entries 1–4). The reaction in toluene at −80°C improved the enantioselectivity by up to 72% ee (entry 5). Other reaction solvents were examined at −80°C, and toluene was again found to be the most suitable solvent (entries 5–7). We also attempted to reduce the amount of catalyst loading necessary to achieve the optimal conditions. Enantioselectivity was improved by up to 78% ee without lowering of the yield when catalyst loading was reduced to 1 mol% (entries 8–10). Changes in the amount of NCS added (2.0 or 1.1 eq) resulted in a slight reduction in enantioselectivity (entries 11, 12, respectively). The optimal conditions, therefore, were determined to be 1 mol% of **4** and 1.5 eq of NCS in toluene at −80°C (entry 10). Among the reported methods for the synthesis of **7a** using organocatalysts, the method reported by Bartoli *et al.* was the only successful procedure to obtain 93% ee[18]; other organocatalytic methods provided moderate enantioselectivities (up to 63% ee).[20]

Next, we examined chlorine sources such as trichloroisocyanuric acid and 1,3-dichloro-5,5-dimethylhydantoin, as shown in Table 3. Among the chlorine sources examined under the optimal reaction conditions, NCS was still found to be the most suitable source.

With these optimal conditions in mind, the scope and limitations of α-chlorinations of various β-keto esters were examined (Table 4). An ethyl ester of 1-oxo-2,3-dihydro-1*H*-indene-2-carboxylic acid (**6b**) reacts with NCS to afford the corresponding product **7b** in an excellent yield with 71% ee (entry 2). Meanwhile, the reported methods for synthesizing **7b** using organocatalysts and metal catalysts did not even provided moderate enantioselectivities (up to 64% ee).[13,14,16,24] The reaction of the benzyl ester **6c** with NCS provided the

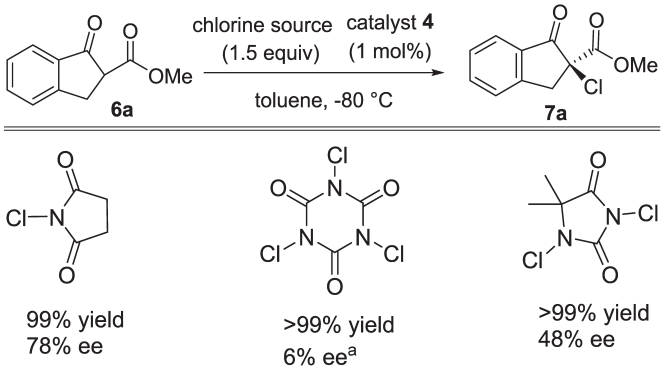
Table 1. Catalyst Screening



Entry	Catalyst	% Yield[a)]	% ee[b)]
1	**1**	99	22
2	**2**	99	−30
3	**3**	99	−5
4	**4**	99	69
5	**5**	99	41

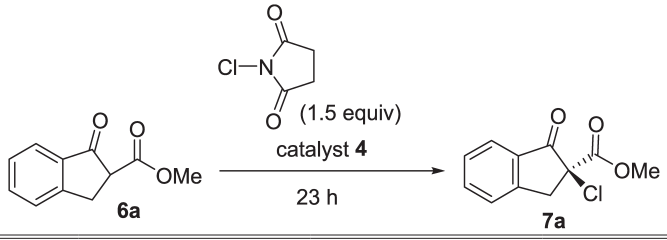
a) Isolated yield. *b*) Determined by chiral HPLC analysis.

Table 3. Study of Chlorine Source



[a] One equivalent of chlorine source was used.

