Catalytic Asymmetric Chlorination of β-Keto Esters with Hypervalent Iodine Compounds

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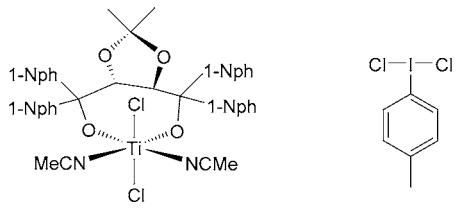
(Dichloroiodo)toluene (=dichloro(4-methylphenyl)iodine; **2**) was found to be a suitable chlorinating agent in the catalytic asymmetric chlorination of β-keto esters **3** catalyzed by the [Ti(TADDOLato)] complex **1** (=bis(acetonitrile)dichloro[(4*R*,5*R*)-2,2-dimethyl-α,α,α′,α′-tetra(naphthalen-1-yl)-1,3-dioxolane-4,5-dimethanolato(2−)-κ*O*,κ*O*′]titanium), whereby α-chlorinated products were obtained in moderate to good yields and enantioselectivities of up to 71% (*Scheme 2*, *Table 2*). The enantioselectivity of the reaction shows a remarkable temperature dependence, the maximum selectivity being obtained at *ca.* 50°.

1. Introduction. – Catalytic asymmetric halogenation reactions are still rare transformations. A breakthrough was achieved recently when efforts from this laboratory resulted in the first catalytic enantioselective fluorination of β-keto esters, with crystalline [Ti(TADDOLato)] complexes such as **1** (=bis(acetonitrile)dichloro-[(4*R*,5*R*)-2,2-dimethyl-α,α,α′,α′-tetra(naphthalen-1-yl)-1,3-dioxolane-4,5-dimethanolato(2−)-κ*O*,κ*O*′]titanium; see *Figure*) as catalyst and F-TEDA (=1-(chloromethyl)-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate), also called *Selectfluor*™; TEDA=triethylenediamine) as the fluorinating agent [1a][1]. This methodology was further extended to the corresponding chlorination and bromination reactions [2]. In the former, *N*-chlorosuccinimide (NCS) was used as the chlorinating agent to yield the corresponding products in good yields and up to 88% ee. To the best of our knowledge, the only other successful approach to a catalytic enantioselective



1 **2**

Figure. *The catalyst precursor* **1** *and the reagent* **2** *used in chlorinations of β-keto esters* (1-Nph=naphthalen-1-yl)

[1]) For more recent developments in the area of catalytic asymmetric fluorination, see [1b] (Pt catalysis) and [1c] (phase-transfer catalysis).

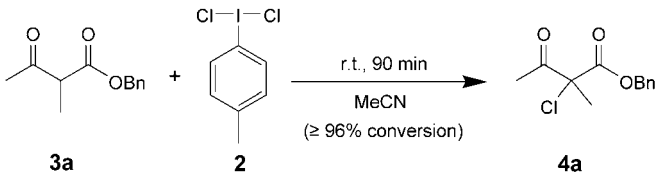
electrophilic chlorination is the tandem asymmetric chlorination/esterification process of acyl halides reported by *Lectka* and co-workers [3]. In that study, a catalytic amount of chinchona alkaloid was employed in the presence of perhaloquinone-derived reagents as electrophilic chlorine source to afford α-halo esters with high enantioselectivity.

Hypervalent iodine compounds have received considerable attention in the past decade resulting in an explosive increase of reports on the reactivity and applications of these unique compounds [4][2]). The number of synthetic applications is, however, in strong contrast to their elaboration in catalytic asymmetric transformations. In fact, apart from iodosylbenzene [5] and its derivative (diacetoxyiodo)benzene (= bis(acetyloxy)phenyliodine) [6] which have been employed in catalytic asymmetric epoxidations, and iminoiodanes which have found application in asymmetric aziridination of olefines and various amidation and imidation reactions [5], we are not aware of any other application of a hypervalent iodine compound in an asymmetric catalytic process. This applies in particular to (dichloroiodo)- and (difluoroiodo)arene (= aryldichloroiodine and aryldifluoroiodine, resp.) compounds that have been recognized as powerful halogenating agents [7].

2. Results and Discussion. – In search for more efficient systems for asymmetric halogenation reactions, we were able to combine the catalytic methodology developed in our group by using catalyst **1** with (dichloroiodo)toluene (= DCIT = dichloro(4-methylphenyl)iodine; **2**) [8] as chlorinating agent to generate enantiomerically enriched α-chlorinated β-keto esters. We report here our first results with this new system.

