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Cooperative Activation with Chiral Nucleophilic Catalysts and *N*-Haloimides: Enantioselective Iodolactonization of 4-Arylmethyl-4-pentenoic Acids**

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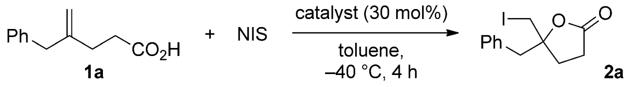
Abstract: *Chiral triaryl phosphates promote the enantioselective iodolactonization of 4-substituted 4-pentenoic acids to give the corresponding iodolactones in high yields with high enantioselectivity. N-Chlorophthalimide (NCP) is employed as a Lewis acidic activator and oxidant of* I_2 *for the present iodolactonization. In combination with 1.5 equivalents of NCP, only 0.5 equivalents of* I_2 *are sufficient to generate the iodinating reagent.*

Electrophilic olefin halocyclizations are powerful tools for stereoselective functionalization of alkenes, the products of which are useful chiral building blocks for the synthesis of biologically relevant molecules.[1] Several recent studies have successfully provided catalytic enantioselective halolactonizations,[2–4] haloetherifications,[5] haloaminocyclizations,[6] and related reactions.[7] Although these methods give the corresponding chiral products with high enantioselectivities, reactivities are not so high and require long reaction times in some cases.

We previously reported a chiral Lewis base promoted enantioselective iodocyclization of isoprenoids.[8] The chiral nucleophilic phosphoramidite acts as a monofunctional Lewis base[8a–e,9] and reacts with *N*-iodosuccinimide (NIS) to generate the corresponding phosphonium salt as an active species. Although this method gives polycyclic 3-iodoterpenoids with high enantioselectivity, stoichiometric use of the phosphoramidite is required for successful promotion of the reaction and arises from the instability of the phosphoramidite under the reaction conditions and the deactivation of the phosphoramidite with the generated acidic succinimide. The development of a catalytic system for enantioselective iodocyclization based on acid-base chemistry[10] is an important issue. We report herein cooperative activation with chiral phosphate catalysts and *N*-haloimides for the enantioselective iodolactonization of 4-arylmethyl-4-pentenoic acids.

To obtain fundamental information of nucleophilic-base-catalyzed iodolactonization of unsaturated carboxylic acids, we began our study with examination of the catalytic activities of various achiral phosphorous bases, which might nucleophilically activate the iodinating reagent. The reaction of 4-benzylpent-4-enoic acid (**1a**) was conducted with NIS (1.1 equiv) in the presence of a base catalyst (30 mol%) in toluene at −40°C for 4 hours (Table 1). As a result, phosphorus(III) compounds such as triphenyl phosphite, tri(isopropyl)phosphite, and triphenylphosphine showed good catalytic activities (entries 1–3).[11,12] In sharp contrast, pentavalent triphenyl phosphate and thiophosphate[13] were almost inert (entries 4 and 5). However, very surprisingly, when the triphenylphosphate- and triphenylthiophosphate-catalyzed reactions were conducted in the presence of I_2 and NIS (1.1 equiv each)[2a,d,f] as iodinating agents, the reactivities were remarkably increased to give **2a** in almost quantitative yield within 1 hour (entries 4 and 5). The combined use of I_2 and NIS was also somewhat effective for trivalent phosphine catalysts (entries 1–3). A highly active iodinating reagent might be generated from I_2 and NIS,[14] since the combined use of I_2 and NIS gave **2a** in 37% yield in the absence of any

Table 1: Catalytic activities of achiral Lewis bases.[a]



Entry	Catalyst	Yield [%][b]
1	$P(OPh)_3$	60 (81)[c] (0)[d]
2	$P(O\textit{i}Pr)_3$	55 (85)[c]
3	PPh_3	63 (80)[c]
4	$O{=}P(OPh)_3$	0 (100)[c] (18)[d]
5	$S{=}P(OPh)_3$	3 (100)[c]
6	no catalyst	1 (37)[c] (2)[d]

[a] The reaction of **1a** (0.1 mmol) was conducted with NIS (1.1 equiv) in the presence of a catalyst (30 mol%) in toluene (1 mL) at −40°C for 4 h. [b] Determined by ^1H NMR analysis. [c] Yield when the reaction was conducted with I_2 (1.1 equiv) and NIS (1.1 equiv) for 1 h. [d] Yield when the reaction was conducted with I_2 (1.1 equiv) for 4 h.

