Stereoselective Ketone Rearrangements with Hypervalent Iodine Reagents

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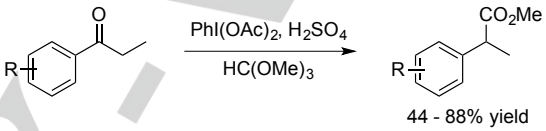
Abstract: The first stereoselective version of an iodine(III)-mediated rearrangement of arylketones in the presence of orthoesters is described. The reaction products, α-arylated esters, are very useful intermediates in the synthesis of bioactive compounds such as ibuprofen. With chiral lactic acid-based iodine(III) reagents product selectivities of up to 73% *ee* have been achieved.

Introduction

Hypervalent iodine reagents became versatile reagents in organic chemistry over the last decades. The mild reaction conditions associated with the low toxicity and the environmentally friendly behaviour of those compounds render them attractive to use in organic synthesis.[1,2] Those reagents are very selective oxidants[3] and several derivatives have been reported as enantiomerically pure reagents.[4] Due to their electrophilic nature and their excellent leaving group ability, they can react with a broad range of nucleophiles in reactions such as the oxidation of sulfides to sulfoxides,[5] the dearomatization of phenols,[6] the α-arylation[7] and the α-oxygenation[8] of carbonyl compounds but also in the functionalization of carbon-carbon double bonds (dioxygenation[9], diamination[10], oxyamination[11], iodoamination[12], oxytrifluoromethylation[13] or aminofluorination[14]). The facile generation of cationic intermediates by hypervalent iodine reagents allows either the direct reaction with a nucleophile or the formation of rearranged products[15] with ring contraction,[16] ring expansion,[17] or aryl migration.[18] Similar rearrangement have previously been reported with some toxic thallium reagents.[19] Finally, intensive efforts have been made towards the catalytic use of those hypervalent iodine reagents.[4b,20]

We have reported the oxidative rearrangement of aryl-substituted unsaturated carboxylic acids to yield furanones[21] and described the first stereoselective rearrangement mediated by hypervalent iodine reagent on chalcone derivatives.[18b] More recently, we developed the stereoselective hypervalent iodine-promoted oxidative rearrangement of 1,1-disubstituted alkenes.[18a] Haruta *et al.* reported the oxidative 1,2-aryl migration of alkyl aryl ketones to synthesize 2-aryl propanoates using diacetoxy(iodobenzene) in moderate to good yields as shown in Scheme 1.[22] 2-Aryl alkanoates are direct precursors of non-steroidal anti-inflammatory drugs (NSAIDs). NSAIDs are sold on the market as racemates but usually one of the two enantiomers is less active or even causes side effects.[23] Therefore, it would be of great interest to synthesize them in enantiomerically pure form. We herein describe the development of a stereoselective reaction which allows access to 2-aryl alkanoates in good enantioselectivities.

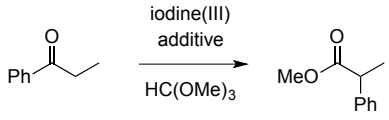


Scheme 1. Rearrangement of aryl alkyl ketones.

Results and Discussion

In order to evaluate hypervalent reagents and their reaction conditions for the oxidative rearrangement, the reaction of propiophenone **1** with hypervalent iodine reagents under different reaction conditions in the presence of acidic additives was investigated as shown in Table 1.

As we had previously much success using iodine(III) bistriflates as reagents, we performed the reaction by replacing the sulfuric acid additive with triflic acid and trimethylsilyl triflate. We also relied on the past performance of chiral hypervalent iodine reagents developed by Ishihara in rearrangement reactions.[18a]



1 **2**

Table 1. Reaction conditions for the stereoselective rearrangement of propiophenone **1** to methyl-2-phenylpropanoate **2**

Entry	Additive	Iodine(III) reagent	Temperature [°C]	Time [h]	*ee* [%]	Yield [%] (Conversion)[a]
1	2 eq. TMSOTf	$PhI(OAc)_2$	20	4	-	62 (99)
2	2 eq. *p*-TsOH•H_2O	$PhI(OAc)_2$	20	3	-	40 (99)
3	2 eq. TMSOTf	**3**	0	22	25 (*R*)	22 (84)
4	2 eq. TfOH	**3**	0	16	10 (*R*)	36 (89)