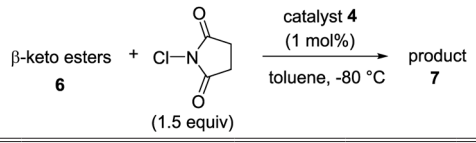
Table 2. Study of Reaction Conditions

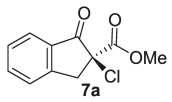
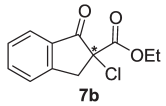
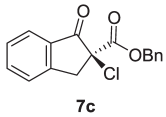
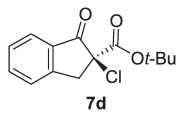
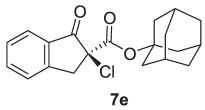
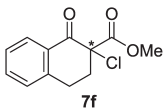
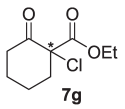
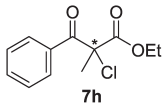


Entry	Solvent	Temp. (°C)	Catalyst (mol%)	% Yield[a)]	% ee[b)]
1	CH_2Cl_2	0	10	95	24
2	$CHCl_3$	0	10	99	26
3	THF	0	10	99	10
4	Toluene	0	10	96	33
5	Toluene	−80	10	99	72
6	EtOAc	−80	10	99	49
7	Et_2O	−80	10	98	32
8	Toluene	−80	5	98	75
9	Toluene	−80	2	93	77
10	Toluene	−80	1	99	78
11[c)]	Toluene	−80	1	99	75
12[d)]	Toluene	−80	1	99	76

a) Isolated yield. *b*) Determined by chiral HPLC analysis. *c*) NCS (2 eq) was used. *d*) NCS (1.1 eq) was used.

Table 4. Study of Substrate Scope



Entry	Product	Time (h)	% Yield[a]	% ee[b]
1	 **7a**	23	99	78
2	 **7b**	19	96	71
3	 **7c**	20	99	79
4	 **7d**	21	96	55
5	 **7e**	22	97	46
6	 **7f**	26	99	56
7	 **7g**	23	99	19
8[c]	 **7h**	41	5	ND[d]

a) Isolated yield. *b*) Determined by chiral HPLC analysis. *c*) Catalyst **4** (10 mol%) was used. *d*) Not determined.

corresponding product **7c** in an excellent yield with 79% ee. An organocatalytic synthesis of **7c** was reported only by Novacek *et al.*, but it could afford moderate enantioselectivities (48% ee).[24] In the reaction of bulky esters, such as *t*-butyl and adamantyl esters **6d** and **e**, the enantioselectivities decreased (entries 4, 5, respectively). Although *β*-keto esters **6f** and **g** as cyclohexanone derivatives were chlorinated under the optimal reaction conditions and gave chiral *α*-chlorinated compounds **7f** and **g** in excellent yields, their stereoselectivities were low to modelate (entries 6, 7, respectively). Ethyl 2-methyl-3-oxo-3-phenylpropanoate (**6h**) gave a low yield for the product **7h** (entry 8).

In conclusion, the DMM organocatalyst **4** can efficiently catalyze the asymmetric chlorination of various cyclic *β*-keto esters, such as **6**, with low catalyst loading (1 mol%) and NCS as a simple chlorine source to afford the corresponding products **7** bearing tertiary chiral carbon in excellent yields with moderate to high enantioselectivities. Particularly, simple cyclic *β*-keto esters, such as methyl ester **6a**, ethyl ester **6b**, and benzyl ester **6c** acted as good substrates as they provided relatively higher stereoselectivities than those provided by previous organocatalytic methods. We have demonstrated that the organocatalyst bearing DMM motif can function as an efficient catalyst for the stereoselective synthesis of *α*-chlorinated carbonyl compounds **7**. Further application of the DMM catalyst in the synthesis of bioactive compounds is currently being investigated in our laboratory.

Experimental

General Methods and Materials ^{1}H- and ^{13}C-NMR spectra were measured with a Bruker DPX 400 spectrometer (400 MHz for ^{1}H-NMR, 100 MHz for ^{13}C-NMR). The chemical shifts are expressed in ppm downfield from tetramethylsilane (δ=0.00) as an internal standard. Mass spectra were recorded by an electrospray ionization-time of flight (ESI-TOF) mass spectrometer (Micromass LCT). For TLC analyses, Merck precoated TLC plates (silica gel 60 F_{254}) were used. Flash column chromatography was performed on neutral silica gel (40–50 μm). Organocatalysts **1**,[31] **2**,[28] **3**,[26] **4**,[25] and **5**[32] were prepared by the previous reported methods.