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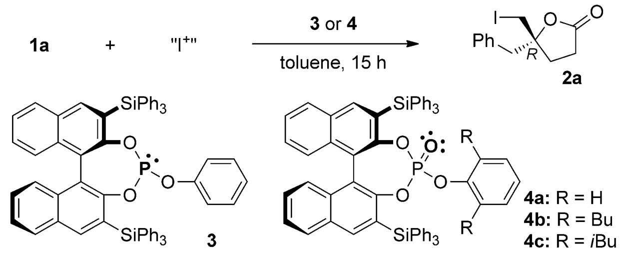
Table 2: Enantioselective iodolactonization of **1a** using **3** or **4**.[a]



Entry	"I$^+$" (equiv)	**3** or **4** (mol %)	T [°C]	Yield [%][b]	*ee* [%]
1	NIS (1.1)	**3** (30)	−40	17	40
2	I_2 (1.1)	**3** (30)	−40	19	19
3[c]	I_2 (1.1), NIS (1.1)	**3** (30)	−78	55	50
4	NIS (1.1)	**4a** (30)	−40	18	38
5	I_2 (1.1)	**4a** (30)	−40	36	38
6[d]	I_2 (1.1), NIS (1.1)	**4a** (5)	−78	98	50
7[d]	I_2 (1.1), NIS (1.1)	**4b** (5)	−78	99	86
8[d]	I_2 (1.1), NIS (1.1)	**4c** (5)	−78	99	88
9[d]	I_2 (1.1), NCS (1.1)	**4c** (5)	−78	99	88
10[d]	I_2 (1.1), NCP (1.1)	**4c** (5)	−78	99	92
11[d]	I_2 (0.5), NCP (1.5)	**4c** (5)	−78	95	93
12[d,e]	I_2 (0.5), NCP (1.5)	**4c** (1)	−78	95[f]	93

[a] The reaction of **1a** (0.1 mmol) was conducted with "I$^+$" in the presence of either **3** or **4** in toluene (1 mL) for 15 h. [b] Determined by ^{1}H NMR analysis. [c] I_2, NIS, and **3** were stirred in toluene at −40 °C for 1 h prior to adding **1a** at −78 °C. [d] I_2 and NIS (or NCS, NCP) were stirred in toluene at −40 °C for 1 h prior to adding **4** and **1a** at −78 °C. [e] On 5 mmol scale for 24 h. [f] Yield of isolated product.

catalysts, and the reaction with NIS or I_2 was very low yielding (entry 6).

Based on these results, we next investigated enantioselective iodolactonization of **1a** using either the chiral phosphite **3** or phosphate **4a** (R = H) as the catalyst (Table 2). When the **3**- or **4a**-catalyzed reaction was conducted with either NIS or I_2 in toluene at −40 °C, moderate enantioselectivity was induced, and the yield of **2a** was low (entries 1, 2, 4, and 5). Since the combined use of I_2 and NIS (1.1 equiv each) significantly increases reactivity, the reaction could be conducted at −78 °C to improve the enantioselectivity (entries 3 and 6). In particular, **4a** showed much higher catalytic activity than **3**, and only 5 mol % of **4a** was sufficient to promote the reaction, but the enantioselectivity induced by **4a** was almost same as that obtained with **3** (entry 6). The absolute stereochemistry of the major enantiomer of **2a** was determined to be *R*.[15]

When I_2 and NIS were stirred in toluene at −40 °C for 1 hour prior to adding **1a** and **4a** at −78 °C, the **4a**-catalyzed reaction showed higher reactivity than the reaction without the premixing protocol.[16] In contrast, for the **3**-catalyzed reaction, the pretreatment of I_2, NIS, and **3** in toluene at −40 °C for 1 hour was required for the successful promotion of the reaction at −78 °C.[14] These experimental results suggested that a complex of I_2 with NIS might be generated as the active iodinating species at −40 °C,[14] and that **3** might be oxidized to **4a** during the pretreatment.[17] The introduction of alkyl groups at the 2,6-position of the phenoxy group of **4** successfully increased the enantioselectivity. The use of **4b** (R = Bu) or **4c** (R = *i*Bu) gave especially high enantioselectivities (Table 2, entries 7 and 8).