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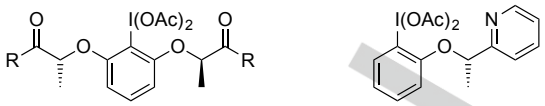
5	2 eq. TfOH	**3**	0	24	-	0[b]
6	2 eq. TfOH, 10 eq. H_2O	**3**	20	24	33 (*R*)	34 (61)[b]
7	2 eq. TfOH, 3 eq. MeOH	**3**	20	23	33 (*R*)	n.d.[c] (66)[b]
8	2 eq. H_2SO_4	**3**	20	23	23 (*R*)	44 (77)
9	2 eq. *p*-TsOH•H_2O	**3**	20	23	13 (*R*)	48 (75)
10	2 eq. TfOH	**3**	–20	24	40 (*R*)	n.d.[c] (96)
11	2 eq. TfOH	**3**	–48	10	-	-[d]
12	2 eq. TfOH	**4**	–20	24	53 (*R*)	49 (91)
13	2 eq. TMSOTf	**4**	–20	24	51 (*R*)	18 (39)
14	2 eq. TfOH	**5**	0	23	15 (*S*)	69 (93)

[a] Conversion determined by ^{1}H NMR of the crude reaction mixture. [b] Dry $HC(OMe)_3$ used as solvent. [c] n.d.: not determined. [d] (1,1-Dimethoxypropyl)benzene was isolated as product in 57% yield.

With (diacetoxyiodo)benzene (Table 1, Entries 1 and 2) the reactions proceeded very well and the product **2** was observed with very good conversion and acceptable isolated yield considering the volatility of methyl 2-phenylpropanoate **2**. The use of the chiral diester **3** provided initial (low) selectivities of the product **2** with 25% and 10% *ee* for TMSOTf and TfOH as additives, respectively (Table 1, Entries 3 and 4). As hypervalent iodine(III) reagents are usually water sensitive, dry $HC(OMe)_3$ was used as solvent/reagent. Surprisingly, the reaction did not lead to the formation of the desired product but to complete degradation of starting material (Table 1, Entry 5). If 10 eq. water or 3 eq. methanol were added to the dry solvent, the reaction proceeded as before when performed with normal grade $HC(OMe)_3$ without inert atmosphere (Table 1, Entries 6 and 7). Other additives such as sulfuric acid or *para*-toluenesulfonic acid led to lower selectivities (Table 1, Entries 8 and 9). Also the use of other solvents together with $HC(OMe)_3$ did reduce yield and selectivity. Different temperatures and hypervalent iodine reagents were investigated next. When the reaction was performed at –20 °C using reagent **3**, the enantioselectivity increased to 40% *ee* (Table 1, Entry 10). The temperature was further lowered down to –48 °C, but this led only to an incomplete formation of (1,1-dimethoxypropyl)-benzene (Table 1, Entry 11).

The hypervalent iodine(III) reagent **4** containing amide moieties led to product formation with very good conversion and a higher enantioselectivity of 53% (Table 1, Entry 12). The effect of the Lewis acid in combination with reagent **4** was also investigated. The stereoselectivity was as good using TMSOTf (51% *ee*) but the conversion dropped to 39% (Table 1, Entry 13). When BF_3•OEt_2 was used, no reaction occurred and starting material was recovered. With the new, pyridine-based chiral hypervalent iodine reagent **5**[24] the enantioselectivity was very low (15% *ee*) while the conversion stayed as high as with the other iodine(III) reagents (Table 1, Entry 14).



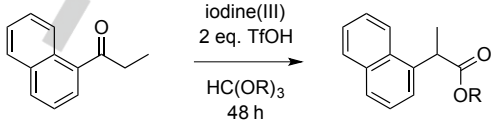
3 R = OMe
4 R = NHMes

5

Figure 1. Selected chiral hypervalent iodine reagents.

As the volatility of methyl-2-phenylpropanoate gives erroneous results, we investigated the rearrangement of the much less volatile 1-(naphthalen-1-yl)propan-1-one **6**, which is easily accessible by a Friedel-Crafts acylation.[25]

The reaction using reagent **4** worked well and product **7** was isolated in 91% yield with a selectivity of 46% *ee* when performed under identical reaction conditions to propiophenone. Reagent **3** is less efficient (Table 2, Entry 1) and also catalytic amounts of Lewis acid are not enough (Table 2, Entry 3) indicating that the Lewis acid must fully activate the iodine(III) reagent and is not only assisting in the equilibrium between the ketone and the enol form.



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7a (R = Me)
7b (R = Et)
7c (R = *i*-Pr)

Table 2. Reaction conditions for the stereoselective rearrangement of naphthalene derivative **6** to alkyl 2-(naphthalen-1-yl)propanoate **7**

Entry	R	Iodine(III) reagent	Temperature [ºC]	Product **7**	*ee* [%]	Yield [%]
1	Me	**3**	–20	**7a**	22 (*R*)	62
2	Me	**4**	–20	**7a**	46 (*R*)	91
3	Me	**4**	–20	**7a**	-	0[a]
4	Et	**4**	–20	**7b**	62 (*R*)	70
5	*i*-Pr	**4**	–20	**7c**	-	0[b]
6	Me	**4**	20	**7a**	44 (*R*)	81
7	Me	**4**	40	**7a**	40 (*R*)	40

[a] 0.2 eq. TfOH used. [b] 2-Isopropoxy-1-(naphthalen-1-yl)propan-1-one isolated in 22% yield.