Uncatalyzed chlorination of ketones and 1,3-diketones with (dichloroiodo)benzene have been reported [9]. Usually, under ionic conditions, these reactions are performed in AcOH. We found that a MeCN solution of **2** is sufficient to α-chlorinate our test substrate **3a** (*Scheme 1*). Complete conversion to **4a** was obtained within 90 min at room temperature, and the only by-product observed by ^{1}H-NMR in the crude reaction mixture was iodotoluene.

Scheme 1



3a **2** **4a**

For the catalytic reaction, **3a** and 5 mol-% of complex **1** were dissolved in MeCN in the presence of 1.2 equiv. of *Hünig*'s base prior to the dropwise addition of **2**. Under these conditions, 63% conversion to **4a** was achieved within 2 h (*Table 1*, *Entry 1*). Chiral HPLC analysis of the product revealed an ee of 34%, which indicated that the reaction proceeded, although probably only partially, through a catalytic pathway

[2]) For a recent review of this area, see [5].

involving complex **1**. Changing the solvent to toluene and the base to pyridine resulted in an improved ee of 45% (*Table 1*, *Entry 2*). A significant increase in reaction rate was observed upon carrying out the reaction at 50° where complete conversion of **3a** to **4** was obtained within 20 min. Pleasingly, HPLC analysis of the reaction product indicated an ee of 71% (*Entry 3*). It is important to note that this ee was only obtained when the solution of **2** was added dropwise, fast addition resulted in a substantially lower ee of 38% (*Entry 4*). This finding suggests that the discrimination between the uncatalyzed background reaction and the enantioselectively catalyzed transformation is effective when **2** is not present in excess with respect to the catalyst. An increase of the reaction temperature to 70° gave the product with a slight decrease in enantioselectivity to 68%, although the reaction rate was enhanced even further (*Entry 5*). Slower addition of **2** with a syringe pump had a detrimental effect on both conversion and selectivity, presumably due to catalyst decomposition/deactivation (*Entry 6*).

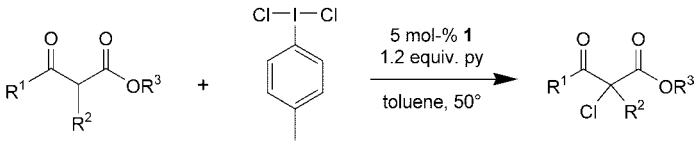
Table 1. *Optimization Studies on the Catalytic Chlorination of* **3a** *with DCIT* (**2**) *in the Presence of Catalyst* **1**

Entry	Base	Solvent[a])	Temp. [°]	Time[b]) [min]	Conversion[c]) [%]	ee[d]) [%]
1	$^{i}Pr_2EtN$	MeCN	r.t.	120	63	34
2	pyridine	toluene	r.t.	60	90	45
3	pyridine	toluene	50	20	≥96	71
4	pyridine	toluene	50	30[e])	≥96	38
5	pyridine	toluene	70	15	≥96	68
6	pyridine	toluene	50	120[f])	60	32

[a]) Dry solvents were used. [b]) Time after the addition of **2**; 1 ml of *ca.* 0.18M **2** was added within 3 min. [c]) Determined by the ^{1}H-NMR spectrum of the crude product. [d]) Determined by chiral HPLC analysis with a *Chiralcel-OJ* column. [e]) Fast addition of **2**. [f]) Time of **2** addition.

The optimized conditions of *Entry 3* in *Table 1* were applied to the chlorination of various β-keto esters **3** to yield the products **4** (*Scheme 2*). The results are summarized in *Table 2*. Generally, the variation of the ester functionality had little effect on selectivities and reaction rates (*Table 2*, *Entries 1–4*). However, benzoyl derivative **3e** and benzyl- and allyl-substituted esters **3f** and **3g** gave clearly lower enantioselectivities (*Entries 5–7*). Noteworthy is that **4a** (71% ee) and **4c** (66% ee) were obtained with higher enantioselectivites than with the NCS system which gave 60% ee [2a] and 42% ee [2b], respectively.

Scheme 2



3[a]) **2** **4**[a])

[a]) For R^1, R^2, and R^3, see *Table 2*.

Table 2. *Catalytic Asymmetric Chlorination of β-Keto Esters* **3** *with DCIT* (**2**) *in the Presence of Catalyst* **1**

Entry	Substrate	R^1	R^2	R^3	Product	Time[a]) [min]	Yield[b]) [%]	ee[c]) [%]
1	**3a**	Me	Me	Bn	**4a**	20	67	71
2	**3b**	Me	Me	(Anth)CH_2[d])	**4b**	20	82	70
3	**3c**	Me	Me	Et	**4c**	20	68	66
4	**3d**	Me	Me	Ph	**4d**	20	37	60
5	**3e**	Ph	Me	Et	**4e**	45	83	15
6	**3f**	Me	Bn	Bn	**4f**	20	82	16
7	**3g**	Me	CH_2=$CHCH_2$	Bn	**4g**	20	83	< 10

[a]) Time for complete conversion as estimated by TLC analysis. [b]) Isolated yields after flash column chromatography. [c]) Determined by chiral HPLC or chiral GC analysis. [d]) (Anth)CH_2 = (anthracen-9-yl)methyl.