Further investigation revealed that when either *N*-chlorosuccinimide (NCS)[18,19] or *N*-chlorophthalimide (NCP), which are more stable and inexpensive than NIS, was used instead of NIS, the reaction successfully proceeded to give **2a** in quantitative yields with excellent enantioselectivity (Table 2, entries 9 and 10).[20] Very interestingly, in the presence of 1.5 equivalents of NCP, the use of only 0.5 equivalents of I_2 successfully promoted the reaction to give **2a** in high yield with high enantioselectivity (entry 11). These results indicated that NCP worked as not only the activator but also the oxidant of I_2 (0.5 equiv) to generate one equivalent of the iodonium ion (I^+). The fact that NCS and NCP were consumed during the reaction to generate succinimide or phthalimide also supported this consideration. Under the optimized reaction conditions, only 1 mol % of **4a** successfully promoted a 5 mmol scale reaction to give **2a** in 95 % yield (1.5 gram) with 93 % *ee* (entry 12). Since I_2 and NCP are much cheaper than other iodinating reagents such as NIS, the present asymmetric iodolactonization should be highly practical.

We propose here a mechanism for the present enantioselective iodolactonization of **1a**. Lewis-acidic NCP might activate I_2 through halogen-bonding interactions in toluene at −40 °C to form the active iodinating species **5** (X = I; Figure 1 a). The generation of **5** is supported by Raman spectra of a mixture of NCP and I_2 in toluene (observed at 114 cm^{-1}).[15] When the phosphite **3** is used as a precatalyst, **5** could oxidize **3** in situ to give the phosphate **4** as an active catalyst. The catalytic cycle would involve the reaction of **5** with **4** to give the chiral iodoxyphosphonium ion **6** as an active species (Figure 1 b).[21] Since this step generates ICl (X = I), which could also act as an iodinating reagent through the activation by NCP,[22,23] the use of 0.5 equivalents of I_2 was sufficient to complete the iodolactonization. Electrophilic iodination of the double bond of **1a** followed by cyclization gives the desired (*R*)-**2a** and phthalimide.

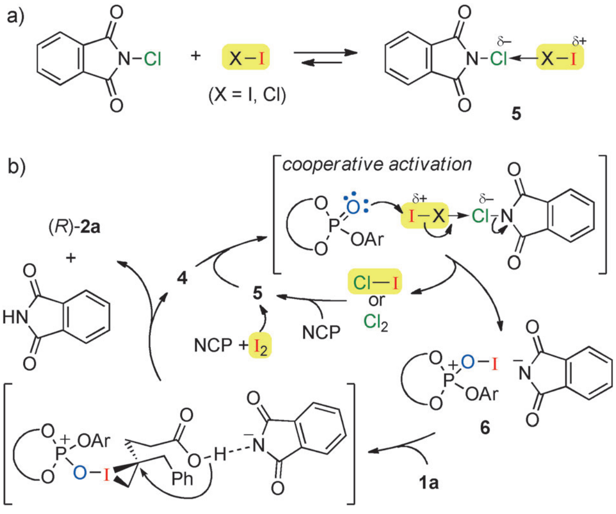
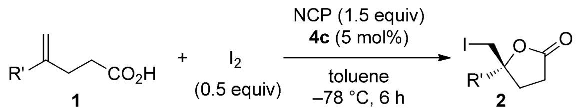


Figure 1. Proposed mechanism.