The influence of the nature of the orthoester was then investigated. Triethyl orthoformate increased the selectivity to 62% *ee* while the yield remained still good (Table 2, Entry 4). This higher enantioselectivity can be explained by the higher bulkiness around the reactive centre where the rearrangement occurs. Therefore, an even bulkier orthoester should induce higher selectivity. However, the reaction with the tri-*iso*-propyl orthoformate did not lead to any rearranged product. It only added the *iso*-propoxy group to the *α*-position of the ketone in 22% yield (Table 2, Entry 5). This might be due to the too high

bulkiness of the *iso*-propyl moiety. Indeed, the formation of the ketal is more favoured in the case of the less bulky trimethyl or triethyl orthoformate. If the equilibrium is shifted to the ketal form (R = Me, Et), the presence of two oxygens will favour the rearranged transformation as they can stabilize the positive charge resulting from the aryl group's migration. On the other hand, if the equilibrium is shifted towards the ketone form (R = ^{i}Pr), the free alcohol is more likely to attack the carbon in *α*-position to generate the *α*-alkoxylated product.

Finally, the effect of the temperature on the selectivity was also investigated. At room temperature, the reaction worked similarly well providing **7** in 81% yield and 44% *ee* (Table 2, Entry 6) while the yield dropped due to side reactions at higher temperatures (Table 2, Entry 7).

Subsequently, a range of other substrates was investigated and the results are summarized in Table 3. When butyrophenone was used instead of propiophenone (Table 1, Entry 12), the selectivity increased by 10% to reach 63% *ee* (Table 3, Entry 1) and the bulkier isovalerophenone led to a rearranged reaction product with 73% *ee* (Table 3, Entry 2). Unfortunately, as the selectivity increased with the bulkiness of the alkyl chain, the conversion dropped significantly. The reaction with isovalerophenone was also performed at room temperature where the enantioselectivity dropped only by 5% and confirmed the small impact of the temperature on the rearrangement (Table 3, Entry 3). The reaction was also carried out with triethyl orthoformate as it was beneficial for the rearrangement of 1-propionylnaphthalene. However, with isovalerophenone the enantioselectivity dropped to 35% *ee* (Table 3, Entry 4).

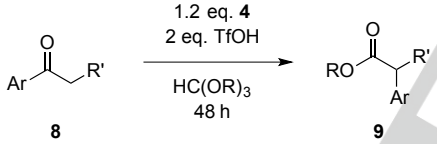


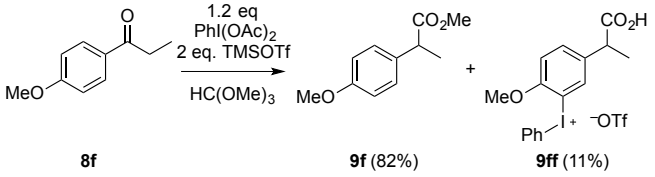
Table 3 Stereoselective rearrangements of aryl ketones **8**

Entry	Ar	R'	R	Temperature [ºC]	**9**	*ee* [%]	Yield [%] (racemate)[a]
1	Ph	Et	Me	–20	**9a**	63 (*R*)	56 (58)
2	Ph	^{i}Pr	Me	–20	**9b**	73 (*R*)	31
3	Ph	^{i}Pr	Me	20	**9b**	68 (*R*)	31 (93)
4	Ph	^{i}Pr	Et	20	**9bb**	35 (*R*)	31 (80)
5	4-Me-C_6H_4	Me	Me	20	**9c**	46	79 (86)
6	4-Et-C_6H_4	Me	Me	20	**9d**	44	87 (91)
7	4-^{i}Bu-C_6H_4	Me	Me	20	**9e**	35	72 (94)
8	4-MeO-C_6H_4	Me	Me	20	**9f**	27	80 (82)
9	1-(6-MeO-naphth)	Me	Me	20	**9g**	-	(traces)
10	4-F-C_6H_4	Me	Me	–20	**9h**	45	50 (92)
11	2-Br-C_6H_4	Me	Me	20	**9i**	44	46 (79)
12	3-Br-C_6H_4	Me	Me	20	**9j**	46	14 (98)
13	4-Br-C_6H_4	Me	Me	20	**9k**	-[b]	28 (76)
14	3-CF_3-C_6H_4	Me	Et	20	**9l**	-	13 (23)[c]
15	3-NO_2-C_6H_4	Me	Me	20	**9m**	-	n.r.[d] (75)
16	2-pyridyl	Me	Me	20	**9n**	-	-[e]
17	Ph	cyclo-C_3H_5	Et	20	**9o**	-	-[f]
18	2-naphthyl	Me	Me	–20	**9p**	24	52 (83)[g]