Typical Procedure for *α*-Chlorination of *β*-Keto Esters 6 Using Organocatalyst 4 (Table 2) To a solution of methyl 1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate (**6a**, 38.0 mg, 0.200 mmol) and organocatalyst **4** (0.9 mg, 0.002 mmol) in toluene (2.0 mL) was added NCS (40.1 mg, 0.300 mmol) at −80°C. After stirring in closed tube at −80°C for 23 h, the reaction mixture was directly purified by flash column chromatography on silica gel with a 9 : 1 mixture of hexane and AcOEt to afford **7a** (44.5 mg, 99%) as a yellow solid. All the products **7a**–**h** in the paper are known compounds that exhibited spectroscopic data identical to those reported in the literature.

Methyl (*S*)-2-Chloro-1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate (**7a**)[11,15,24]

Enantiomeric excess was determined by HPLC with ChiralPak AD-H column (hexane–2-propanol=95 : 5), flow rate=0.7 mL/min; λ=254 nm; t_{major}=14.4 min, t_{minor}=15.4 min.

Ethyl 2-Chloro-1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate (**7b**)[13]

Enantiomeric excess was determined by HPLC with ChiralCel OJ-H column (hexane–2-propanol=95 : 5), flow rate=0.8 mL/min; λ=254 nm; t_{major}=25.3 min, t_{minor}=37.1 min.

Benzyl (*S*)-2-Chloro-1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate (**7c**)[12,24]

Enantiomeric excess was determined by HPLC with ChiralPak OD-H column (hexane–2-propanol=70 : 30), flow rate=0.7 mL/min; λ=254 nm; t_{minor}=8.7 min, t_{major}=9.7 min.

tert-Butyl (*S*)-2-Chloro-1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate (**7d**)[12,15,24]

Enantiomeric excess was determined by HPLC with ChiralCel OJ-H column (hexane–2-propanol=80 : 20), flow rate=0.7 mL/min; λ=254 nm; t_{major}=9.3 min, t_{minor}=11.4 min.

Adamantan-1-yl (*S*)-2-Chloro-1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate (**7e**)[13,24]

Enantiomeric excess was determined by HPLC with ChiralPak AD-H column (hexane–2-propanol=95 : 5), flow rate=0.75 mL/min; λ=254 nm; t_{major}=11.8 min, t_{minor}=13.7 min.

Methyl 2-Chloro-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate (**7f**)[11,12]

Enantiomeric excess was determined by HPLC with ChiralPak IC column (hexane–2-propanol=90 : 10), flow rate=0.7 mL/min; λ=254 nm; t_{major}=23.2 min, t_{minor}=28.7 min.

Ethyl 1-Chloro-2-oxocyclohexane-1-carboxylate (**7g**)[8,10,18,19]

Enantiomeric excess was determined by HPLC with ChiralPak AD-H column (hexane–2-propanol=99 : 1), flow rate=0.7 mL/min; λ=200 nm; t_{minor}=10.9 min, t_{major}=11.7 min.

Acknowledgments This work was supported by JSPS KAKENHI Grant Number 16K08178. The authors would like to thank Enago (www.enago.jp) for the English language review.

Conflict of Interest The authors declare no conflict of interest.