Table 3: Enantioselective iodolactonization of **1**.[a]

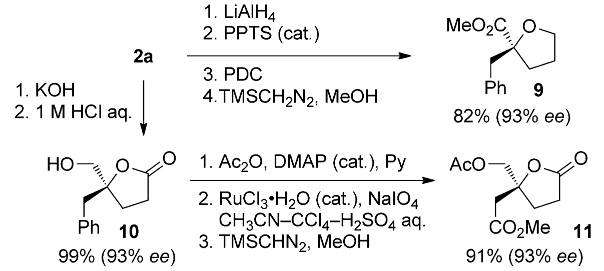


Entry	**1** (R′)	Yield [%][b]	*ee* [%]
1	**1b** (4-FC$_6$H$_4$CH$_2$)	95	93
2	**1c** (2-FC$_6$H$_4$CH$_2$)	99	2
3	**1d** (4-ClC$_6$H$_4$CH$_2$)	92	94
4	**1e** (4-(MeO)C$_6$H$_4$CH$_2$)	97	92
5	**1f** (4-MeC$_6$H$_4$CH$_2$)	90	92
6	**1g** (3-furylCH$_2$)	97	92
7	**1h** (2-naphthylCH$_2$)	99	90
8	**1i** (*c*-C$_6$H$_{12}$CH$_2$)	95	90
9	**1j** (*i*Bu)	95	80
10	**1k** (Ph)	72	10
11	**1l** (*n*-C$_8$H$_{15}$)	63	22

[a] The reaction of **1** (0.1 mmol) was conducted with I$_2$ (0.5 equiv) and NCP (1.5 equiv) in the presence of **3d** (5 mol%) in toluene (1 mL) at −78 °C. [b] Yield of isolated product.

With the optimized catalyst and reaction conditions in hand, we next examined the enantioselective iodolactonization of 4-pentenoic acids (**1**) bearing various substituents at the 4-position. As shown in Table 3, the present method could be applied to a variety of 4-(arylmethyl)pent-4-enoic acids to give the corresponding iodolactones with high enantioselectivities within a short reaction time. For example, the **4c**-catalyzed reaction of 4-benzylpent-4-enoic acids bearing an electron-withdrawing fluoro and chloro substituent, and electron-donating methoxy and methyl substituents on the phenyl group gave the corresponding iodolactones **2b** and **2d**–**f** with respective enantiomeric excesses between 92 % and 94 % within 6 hours (entries 1, and 3–5). The high enantioselectivities were also observed in the reaction of the 3-furylmethyl-substituted **1g** and 2-naphthylmethyl-substituted **1h** (entries 6 and 7). In addition to the 4-(arylmethyl)-substituted substrates, the 4-(cyclohexylmethyl)-substituted **1i**, and 4-isobutyl-substituted **1j** were successfully converted into **2i** and **2j**, respectively, with high enantioselectivities (entries 8 and 9). In contrast, the introduction of a fluoro substituent at the 2-position significantly decreased the enantioselectivity (entry 2). In addition, the reaction of phenyl- and *n*-octyl-substituted substrates showed poor enantioselectivity, albeit with good reactivity (entries 10 and 11).

The synthetic applications of **2a** were demonstrated by the several transformations shown in Scheme 1. A four-step sequence of reduction with LiAlH$_4$, acid treatment, oxidation with PDC, and methyl ester formation converted **2a** into the ester **9** in 82 % yield without any loss of enantiomeric excess. The compound **9** has the same carbon skeleton as PPAR agonists.[24] Alkaline hydrolysis of **2a** and subsequent acid-catalyzed cyclization gave the hydroxylactone **10** in quantitative yield. The compound **10** is a key intermediate for the synthesis of nucleoside analogues, therapeutic agents against AIDS and cancer.[25] The three-step transformation of **10** gave the corresponding ester **11** in 91 % yield.



Scheme 1. Transformations of the chiral iodolactones **2**. DMAP = 4-(*N*,*N*-dimethylamino)pyridine, DIC = diisopropylcarbodiimide, PDC = pyridinium dichromate, PPTS = pyridinium *p*-toluenesulfonate, TMS = trimethylsilyl.