[a] Yield for the racemate using $PhI(OAc)_2$ as reagent. [b] *ee* could not be determined by HPLC as the enantiomers could not be separated. The product showed optical rotation. [c] 2-Ethoxy-1-(3-(trifluoromethyl)phenyl)propan-1-one was isolated as only product. With $PhI(OAc)_2$ also 73% rearranged product are obtained. [d] n.r.: no reaction occurred with reagent **4**. [e] 2-(1,1-Dimethoxypropyl)pyridine trifluoromethanesulfonic acid adduct was isolated as only product. [f] 4-Ethoxy-1-phenylbutan-1-one as ring-opened product was isolated in 98% yield. Further rearrangement occurred only with $PhI(OAc)_2$, not with **4**. [g] Reagent **3** was used instead of **4**.

Subsequently, the influence of the electronic properties of the aromatic ring in the rearrangement process was investigated. Propiophenone derivatives with electron-rich aryl moieties gave the rearranged products in very good yields but only moderate enantioselectivities (Table 3, Entries 5-7). Hydrolysis of the methyl ester product shown in Table 3, Entry 7, was achieved with 1N sodium hydroxide in THF/methanol to yield ibuprofen in 93% yield, but with reduced enantioselectivity (22% *ee*). The reaction proceeded similarly well with 4-methoxypropiophenone, but surprisingly did not work with 1-(6-methoxynaphthalen-1-yl)propan-1-one (Table 3, Entries 8 and 9).

In the reaction with 4-methoxypropiophenone, the reaction product **9f** reacted further with an excess of (diacetoxyiodo)benzene to generate the diaryliodonium salt **9ff**, its structure was also confirmed by X-ray analysis[24] (see Scheme 2 and supporting information). Compound **9f** can also be converted into **9ff** under the reaction conditions in 90% yield. The formation of **9ff** can be suppressed completely when only 1 equivalent of (diacetoxyiodo)benzene is used.

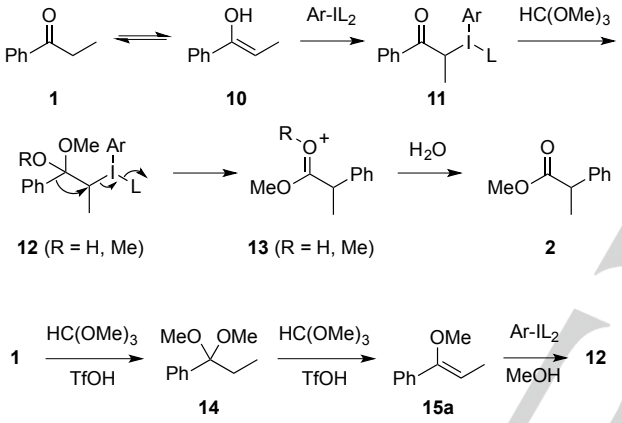


Scheme 2. Rearrangement and formation of diaryliodonium salt **9ff**.

Electron-withdrawing groups on the aromatic moiety do not seem to affect the enantioselectivity. Indeed, for all the compounds where the enantioselectivity could be determined, the enantiomeric excess was between 44 and 46% (Table 3, Entries 10-12). However, the yield of the reaction is depending on the nature of the electron-withdrawing group. Compared to fluorine, the yield decreased to 28% when a bromine substituent is in *para*-position (Table 3, Entries 10 and 13). The position on the aromatic ring is also important. While *para*- and *meta*-

substituents are giving poor yields (28% and 14%), the *ortho*-substituted product can be obtained in moderate yield (46%) (Table 3, Entries 11-13). With a trifluoromethyl substituent in *meta*-position, the rearranged product could only be obtained in trace amounts and the α-ethoxylated product was obtained as the major product in 13% yield (Table 3, Entry 14). 3-Nitro propiophenone was not reactive enough (Table 3, Entry 15) and and a pyridine derivative led only to the corresponding ketal (Table 3, Entry 16). A cyclopropyl-substituted derivative ring-opened but did not rearrange with the chiral reagent **4** (Table 3, Entry 17).

Electron-rich aryl moieties migrate faster as they stabilize the intermediate phenonium ion. However, the enantioselectivity seems to follow the opposite trend. This may be due to the fact that the reaction rate is faster for electron-rich aryl moieties and the interaction with the chiral reagent is less strong to induce high selectivity.

