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Published on Web 04/08/2006

Catalytic Enantioselective Synthesis of Chiral Phthalides by SmI_2-Mediated Reductive Cyclization of 2-Acylarylcarboxylates

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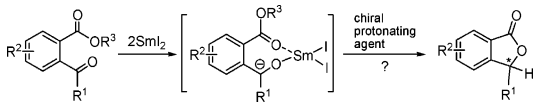
This paper was retracted on May 16, 2007 (*J. Am. Chem. Soc.* 2007, *129*, 6662).

Phthalide (1(3*H*)-isobenzofuranone) frameworks are present in a large number of natural products and biologically active compounds.[1] Chiral 3-substituted phthalides therefore are very useful molecules as valuable pharmacological compounds and versatile building blocks for medicinal chemistry.[2] Over the past two decades, there have been considerable efforts in the asymmetric synthesis of chiral phthalides, and a variety of methods toward introducing C-3 chirality have been developed.[3,4] Although catalytic approaches appear to be the best and thus are of particular interest, only a few cases on the synthesis of chiral phthalides by catalytic hydrogenation and transfer hydrogenation have been reported to date.[4] Novel strategies are still in high demand. In this communication, we report an efficient and highly enantioselective SmI_2-induced reductive cyclization of 2-acylarylcarbonylates to the corresponding enantiomerically enriched phthalides using a chiral oxazolidinone catalyst. To our knowledge, this is a significant new example of asymmetric reaction in carbonyl reduction chemistry[5] and samarium diiodide chemistry.[6]

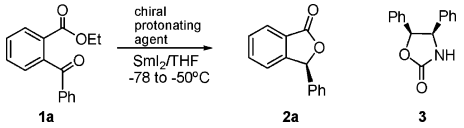
We have recently been involved in the SmI_2-induced highly selective reactions toward the asymmetric synthesis of some structurally important molecules, such as γ-butyrolactones,[7a−d,g] vicinal diamines,[7e,f] and β-amino alcohols.[7h] In considering phthalide frameworks, we envisioned that the possible chelation of Sm(III) with the *ortho*-ester carbonyl of 2-acylarylcarbonylate substrates might be able to effectively stabilize and organize the reaction transition state, thereby allowing the enantioselective reduction to be achieved using SmI_2 in the presence of an appropriate chiral protonating agent. Optically active phthalides thus could be formed after the subsequent lactonization (Scheme 1).

Initial experiments were carried out by the reactions of ethyl 2-benzoylbenzoate (**1a**) with samarium diiodide in the presence of *tert*-butyl alcohol. As expected, the reaction proceeded smoothly under 2 equiv of SmI_2 and converted **1a** into the corresponding phthalide product in one step in 88% yield within 2 h at room temperature.[8] Attempts using (*R*)-BINOL as proton donor instead of ^{t}BuOH gave the product with 14% ee and in 67% yield at −78 °C. Despite a low enantioselectivity, it implies the potential of asymmetric reduction as we hypothesized above (see Scheme 1). To achieve high enantioselectivity, the reaction conditions were carefully screened, and various chiral compounds, including chiral alcohols, amines, amides, and amino alcohols, were examined as proton sources. Eventually, we were pleased to find that the optically active phthalide product **2a** could be successfully obtained in high yield (88%) and excellent enantiomeric excess (98% ee) when the reaction was performed at −78 to −50 °C in the presence of a stoichiometric amount of (4*S*,5*R*)-4,5-diphenyloxazolidin-2-one (**3**)[9] (Scheme 2). Notably, the enantioselectivity was found be very

Scheme 1



Scheme 2



sensitive to the reaction temperature, only 39% ee could be attained under similar conditions at −78 °C.

Having established that (4*S*,5*R*)-4,5-diphenyloxazolidin-2-one (**3**) could serve as a highly enantioselective protonating agent, we began to consider that a catalytic enantioselective process of this reaction might be accomplished using a catalytic amount of **3** in the presence of a proper achiral protonating agent. The achiral protonating agent is a proton donor, which can selectively transfer proton to the deprotonated chiral protonating agent to reproduce the original chiral protonating agent in the catalytic cycle. Some advances concerning this concept have recently been reported in the catalytic enantioselective protonation of enolate substrates.[10]

Following the idea, we then focused our efforts on developing a suitable achiral protonating agent. Several achiral alcohol, phenol, and amine compounds were screened in the reaction of **1a** with SmI_2.[11] Among them, we found that 2,6-diisopropylphenol, diethylamine, and piperidine provided very low yields (<15%) even at room temperature. Specifically, when more sterically bulky diisopropylamine or 2,2,6,6-tetramethylpiperidine was used, no reaction was observed. The results suggest that these achiral proton donors are less reactive and should not compete with the chiral **3** if they coexist in the same reaction. To see the possibility of the catalytic process, a combination of *tert*-butyl alcohol (0.1 equiv) and 2,2,6,6-tetramethylpiperidine (1 equiv) was tested in the reaction of **1a** at room temperature. To our delight, the reaction worked well and gave the racemic product **2a** in 85% yield, which demonstrates the occurrence of the catalytic reaction.

