

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.

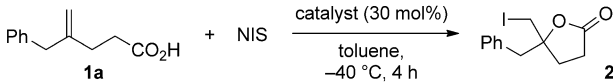
Electrophilic olefin halocyclizations are powerful tools for stereoselective functionalization of alkenes, the products of which are useful chiral building blocks for the synthesis of biologically relevant molecules.^[1] Several recent studies have successfully provided catalytic enantioselective halolactonizations,^[2–4] 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–c,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 phosphorami-

dite 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,

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

		
Entry	Catalyst	Yield [%] ^[b]
1	$\text{P}(\text{OPh})_3$	60 (81) ^[c] (0) ^[d]
2	$\text{P}(\text{OiPr})_3$	55 (85) ^[c]
3	PPh_3	63 (80) ^[c]
4	$\text{O}=\text{P}(\text{OPh})_3$	0 (100) ^[c] (18) ^[d]
5	$\text{S}=\text{P}(\text{OPh})_3$	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.

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

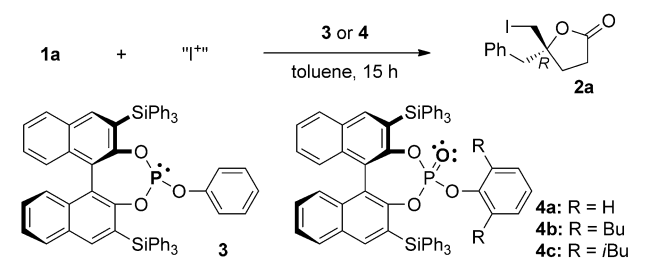
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Table 2: Enantioselective iodolactonization of **1a** using **3** or **4**.^[a]


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 ¹H NMR analysis. [c] I₂, NIS, and **3** were stirred in toluene at −40°C for 1 h prior to adding **1a** at −78°C. [d] I₂ 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 I₂ was very low yielding (entry 6).

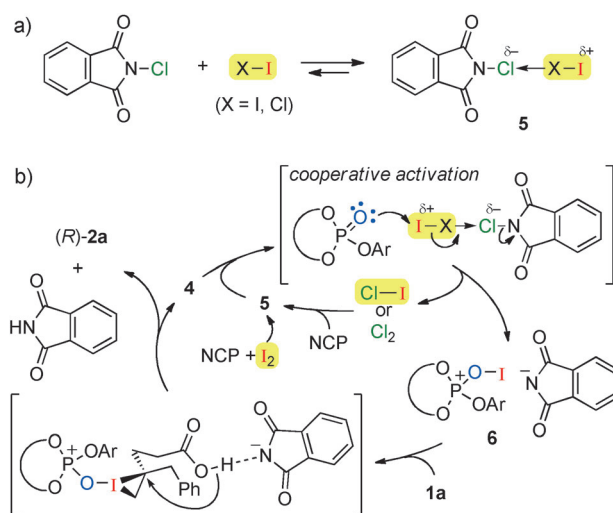
Based on these results, we next investigated enantioselective iodolactonization of **1a** using either the chiral phosphite **3** or phosphate **4a** (R=H) as the catalyst (Table 2). When the **3**- or **4a**-catalyzed reaction was conducted with either NIS or I₂ in toluene at −40°C, moderate enantioselectivity was induced, and the yield of **2a** was low (entries 1, 2, 4, and 5). Since the combined use of I₂ 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 I₂ 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 I₂, 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 I₂ 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 I₂ 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 I₂ (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 I₂ 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 I₂ through halogen-bonding interactions in toluene at −40°C to form the active iodinating species **5** (X=I; Figure 1a). The generation of **5** is supported by Raman


Figure 1. Proposed mechanism.

spectra of a mixture of NCP and I₂ 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 1b).^[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 I₂ was sufficient to complete the iodolactonization. Electrophilic iodination of the double bond of **1a** followed by cyclization gives the desired (*R*)-**2a** and phthalimide.

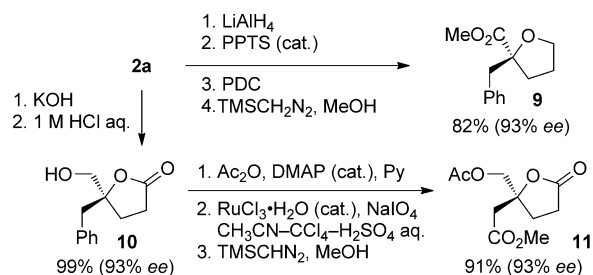
Table 3: Enantioselective iodolactonization of **1**.^[a]

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 ₁₁ CH ₂)	95	90
9	1j (iBu)	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 I₂ (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 LiAlH₄, 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 I₂ for the present enantioselective iodolactonization. Since I₂ 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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