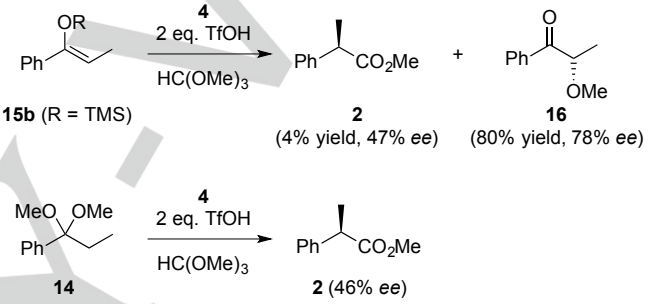


Scheme 3. Proposed mechanism for the rearrangement.

The proposed mechanism for the rearrangement as shown in Scheme 3 is similar to the mechanism proposed by Haruta.[22] In the generation of intermediate **11** the stereochemistry of the rearrangement process is defined. The presence of large amounts of nucleophiles will directly interfere with the intermediate **11** in a direct substitution of the iodine(III) moiety leading to α-functionalized ketones, as we and others have shown previously. Protected enolethers have been used by us and others recently as efficient substrates for stereoselective iodine(III) mediated reactions. Under the reaction conditions employed, it is also plausible that the presence of triflic acid and trimethyl orthoformate will lead to the formation of the enol **15a** via ketal **14**.[26] Although it is not identifiable in the NMR,[8a] it could react with the iodine(III) species in the presence of methanol to form intermediate **12**.

As shown in Scheme 4, silylenolether **15b** provides a mixture of rearranged product **2** and direct substitution product **16**, while the acetyl-substituted enolether **15c** (R = Ac) only forms α-substituted product **16** (57% yield using $PhI(OAc)_2$), probably because the formation of the corresponding ketal is less efficient. The pre-generated ketal **14** is similarly efficient in the rearrangement reaction and gives the rearrangement product **2** in similar conversion and selectivity to propiophenone. A rapid interconversion between **1** and **14** via the hemiketal under the reaction conditions was confirmed by NMR spectroscopy (see supporting information).

The absolute stereochemistry of the products **2** and **16** indicates the common intermediate **12** resulting from a *Si*-attack of the iodine(III) electrophile **4** to the enol **10**/**15a**. Reaction by rearrangement (path **A**) generates compound **2** with (*R*) configuration while backside substitution with methanol (path **B**) leads to **16** with (*S*) configuration. The different stereochemical descriptors are due to the CIP priorities and not to different stereochemical pathways. The absolute configuration of **16** was confirmed by its independent synthesis from lactic acid (see supporting information).



Scheme 4. Enols and ketals as substrates for the rearrangement reaction.

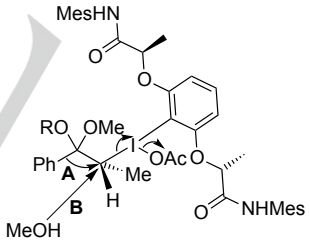
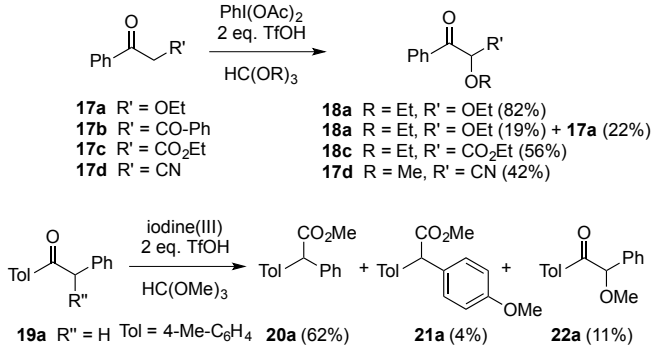


Figure 2. Intermediate **12** (R = H, Me).

Other substrates, however, seem not to be suitable for the rearrangement reaction. Compounds of type **17** with substituents R changing the electronic properties only lead to the α-ethoxylated products (Scheme 5). Only in the case of an aryl substitution such as in **19a** the rearranged product **20a** is formed together with methoxylation at the phenyl substituent of the rearranged compound (**21a**) and some α-methoxylated product **22a**. The selectivities obtained with reagent **4** are 25% *ee* (62% yield) for **20a**, 5% *ee* (4% yield) for **21a** and 7% *ee* (11% yield) for **22a**, but the absolute configurations of the products could not be determined. Similar yields (**20a**: 70%, **21a**: 10%, **22a**: 10%) are obtained when (diacetoxyiodo)benzene is employed as iodine(III) reagent. Compound **19b** (R'' = Me), which would lead to products with stereogenic tetrasubstituted

carbon atoms, is unreactive and completely recovered under the reaction conditions.