References

1) March J., "Advanced Organic Chemistry: Reactions, Mechanisms and Structure," Wiley, New York, 1992.
2) De Kimpe N., Verhe R., "The Chemistry of α-Haloketones, α-Haloaldehydes, and α-Haloimines," John Wiley & Sons, New York, 1988.
3) Thomas G., "Medicinal Chemistry: An Introduction," John Wiley & Sons, New York, 2000.
4) Ramachandran P. V., "Asymmetric Fluoroorganic Chemistry: Synthesis, Applications, and Future Directions, ACS Symposium Series 746," American Chemical Society, Washington, DC, 2000.
5) Czekelius C., Tzschucke C. C., *Synthesis*, **2010**, 543–566 (2010).
6) Hintermann L., Togni A., *Helv. Chim. Acta*, **83**, 2425–2435 (2000).
7) Ibrahim H., Kleinbeck F., Togni A., *Helv. Chim. Acta*, **87**, 605–610 (2004).
8) Marigo M., Kumaragurubaran N., Jorgensen K. A., *Chemistry*, **10**, 2133–2137 (2004).
9) Shibata N., Kohno J., Takai K., Ishimaru T., Nakamura S., Toru T., Kanemasa S., *Angew. Chem. Int. Ed.*, **44**, 4204–4207 (2005).
10) Frings M., Bolm C., *Eur. J. Org. Chem.*, **2009**, 4085–4090 (2009).
11) Qi M. H., Wang F. J., Shi M., *Tetrahedron: Asymmetry*, **21**, 247–253 (2010).
12) Jiang J. J., Huang J., Wang D., Yuan Z. L., Zhao M. X., Wang F. J., Shi M., *Chirality*, **23**, 272–276 (2011).
13) Li J., Pan W., Wang Z., Zhang X., Ding K. L., *Adv. Synth. Catal.*, **354**, 1980–1986 (2012).
14) Kang Y. K., Kim H. H., Koh K. O., Kim D. Y., *Tetrahedron Lett.*, **53**, 3811–3814 (2012).
15) Shibatomi K., Soga Y., Narayama A., Fujisawa I., Iwasa S., *J. Am. Chem. Soc.*, **134**, 9836–9839 (2012).
16) Jia S.-J., Du D.-M., *Chin. Chem. Lett.*, **25**, 1479–1484 (2014).
17) Shibatomi K., Kotozaki M., Sasaki N., Fujisawa I., Iwasa S., *Chemistry*, **21**, 14095–14098 (2015).
18) Bartoli G., Bosco M., Carlone A., Locatelli M., Melchiorre P., Sambri L., *Angew. Chem. Int. Ed.*, **44**, 6219–6222 (2005).
19) Cai Y., Wang W., Shen K., Wang J., Hu X., Lin L., Liu X., Feng X., *Chem. Commun.*, **46**, 1250–1252 (2010).
20) Etayo P., Badorrey R., Díaz-de-Villegas M. D., Gálvez J. A., *Adv. Synth. Catal.*, **352**, 3329–3338 (2010).
21) Luo J., Wu W., Xu L.-W., Meng Y., Lu Y., *Tetrahedron Lett.*, **54**, 2623–2626 (2013).
22) Shirakawa S., Tokuda T., Kasai A., Maruoka K., *Org. Lett.*, **15**, 3350–3353 (2013).
23) Li Z., Yang F., Meng Q., Gao Z., *Tetrahedron: Asymmetry*, **25**, 1215–1220 (2014).
24) Novacek J., Monkowius U., Himmelsbach M., Waser M., *Monatsh. Chem.*, **147**, 533–538 (2016).
25) Kanada Y., Yuasa H., Nakashima K., Murahashi M., Tada N., Itoh A., Koseki Y., Miura T., *Tetrahedron Lett.*, **54**, 4896–4899 (2013).
26) Nakashima K., Hirashima S., Kawada M., Koseki Y., Tada N., Itoh A., Miura T., *Tetrahedron Lett.*, **55**, 2703–2706 (2014).
27) Hirashima S., Sakai T., Nakashima K., Watanabe N., Koseki Y., Mukai K., Kanada Y., Tada N., Itoh A., Miura T., *Tetrahedron Lett.*, **55**, 4334–4337 (2014).
28) Hirashima S., Nakashima K., Fujino Y., Arai R., Sakai T., Kawada M., Koseki Y., Murahashi M., Tada N., Itoh A., Miura T., *Tetrahedron Lett.*, **55**, 4619–4622 (2014).
29) Nakashima K., Hirashima S., Akutsu H., Koseki Y., Tada N., Itoh A., Miura T., *Tetrahedron Lett.*, **56**, 558–561 (2015).
30) Nakashima K., Kawada M., Hirashima S., Kato M., Koseki Y., Miura T., *Synlett*, **26**, 1248–1252 (2015).
31) Hirashima S., Arai R., Nakashima K., Kawai N., Kondo J., Koseki Y., Miura T., *Adv. Synth. Catal.*, **357**, 3863–3867 (2015).
32) Nakashima K., Kawada M., Hirashima S., Kosugi A., Kato M., Yoshida A., Koseki Y., Miura T., *Tetrahedron: Asymmetry*, **27**, 888–895 (2016).