Encouraged by this result, we further investigated the catalytic enantioselective reaction using different combinations of proton donors. Reaction of **1a** with SmI_2 in the presence of chiral oxazolidinone **3** (0.1 equiv) and achiral protonating agent (1 equiv) produced optically active **2a**. As revealed in Table 1, 2,6-diisopropylphenol, diethylamine, and piperidine provided moderate stereocontrol (entries 1, 2, and 4). The enantioselectivity was found to be largely influenced by the steric hindrance of the achiral protonating agent. With more sterically bulky diisopropylamine or 2,2,6,6-tetramethylpiperidine, much higher enantiomeric excess (94−96%) was obtained (entries 3 and 5). In entry 5, the highest enantiomeric excess (96%) as well as good yield (80%) was achieved. This result

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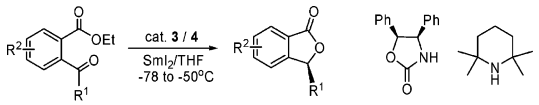
10.1021/ja061114z CCC: $33.50

Table 1. Screen of Achiral Protonating Agent for Catalytic Enantioselective Reaction

entry	achiral protonating agent	yield (%)[a]	ee[b]
1	2,6-diisopropylphenol	85	55
2	diethylamine	79	65
3	diisopropylamine	65	94
4	piperidine	75	76
5	2,2,6,6-tetramethylpiperidine	80	96
6[c]	2,2,6,6-tetramethylpiperidine	45	96

[a] Isolated yield. [b] Determined by chiral HPLC analysis. [c] 0.5 equiv of catalyst **3** was used.

Table 2. The SmI_2-Induced Catalytic Enantioselective Synthesis of Chiral Phthalides



entry[a]	1	R_1	R_2	2	yield (%)[b]	ee[c]
1	**1a**	C_6H_5	H	**2a**	80	96
2	**1b**	4-$CH_3C_6H_4$	H	**2b**	81	94
3	**1c**	4-$OCH_3C_6H_4$	H	**2c**	82	96
4	**1d**	4-FC_6H_4	H	**2d**	83	97
5	**1e**	4-BrC_6H_4	H	**2e**	85	92
6	**1f**	3,4-$(CH_3)_2C_6H_3$	H	**2f**	75	97
7	**1g**	3,4-$(OCH_3)_2C_6H_3$	H	**2g**	72	97
8	**1h**	2-naphthyl	H	**2h**	83	95
9	**1i**	2-furanyl	H	**2i**	65	96
10	**1j**	2-thiophenyl	H	**2j**	62	97
11	**1k**	4-BrC_6H_4	4-Br	**2k**	76	97
12	**1l**	C_6H_5	4-OCH_3	**2l**	76	95
13	**1m**	4-$CH_3C_6H_4$	4,5-C_4H_4	**2m**	80	98
14	**1n**	4-$CH_3C_6H_4$	4,5-$(Cl)_2$	**2n**	76	97
15	**1o**	4-$CH_3C_6H_4$	4-CH_3	**2o**	83	99
16	**1p**	C_6H_5	3,6-$(CH_3)_2$	**2p**	80	97

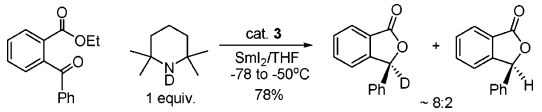
[a] See Supporting Information for reaction details. [b] Isolated yield. [c] Determined by chiral HPLC analysis.

is almost comparable to that obtained with a stoichiometric amount of **3**. Further decreasing the loading of **3** to 0.05 equiv resulted in a dramatic decrease of the reaction yield (45%), though the enantiomeric excess was retained (entry 6). Thus, 2,2,6,6-tetramethylpiperidine turned out to be the best achiral protonating agent examined.

With the catalytic system optimized, we then turned our attention to substrate generality. A wide variety of 2-acylarylcarbonylates (**1**) were evaluated using the conditions in entry 5 of Table 1. Gratifyingly, all the reactions afforded phthalide products **2** in relatively good yields and excellent enantioselectivities (92−99% ee) (Table 2). It is noteworthy that the enantioselectivity of the reaction is generally not affected by the substitution of **1**. R^1 could be a broad range of aromatic substituents, such as phenyl, naphthyl, furanyl, or thiophenyl (entries 1−10). Substrates with either electron-donating or electron-withdrawing groups (R^2) on each aromatic carbon were found to be efficient (entries 11−16). Assuming an analogous reaction mechanism, the absolute configuration of the phthalides obtained was determined to be *S* by comparison of optical rotation value[11] with that reported for **2a**.[3h,i]

To gain some information on the catalyst system, an experiment using deuterated 2,2,6,6-tetramethylpiperidine as achiral protonating agent was conducted. When substrate **1a** was reacted under similar reaction conditions in the combination of 10 mol % of catalyst **3**, formation of the corresponding phthalide product with high deuterium incorporation at the 3-position (**2a**−*d*, ∼80%) was observed by ^{1}H NMR spectral analysis[11] (Scheme 3). This result strongly indicates that this proton is indeed transferred from the ND proton of deuterated 2,2,6,6-tetramethylpiperidine. It has already

Scheme 3



shown that no formation of **2a** took place with 2,2,6,6-tetramethylpiperidine alone, thus suggesting that achiral 2,2,6,6-tetramethylpiperidine is responsible for the regeneration of chiral oxazolidinone catalyst **3** in the catalytic cycle, as proposed.

In summary, we have discovered a novel catalytic asymmetric approach for the highly enantioselective synthesis of chiral phthalides (up to 99% ee) using samarium diiodide protocol. The combination of chiral oxazolidinone **3** and achiral amine **4** constitutes an efficient catalyst system for the asymmetric reductive cyclization of a wide range of 2-acylarylcarbonylates. This method provides new insights to the asymmetric reduction of carbonyl as well as the asymmetric protonation. Further mechanistic studies of the new catalytic system and the extension of the method are currently underway.

Acknowledgment. Financial support from the National Natural Science Foundation of China (20402018, 203900506), Shanghai Rising-Star Program (05QMX1467), and the Chinese Academy of Sciences is acknowledged.

Supporting Information Available: Experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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JA061114Z