Scheme 5. Substituted substrates for the rearrangement reaction.

The catalytic transformation was investigated using $PhI(OAc)_2$ as the *in situ* synthesized hypervalent iodine reagent. Different oxidants ($NaBO_3$•$4H_2O$, *m*-CPBA) were investigated together with iodobenzene, propiophenone and trimethyl orthoformate, but no rearranged product was obtained under the reaction conditions investigated.

Conclusions

In summary, we have developed a stereoselective rearrangement of aryl alkyl ketones mediated by chiral hypervalent iodine (III) reagents. 2-Arylpropionate derivatives were synthesized in moderate to good yields with enantioselectivities up to 73% using a lactic acid-based reagent in the presence of TfOH and trimethyl orthoformate. Further investigations to improve the enantioselectivity and the development of a catalytic protocol are in progress.

Experimental Section

Rearrangement of propiophenone derivatives: To a solution of propiophenone derivative **8** (0.305 mmol) and the Ishihara amide **4** (267 mg, 0.365 mmol) in $HC(OMe)_3$ (1.5 mL), TfOH (57 µL, 0.609 mmol) was added dropwise at the temperature mentioned in Table 3. The resulting mixture was stirred at this temperature for 48 h, quenched with water (1 mL), extracted with CH_2Cl_2 (3 x 2 mL), dried over a Telos® phase separator and the solvent was removed under reduced pressure. After column chromatography (0 to 10% Et_2O in hexane), the corresponding product **9** was obtained.

Acknowledgements

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Keywords: addition • alkenes • iodine(III) • rearrangement • stereoselective synthesis

[1] a) *Hypervalent Iodine Chemistry*, Ed. T. Wirth, *(Topics in Current Chemistry)*, Springer, Berlin, **2003**, vol. 224. b) *Hypervalent Iodine Chemistry*, Ed. T. Wirth, *(Topics in Current Chemistry)*, Springer, Berlin, **2016**, vol. 373.

[2] V. V. Zhdankin, *Hypervalent Iodine Chemistry*, Wiley, Chichester, **2014**.

[3] T. Wirth, *Angew. Chem. Int. Ed.* **2005**, *44*, 3656-3665.

[4] a) R. Kumar, T. Wirth, *Top. Curr. Chem.* **2016**, *373*, 243-261; b) F. Berthiol, *Synthesis* **2015**, *47*, 587-603; c) F. V. Singh, T. Wirth, *Chem. Asian J.* **2014**, *9*, 950-971; d) R. M. Romero, T. H. Wöste, K. Muñiz, *Chem. Asian J.* **2014**, *9*, 972-983; e) A. Parra, S. Reboredo, *Chem. Eur. J.* **2013**, *19*, 17244-17260; f) U. Farid, T. Wirth, in *Asymmetric Synthesis – The Essentials*, Eds.: S. Bräse, C. Christmann, Wiley VCH, **2012**, 197-203; g) M. Uyanik, K. Ishihara, *J. Synth. Org. Chem. Jpn.* **2012**, *70*, 1116-1122; h) H. Liang, M. A. Ciufolini, *Angew. Chem. Int. Ed.* **2011**, *50*, 11849-11851; i) M. Ngatimin, D. W. Lupton, *Aust. J. Chem.* **2010**, *63*, 653-658.

[5] a) S. M. Altermann, S. Schäfer, T. Wirth, *Tetrahedron* **2010**, *66*, 5902-5907; b) V. V Zhdankin, J. T. Smart, P. Zhao, P. Kiprof, *Tetrahedron Lett.* **2000**, *41*, 5299-5302; c) H. Tohma, S. Takizawa, H. Watanabe, Y. Fukuoka, T. Maegawa, Y. Kita, *J. Org. Chem.* **1999**, *64*, 3519-3523; d) D. G. Ray, G. F. Koser, *J. Am. Chem. Soc.* **1990**, *112*, 5672-5673; e) T. Imamoto, H. Koto, *Chem. Lett.* **1986**, 967-968.

[6] a) A. M. Harned, *Tetrahedron Lett.* **2014**, *55*, 4681-4689; b) K. A. Volp, A. M. Harned, *Chem. Commun.* **2013**, *49*, 3001-3003; c) M. Uyanik, T. Yasui, K. Ishihara, *Angew. Chem. Int. Ed.* **2013**, *52*, 9215-9218; d) T. Dohi, N. Takenaga, T. Nakae, Y. Toyoda, M. Yamasaki, M. Shiro, H. Fujioka, A. Maruyama, Y. Kita, *J. Am. Chem. Soc.* **2013**, *135*, 4558-4566; e) S. Quideau, G. Lyvinec, M. Marguerit, K. Bathany, A. Ozanne-Beaudenon, T. Buffeteau, D. Cavagnat, A. Chénedé, *Angew. Chem. Int. Ed.* **2009**, *48*, 4605-4609.