In conclusion, we have demonstrated that the chiral triaryl phosphate **4c** and NCP cooperatively promote the enantioselective iodolactonization of 4-substituted 4-pentenoic acids (**1**) to give the corresponding iodolactones **2** in high yields with high enantioselectivity within a short reaction time. The stable but less nucleophilic phosphate **4c** shows better catalytic activities than the phosphite **3** in the presence of NCP as a Lewis acid. NCP is an effective activator and oxidant of I$_2$ for the present enantioselective iodolactonization. Since I$_2$ and NCP are much less expensive than other iodinating reagents such as NIS, the present iodolactonization should be highly practical. The present method was successfully applied to 4-alkyl-substituted 4-pentenoic acids (**1**) with high enantioselectivities, while most previous methods are applicable to only 4-aryl-substituted substrates.

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[1] For recent reviews, see: a) U. Hennecke, *Chem. Asian J.* **2012**, *7*, 456; b) S. E. Denmark, W. E. Kuester, M. T. Burk, *Angew. Chem.* **2012**, *124*, 11098; *Angew. Chem. Int. Ed.* **2012**, *51*, 10938; c) C. K. Tan, Y.-Y. Yeung, *Chem. Commun.* **2013**, *49*, 7985.

[2] For recent reports of enantioselective iodolactonizations, see: a) G. E. Veitch, E. N. Jacobsen, *Angew. Chem.* **2010**, *122*, 7490; *Angew. Chem. Int. Ed.* **2010**, *49*, 7332; b) Z.-L. Ning, J.-Y. Ding, R.-Z. Jin, C.-Q. Kang, Y.-Q. Cheng, L.-X. Gao, *Chem. Res. Chin. Univ.* **2011**, *27*, 45; c) M. C. Dobish, J. N. Johnston, *J. Am. Chem. Soc.* **2012**, *134*, 6068; d) J. E. Tungen, J. M. J. Nolsøe, T. V. Hansen, *Org. Lett.* **2012**, *14*, 5884; e) C. Fang, D. H. Paull, J. C. Hethcox, C. R. Shugrue, S. F. Martin, *Org. Lett.* **2012**, *14*, 6290; f) T. Arai, S. Kajikawa, E. Matsumura, *Synlett* **2013**, *24*, 2045; g) T. Arai, N. Sugiyama, H. Masu, S. Kado, S. Yabe, M. Yamanaka, *Chem. Commun.* **2014**, DOI: 10.1039/C4CC02415J.

[3] For recent reports of enantioselective bromolactonizations, see: a) H. J. Lee, D. Y. Kim, *Tetrahedron Lett.* **2012**, *53*, 6984; b) K. Ikeuchi, S. Ido, S. Yoshimura, T. Asakawa, M. Inai, Y. Hamashima, T. Kan, *Org. Lett.* **2012**, *14*, 6016; c) D. H. Paull, C. Fang, J. R. Donald, A. D. Pansick, S. F. Martin, *J. Am. Chem. Soc.* **2012**, *134*, 11128; d) C. K. Tan, C. Le, Y.-Y. Yeung, *Chem. Commun.* **2012**, *48*, 5793; e) W. Zhang, N. Liu, C. M. Schienebeck, K. Decloux, S. Zheng, J. B. Werness, W. Tang, *Chem. Eur. J.*

2012, *18*, 7296; f) K. Murai, A. Nakamura, T. Matsushita, M. Shimura, H. Fujioka, *Chem. Eur. J.* **2012**, *18*, 8448; g) X. Jiang, C. K. Tan, L. Zhou, Y.-Y. Yeung, *Angew. Chem.* **2012**, *124*, 7891; *Angew. Chem. Int. Ed.* **2012**, *51*, 7771; h) K. Murai, T. Matsushita, A. Nakamura, N. Hyogo, J. Nakajima, H. Fujioka, *Org. Lett.* **2013**, *15*, 2526; i) M. Wilking, C. Mück-Lichtenfeld, C. G. Daniliuc, U. Hennecke, *J. Am. Chem. Soc.* **2013**, *135*, 8133.