The use of 1-(dichloroiodo)-4-nitrobenzene [8] or 1-(dichloroiodo)-4-methoxybenzene [10] instead of **2** did not affect the stereoselectivity of the chlorination of **3a** significantly. In both cases, **4a** was obtained in 37% and 28% yield and with 67% ee and 69% ee, respectively.

Comparing the sign of $[\alpha]_D$ for **4a** obtained in the presence of **1** and **2** with that reported [2] from the reaction in the presence of the same catalyst and NCS reveals that the sense of chiral induction is the same for both systems when the same enantiomer of the catalyst is used. The same is true when **2** is replaced by the corresponding iodonium species generated *in situ* from **2** and $AgBF_4$, or even when elemental chlorine is used! Thus, adding the iodonium cation solution in the same manner as for *Entry 3* in *Table 1* gave 60% conversion of **3a** and an ee of 33%, whereas slow injection of Cl_2 *via* a syringe afforded the same product **4a** in 61% yield and with 30% ee. We think that the different levels of enantioselectivity are mainly due to the varying extent of the uncatalyzed reaction for different chlorinating agents. We speculate that these observations are indicative of the mechanistic resemblance of the chlorination with DCIT (**2**), the chloroiodonium salt, or Cl_2, to the one with NCS, and hence to the fluorination with F-TEDA. For the latter reaction, we performed a *Car–Parrinello* molecular dynamics (CPMD) study showing the reaction to proceed *via* single-electron transfer (SET) [11]. The halogenating agent abstracts one electron from the [Ti(enolato)] complex generating a short-lived singlet diradical. The ensuing radical recombination of such a species occurs *via* halogen-atom transfer to the α-C-atom. That hypervalent iodine(III) compounds might react *via* SET has been postulated before [12] and constitutes the working hypothesis for our ongoing mechanistic investigations that should also help to understand the peculiar temperature dependence of enantioselectivity.

3. Conclusion. – We showed for the first time that the highly reactive hypervalent dichloroiodine compound **2** can be employed in a catalytic asymmetric chlorination, in this case of β-keto esters. Moderate to good yields of the chlorinated products were obtained with enantioselectivities of up to 71%. We would like to point out that considering the great number of $ArI(FG)_2$ (FG = functional group) compounds known, the concept outlined in this article could be of great potential in the asymmetric functionalization of enolizable substrates. From a synthetic point of view, current work

in our laboratory involves the elaboration of (difluoroiodo)arenes as well as elemental chlorine for catalytic asymmetric halogenation reactions.

Experimental Part

General. HPLC: *Chiralcel-OD-H* column; eluent hexane/^{i}PrOH 99.5:0.5, 0.6 ml/min; t_R in min. GC: *Supelco-β-DEX-120* column (30 m), 120° isotherm; t_R in min. IR: in cm^{-1}. NMR: δ in ppm, J in Hz. MS: in m/z (rel. %).

General Procedure: Chlorination **3a** → **4a**. β-Keto ester **3a** (146 mg, 0.71 mmol) and catalyst **1** (29 mg, 0.035 mmol) were placed in a heat-gun-dried *Schlenk* tube. Dry toluene (3 ml) was added, and the mixture was placed in an oil bath heated to 50°. After 10 min, pyridine (67 µl, 0.85 mmol) was added. Then **2** (92%; 230 mg, 0.75 mmol) dissolved in toluene (4.5 ml) was added dropwise *via* a syringe (→ precipitation of pyridine hydrochloride). ^{t}BuOMe (20 ml) was added after 20 min, and the resulting suspension was filtered over a pad of alumina. Further elution with ^{t}BuOMe (100 ml) and evaporation of the filtrate gave a yellow oil, which was purified by FC (SiO_2; hexane/^{t}BuOMe 100:0 → 95:5): 114 mg (67%) of **4a** [2a]. Colorless oil.