[7] a) M. Brown, M. Delorme, F. Malmedy, J. Malmgren, B. Olofsson, T. Wirth, *Synlett* **2015**, *26*, 1573-1577; b) V. K. Aggarwal, B. Olofsson, *Angew. Chem. Int. Ed.* **2005**, *44*, 5516-5519; c) M. Ochiai, Y. Kitagawa, N. Takayama, Y. Takaoka, M. Shiro, *J. Am. Chem. Soc.* **1999**, *121*, 9233-9234.

[8] a) B. Basdevant, C. Y. Legault, *J. Org. Chem.* **2015**, *80*, 6897-6902; b) B. Basdevant, C. Y. Legault, *Org. Lett.* **2015**, *17*, 4918-4921; c) P. Mizar, T. Wirth, *Angew. Chem. Int. Ed.* **2014**, *53*, 5993-5997; d) U. Farooq, S. Schäfer, A.-H. Shah, D. Freudendahl, T. Wirth, *Synthesis* **2010**, *2010*, 1023-1029; e) S. M. Altermann, R. D. Richardson, T. K. Page, R. K. Schmidt, E. Holland, U. Mohammed, S. M. Paradine, A. N. French, C. Richter, A. M. Bahar, B. Witulski, T. Wirth, *Eur. J. Org. Chem.* **2008**, 5315-5328; f) R. Richardson, T. Page, S. Altermann, S. Paradine, A. French, T. Wirth, *Synlett* **2007**, 538-542; E. Hatzigrigoriou, A. Varvoglis, M. Bakola-Christianopoulou, *J. Org. Chem.* **1990**, *55*, 315-318.

[9] a) S. Haubenreisser, T. H. Wöste, C. Martínez, K. Ishihara, K. Muñiz, *Angew. Chem. Int. Ed.* **2016**, *55*, 413-417; b) T. Takesue, M. Fujita, T. Sugimura, H. Akutsu, *Org. Lett.* **2014**, *16*, 4634-4637; c) M. Shimogaki, M. Fujita, T. Sugimura, *Eur. J. Org. Chem.* **2013**, 7128-7138; d) M. Fujita, K. Mori, M. Shimogaki, T. Sugimura, *Org. Lett.* **2012**, *14*, 1294-1297; e) M. Fujita, Y. Yoshida, K. Miyata, A. Wakisaka, T. Sugimura, *Angew. Chem. Int. Ed.* **2010**, *49*, 7068-7071; f) M. Fujita, Y. Ookubo, T. Sugimura, *Tetrahedron Lett.* **2009**, *50*, 1298-1300; g) M. Fujita, S. Okuno, H. J. Lee, T. Sugimura, T. Okuyama, *Tetrahedron Lett.* **2007**, *48*, 8691-8694; h) U. H. Hirt, M. F. H. Schuster, A. N. French, O. G.

Wiest, T. Wirth, *Eur. J. Org. Chem.* **2001**, 1569-1579; i) T. Wirth, U. H. Hirt, *Tetrahedron: Asymmetry* **1997**, *8*, 23-26.

[10] a) P. Mizar, A. Laverny, M. El-Sherbini, U. Farid, M. Brown, F. Malmedy, T. Wirth, *Chem. Eur. J.* **2014**, *20*, 9910-9913; b) C. Röben, J. A. Souto, E. C. Escudero-Adán, K. Muñiz, *Org. Lett.* **2013**, *15*, 1008-1011; c) C. Röben, J. A. Souto, Y. González, A. Lishchynskyi, K. Muñiz, *Angew. Chem. Int. Ed.* **2011**, *50*, 9478-9482.

[11] U. Farid, T. Wirth, *Angew. Chem. Int. Ed.* **2012**, *51*, 3462-3465.

[12] P. Mizar, A. Burrelli, E. Günther, M. Söftje, U. Farooq, T. Wirth, *Chem. Eur. J.* **2014**, *20*, 13113-13116.

[13] R. Zhu, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2013**, *52*, 12655-12658.

[14] a) H. Chen, A. Kaga, S. Chiba, *Org. Biomol. Chem.* **2016**, *16*, 5481-5485; b) W. Kong, P. Feige, T. de Haro, C. Nevado, *Angew. Chem. Int. Ed.* **2013**, *52*, 2469-2473.