[4] For enantioselective chlorolactonizations, see: a) R. Yousefi, D. C. Whitehead, J. M. Mueller, R. J. Staples, B. Borhan, *Org. Lett.* **2011**, *13*, 608; b) D. C. Whitehead, R. Yousefi, A. Jaganathan, B. Borhan, *J. Am. Chem. Soc.* **2010**, *132*, 3298.

[5] For recent reports of enantioselective haloetherifications, see: a) X. Zeng, C. Miao, S. Wang, C. Xia, W. Sun, *Chem. Commun.* **2013**, *49*, 2418; b) C. B. Tripathi, S. Mukherjee, *Angew. Chem.* **2013**, *125*, 8608; *Angew. Chem. Int. Ed.* **2013**, *52*, 8450. See also Ref. [1f].

[6] For enantioselective haloaminocyclizations, see: a) J. Chen, L. Zhou, Y.-Y. Yeung, *Org. Biomol. Chem.* **2012**, *10*, 3808; b) L. Zhou, J. Chen, C. K. Tan, Y.-Y. Yeung, *J. Am. Chem. Soc.* **2011**, *133*, 9164; c) M. T. Bovino, S. R. Chemler, *Angew. Chem.* **2012**, *124*, 3989; *Angew. Chem. Int. Ed.* **2012**, *51*, 3923; d) F. Chen, C. K. Tan, Y.-Y. Yeung, *J. Am. Chem. Soc.* **2013**, *135*, 1232; e) D. H. Miles, M. Veguillas, F. D. Toste, *Chem. Sci.* **2013**, *4*, 3427; f) D. Huang, X. Liu, L. Li, Y. Cai, W. Liu, Y. Shi, *J. Am. Chem. Soc.* **2013**, *135*, 8101.

[7] For other enantioselective halocyclizations, see: a) V. Rauniyar, A. D. Lackner, G. L. Hamilton, F. D. Toste, *Science* **2011**, *334*, 1681; b) A. Jaganathan, A. Garzan, D. C. Whitehead, R. J. Staples, B. Borhan, *Angew. Chem.* **2011**, *123*, 2641; *Angew. Chem. Int. Ed.* **2011**, *50*, 2593; c) Y.-M. Wang, J. Wu, C. Hoong, V. Rauniyar, F. D. Toste, *J. Am. Chem. Soc.* **2012**, *134*, 12928; d) C. S. Brindle, C. S. Yeung, E. N. Jacobsen, *Chem. Sci.* **2013**, *4*, 2100; e) Y. Zhao, X. Jiang, Y.-Y. Yeung, *Angew. Chem.* **2013**, *125*, 8759; *Angew. Chem. Int. Ed.* **2013**, *52*, 8597.

[8] a) A. Sakakura, A. Ukai, K. Ishihara, *Nature* **2007**, *445*, 900; b) A. Sakakura, K. Ishihara, *Chim. Oggi Chem. Today* **2007**, *25*, 9; c) A. Sakakura, G. Shomi, A. Ukai, K. Ishihara, *Heterocycles* **2011**, *82*, 249; d) A. Sakakura, M. Sakuma, K. Ishihara, *Org. Lett.* **2011**, *13*, 3130; e) M. Sakuma, A. Sakakura, K. Ishihara, *Org. Lett.* **2013**, *15*, 2838; f) Y. Sawamura, H. Nakatsuji, A. Sakakura, K. Ishihara, *Chem. Sci.* **2013**, *4*, 4181; g) Y. Sawamura, H. Nakatsuji, M. Akakura, A. Sakakura, K. Ishihara, *Chirality*, DOI: 10.1002/chir.22297.

[9] a) S. E. Denmark, D. J. P. Kornfilt, T. Vogler, *J. Am. Chem. Soc.* **2011**, *133*, 15308; b) D. W. Tay, I. T. Tsoi, J. C. Er, G. Y. C. Leung, Y.-Y. Yeung, *Org. Lett.* **2013**, *15*, 1310; c) Z. Ke, C. K. Tan, F. Chen, Y.-Y. Yeung, *J. Am. Chem. Soc.* **2014**, *136*, 5627.