Anthracen-9-ylmethyl 2-Chloro-2-methyl-3-oxobutanoate (**4b**): HPLC (230 nm): t_R 33.4 (minor), 37.1 (major); 70% ee. $[\alpha]_D^{rt} = -13.5$ ($c = 1.01$, MeOH). IR (KBr): 1738*s* (ester C=O), 1710*s* (C=O), 734*s* (C–Cl). ^{1}H-NMR (250 MHz, $CDCl_3$): 1.79 (*s*, MeCCl); 2.15 (*s*, MeCO); 6.23 (*AB*('*d*'), $J = 12.5$, 1 H, (Anth)CH_2O); 6.32 (*AB*('*d*'), $J = 12.5$, 1 H, (Anth)CH_2O); 7.48–7.60 (*m*, 4 arom. H); 8.04 (*d*, $J = 8.2$, 2 arom. H); 8.29 (*d*, $J = 8.7$, 2 arom. H); 8.53 (*s*, 1 arom. H). ^{13}C-NMR (63 MHz, $CDCl_3$): 24.2 (*Me*CCl); 25.0 (*Me*CO); 61.5 ((Anth)-*C*H_2O)); 70.9 (MeCCl); 123.5 (2 arom. CH); 124.6 (C_{ipso}); 125.2 (2 arom. CH); 127.0 (2 arom. CH); 129.2 (2 arom. CH); 129.8 (arom. CH); 131.1 (2 arom. C); 131.3 (2 arom. C); 166.9 (ester C=O); 198.6 (C=O). EI-MS: 340 (3, M^+), 260 (3), 191 (100, $C_{15}H_{11}^+$). Anal. calc. for $C_{20}H_{17}ClO_3$ (340.80): C 70.49, H 5.03; found: C 71.21, H 5.51.

Benzyl 2-Benzyl-2-chloro-3-oxobutanoate (**4f**): HPLC (210 nm): t_R 20.1 (major), 21.7 (minor); 26% ee. $[\alpha]_D^{rt} = -9.6$ ($c = 0.56$, MeOH). IR (neat): 1753*s* (ester C=O), 1732*s* (C=O), 700*s* (C–Cl). ^{1}H-NMR (250 MHz, $CDCl_3$): 2.19 (*s*, Me); 3.44 (*AB*('*d*'), $J = 14.4$, 1 H, PhCH_2); 3.55 (*AB*('*d*'), $J = 14.7$, 1 H, PhCH_2); 5.17 (*AB*('*d*'), $J = 14.4$, 1 H, PhCH_2); 5.22 (*AB*('*d*'), $J = 14.3$, 1 H, PhCH_2); 7.15–7.38 (*m*, 10 arom. H). ^{13}C-NMR (63 MHz, $CDCl_3$): 26.4 (Me); 42.2 (Ph*C*H_2); 68.5 (Ph*C*H_2O); 75.3 (CCl); 127.5 (arom. CH); 128.2 (2 arom. CH); 128.5 (2 arom. CH); 128.7 (2 arom. CH); 128.8 (arom. CH); 130.6 (2 arom. CH); 133.8 (arom. C); 134.3 (arom. C); 166.9 (ester C=O); 198.6 (C=O). EI-MS: 316 (0.1, M^+), 281 (3, $[M - Cl]^+$), 228 (10), 221 (12), 180 (15), 168 (12), 131 (21), 91 (100, $C_7H_7^+$). Anal. calc. for $C_{18}H_{17}ClO_3$ (316.78): C 68.25, H 5.41; found: C 68.37, H 5.54.

Benzyl 2-Acetyl-2-chloropent-4-enoate (**4g**): GC: t_R 288 (major), 291 (minor); < 10% ee (incomplete baseline separation). IR (neat): 1755*s* (ester C=O), 1731*s* (C=O), 698 (C–Cl). ^{1}H-NMR (300 MHz, $CDCl_3$): 2.26 (*s*, Me); 2.83–2.99 (*m*, CH_2=CHCH_2); 5.08–5.15 (*m*, CH_2=CHCH_2); 5.20 (*AB*('*d*'), $J = 12.2$, 1 H, PhCH_2O); 5.25 (*AB*('*d*'), $J = 12.2$, 1 H, PhCH_2O); 5.68–5.82 (*m*, 1 H, CH_2=C*H*CH$_2$); 7.31–7.35 (*m*, 5 arom. H). ^{13}C-NMR (75 MHz, $CDCl_3$): 25.9 (Me); 41.0 (CH_2=CH*C*H$_2$); 68.5 (Ph*C*H$_2$O); 74.5 (CCl); 120.5 (*C*H_2=CHCH$_2$); 128.5 (2 arom. CH); 128.7 (2 arom. CH); 128.8 (arom. CH); 130.5 (CH_2=*C*HCH$_2$); 134.5 (arom. C); 166.8 (ester C=O); 197.8 (C=O). EI-MS: 266 (1, M^+), 189 (2, $[M - Cl - C_2H_2O]^+$), 188 (3), 160 (2), 155 (2), 133 (4), 125 (8), 107 (4), 91 (100, $C_7H_7^+$). Anal. calc. for $C_{14}H_{15}ClO_3$ (266.72): C 63.04, H 5.67; found: C 63.32, H 5.86.

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