[15] a) G. Maertens, S. Canesi, *Top. Curr. Chem.* **2016**, *373*, 223-242; b) S. Desjardins, G. Maertens, S. Canesi, *Org. Lett.* **2014**, *16*, 4928-4931; c) F. V. Singh, T. Wirth, *Synthesis* **2013**, *45*, 2499-2511; d) G. Jacquemot, S. Canesi, *J. Org. Chem.* **2012**, *77*, 7588-7594; e) M.-A. Beaulieu, K. C. Guérard, G. Maertens, C. Sabot, S. Canesi, *J. Org. Chem.* **2011**, *76*, 9460-9471; f) M.-A. Beaulieu, C. Sabot, N. Achache, K. C. Guérard, S. Canesi, *Chem. Eur. J.* **2010**, *16*, 11224-11228; g) A. A. Zagulyaeva, C. T. Banek, M. S. Yusubov, V. V Zhdankin, *Org. Lett.* **2010**, *12*, 4644-4647; h) J.-M. Vatèle, *Synlett* **2008**, 1785-1788.

[16] a) L. F. Silva, F. A. Siqueira, E. C. Pedrozo, F. Y. M. Vieira, A. C. Doriguetto, *Org. Lett.* **2007**, *9*, 1433-1436; b) L. F. Silva, *Molecules* **2006**, *11*, 421-434; c) F. A. Siqueira, E. E. Ishikawa, A. Fogaça, A. T. Faccio, V. M. T. Carneiro, R. R. S. Soares, A. Utaka, I. R. M. Tébéka, M. Bielawski, B. Olofsson, L. F. Silva, *J. Braz. Chem. Soc.* **2011**, *22*, 1795-1807.

[17] a) L. F. Silva, R. S. Vasconcelos, M. A. Nogueira, *Org. Lett.* **2008**, *10*, 1017-1020; b) M. Justik, G. Koser, *Molecules* **2005**, *10*, 217-225.

[18] a) M. Brown, R. Kumar, J. Rehbein, T. Wirth, *Chem. Eur. J.* **2016**, *22*, 4030-4035; b) U. Farid, F. Malmedy, R. Claveau, L. Albers, T. Wirth, *Angew. Chem. Int. Ed.* **2013**, *52*, 7018-7022; c) A. C. Boye, D. Meyer, C. K. Ingison, A. N. French, T. Wirth, *Org. Lett.* **2003**, *5*, 2157-2159.

[19] a) H. M. Ferraz, A. M. Aguilar, L. F. Silva, *Synthesis* **2003**, 1031-1034; b) A. McKillop, B. P. Swann, E. C. Taylor, *J. Am. Chem. Soc.* **1973**, *95*, 3340-3343.

[20] R. D. Richardson, T. Wirth, *Angew. Chem. Int. Ed.* **2006**, *45*, 4402-4404.

[21] F. V Singh, J. Rehbein, T. Wirth, *ChemistryOpen* **2012**, *1*, 245-250.

[22] Y. Tamura, T. Yakura, Y. Shirouchi, J.-I. Haruta, *Chem. Pharm. Bull.* **1985**, *33*, 1097-1103.

[23] a) S. S. Adams, P. Bresloff, C. G. Mason, *Curr. Med. Res. Opin.* **2008**, *3*, 552-552; b) I. Agranat, H. Caner, J. Caldwell, *Nat. Rev. Drug Discov.* **2002**, *1*, 753-768; c) A. H. Beckett, *Biochem. Soc. Trans.* **1991**, *19*, 443-446.

[24] CCDC-1487361 (**5**) and CCDC-1487362 (**9ff**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[25] A. K. Ghosh, J. Takayama, Y. Aubin, K. Ratia, R. Chaudhuri, Y. Baez, K. Sleeman, M. Coughlin, D. B. Nichols, D. C. Mulhearn, B. S. Prabhakar, S. C. Baker, M. E. Johnson, A. D. Mesecar, *J. Med. Chem.* **2009**, *52*, 5228-5240.

[26] a) S. Manojveer, R. Balamurugan, *Org. Lett.* **2014**, *16*, 1712-1715; b) F. Wu, R. Bai, Y. Gu, *Adv. Synth. Catal.* **2016**, in press, DOI: 10.1002/adsc.201600048.

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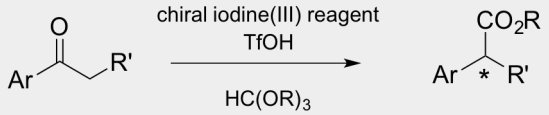

15 examples, up to 73% *ee*

Now stereoselective: Iodine(III)-mediated rearrangement of arylketones in the presence of orthoesters are possible leading to α-arylated esters in selectivities of up to 73% *ee*.

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