[10] For reviews on acid-base chemistry, see: a) M. Kanai, N. Kato, E. Ichikawa, M. Shibasaki, *Synlett* **2005**, 1491; b) K. Ishihara, A. Sakakura, M. Hatano, *Synlett* **2007**, 0686–0703; c) K. Ishihara, *Proc. Jpn. Acad. Ser. B* **2009**, *85*, 290; d) M. Shibasaki, M. Kanai, S. Matsunaga, N. Kumagai, *Acc. Chem. Res.* **2009**, *42*, 1117.

[11] The catalytic activities of tertiary amines were low (15–36 % yield). These Brønsted bases might activate the carboxyl group of **1a** through the formation of ammonium salts to promote the reaction. See the Supporting Information for details.

[12] The reaction did not give any other diastereomers.

[13] S. E. Denmark, M. T. Burk, *Proc. Natl. Acad. Sci. USA* **2010**, *107*, 20655.

[14] V. K. Chaikovskii, A. A. Funk, V. D. Filimonov, T. V. Petrenko, T. S. Kets, *Russ. J. Org. Chem.* **2008**, *44*, 935.

[15] See the Supporting Information for details.

[16] The phosphite **3** was almost inert under the reaction conditions without the pretreatment with I_2 and NIS at −40 °C (7 % yield, 7 % *ee*). In contrast, the use of **4a** gave **2a** in 55 % yield with 47 % *ee*, even when the reaction was conducted without the pretreatment. These results are also comparable with entries 3 and 6, respectively, in Table 2.

[17] The fact that the reaction of **1a** catalyzed by **3** gave **2a** with similar enantioselectivity to that catalyzed by **4a** might support this proposal. The oxidation of **3** was also strongly suggested by ^{31}P NMR study. See the Supporting Information for details.

[18] a) S. H. Kang, S. B. Lee, C. M. Park, *J. Am. Chem. Soc.* **2003**, *125*, 15748; b) S. H. Kang, C. M. Park, S. B. Lee, M. Kim, *Synlett* **2004**, 1279; c) H. Y. Kwon, C. M. Park, S. B. Lee, J.-H. Youn, S. H. Kang, *Chem. Eur. J.* **2008**, *14*, 1023.

[19] In Ref. [18c], the authors proposed that NCS reacts with iodide anion to release ICl or that NCS oxidizes Cr^{III} to higher oxidation state(s) to enhance its Lewis acidity.

[20] The corresponding chlorolactone was not obtained at all.

[21] The generation of phthalimide was confirmed by ^{1}H NMR studies. ^{1}H NMR experiments also suggested that *N*-iodoimide was not generated under the reaction conditions. See the Supporting Information for details.

[22] In contrast to I_2, ICl might be activated by NCP at −78 °C to give the corresponding active iodinating species **6** (X = Cl) because ICl is more reactive than I_2. For reports of ICl as iodination reagent, see: a) J. Haas, S. Piguel, T. Wirth, *Org. Lett.* **2002**, *4*, 297; b) J. Haas, S. Bissmire, T. Wirth, *Chem. Eur. J.* **2005**, *11*, 5777.

[23] The use of ICl as an iodinating agent decreased the yield and enantioselectivity of **2a** (30 %, 0 % *ee*) because of the generation of significant amounts of byproducts. The slow generation of ICl might be key to high yield and enantioselectivity.

[24] R. Clark, F. Matsuura, E. Emori, M. Shinoda, S. Kasai, H. Yoshitomi, K. Yamazaki, T. Inoue, S. Miyashita, T. Hihara, *Jpn. Kokai Tokkyo Koho* JP 2003016265 A1 20030227, **2003**.

[25] a) A. Paju, M. Laos, A. Jõgi, M. Päri, R. Jäälaid, T. Pehk, T. Kanger, M. Lopp, *Tetrahedron Lett.* **2006**, *47*, 4491; b) A. Jõgi, M. Ilves, A. Paju, T. Pehk, T. Kailas, A. Müürisepp, M. Lopp, *Tetrahedron: Asymmetry* **2008**, *19*, 628.