



An asymmetric iodolactonization reaction catalyzed by a zinc bis-proline–phenol complex



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ARTICLE INFO

Article history:

Received 5 July 2013

Revised 6 November 2013

Accepted 12 November 2013

Available online 16 November 2013

Keywords:

Asymmetric synthesis

Iodolactonization

δ -Iodolactones

Trost ligand

Zinc complex

ABSTRACT

The intramolecular zinc bis-proline–phenol complex **2a** was found to promote enantioselective iodolactonization reactions of both electron-rich and electron-poor 5-aryl-5-hexenoic acids affording δ -iodolactones in good chemical yields with up to 82% enantiomeric excess. The reactions were found to be insensitive to air and moisture, providing an experimentally simple protocol for synthetically useful compounds.

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The halolactonization of alkenoic acids has been known for more than a century.¹ This reaction presents an attractive route to halolactones which can be key intermediates in the synthesis of natural products and are used as starting materials for further synthetic transformations.² Catalytic enantioselective versions of halolactonizations have been developed, but mostly for chloro- and bromo-lactonization reactions.³ Some reagent-controlled and selective iodolactonization protocols have been reported.^{4–6} For example, Taguchi and co-workers reported the use of one equivalent of a chiral titanium complex in the synthesis of γ -lactones with 65% ee.⁴ Grossman and Trupp⁵ reported, in 1998, the first successful reagent-controlled enantioselective iodolactonization. However, the stereoselectivity was disappointingly low with ee values in the range of 3–7%, and as such demonstrated the principle without any practical impact. Rousseau and co-workers⁶ reported the preparation of 5-endo- γ -lactones with ee values between 10% and 20% in the presence of stoichiometric amounts of a chiral silver-ephedrine complex. Although some improvements were made in the enantioselectivity, it was still very low. The first catalytic, enantioselective iodolactonization was reported in 2004 by Gao and co-workers,^{7a} using quaternary ammonium salts derived from cinchonidine, but with only moderate enantioselectivity. Moreover, the formation of mixtures of both γ - and δ -lactones was observed. The same group later reported that a salen-Co(II) complex catalyzed the enantioselective iodolactoniza-

tion reaction of several 4-aryl-4-pentenoic acids to give γ -lactones with up to 85% ee.^{7b} Veitch and Jacobsen^{7c} reported that 5-aryl-5-hexenoic acids underwent iodolactonizations in the presence of a tertiary aminourea catalyst yielding the desired δ -iodolactones in high chemical yields with ee values between 48% and 96%. Dobish and Johnston^{7d} employed a chiral Brønsted acid catalyst in their studies of the same type of acids; the obtained aryl substituted δ -iodolactones had ee values between 57% and 96%. In addition Hansen and co-workers^{7e} recently published their work on using squaramides as organocatalysts for obtaining δ -iodolactones with enantiomeric excesses between 12% and 96% with 5-aryl-5-hexenoic acids as substrates. The research group of Martin^{7f} reported a BINOL-derived, bifunctional catalyst that was employed for the preparation of a few δ -iodolactones in high yields and with ee values $\geq 98\%$; several γ -iodolactones were obtained in a highly enantioselective manner with the same catalyst.

In connection with our ongoing projects on the synthesis of polyunsaturated fatty acid derived natural products employing iodolactonizations,⁸ we became interested in developing a new enantioselective protocol. The commercially available semi-azacrown ether ligand **1**⁹ and the corresponding di-nuclear zinc complexes **2a** and **2b** (Fig. 1) attracted our attention.¹⁰ The dinuclear zinc complex **2a** has successfully been applied in a large variety of asymmetric transformations.¹¹ Similarly the bis-proline derived ligand **1**, containing two tertiary amines and a phenol, could exhibit catalytic activity in an enantioselective iodolactonization. The tertiary amines should provide H-bonding motifs¹² which have been reported to be of great importance in some organocatalytic

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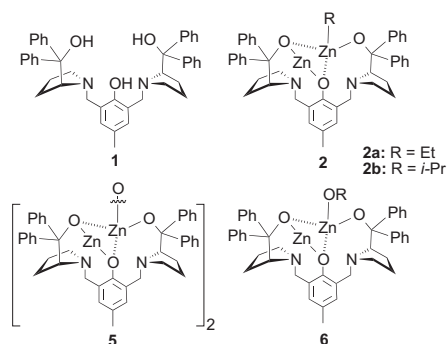


Figure 1. Structures of the semi-azacrown ether ligand **1**, the dinuclear zinc complex **2**, the oxo-bridged dimer **5**, and the alkoxy derivative **6**.

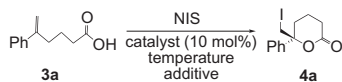
iodolactonizations.^{7c,e} Herein, we report the results of our study on asymmetric iodolactonization mediated by the zinc complex **2a**.

Initially, the ability of the Trost-ligand **1** to catalyze the iodolactonization of 5-phenylhex-5-enoic acid (**3a**) in the presence of *N*-iodosuccinimide (NIS) in toluene at $-20\text{ }^{\circ}\text{C}$ was investigated. The ligand **1** yielded the racemic product **4a** in 30–48% yield (**Table 1**, entries 1 and 2). The ^1H NMR spectrum of a 1:1 mixture of **1** and **3a**, respectively, revealed that the chemical shift values of the alpha protons in **3a** were only slightly affected (see **Fig. 2b**). On the other hand, ^1H NMR-analyses of various mixtures of **2a** and **3a** showed a linear effect on the $\Delta\delta$ -values for the protons at C2 in **3a** indicating weak interactions between the acid and the zinc-complex (**Fig. 2c** and **Supplementary data**).

Moreover, the ^{13}C NMR spectra of mixtures of **2a** and **3a** also revealed the same type of interactions (see **Supplementary data**). These NMR observations encouraged us to use the adduct **2a**, previously reported by Trost et al.,^{9,10a} as a catalyst in an enantioselective iodolactonization protocol. Adding a THF solution of **2a** to a solution of **3a** and NIS in toluene yielded the desired iodolactone **4a** in 70% chemical yield with variable enantioselectivity (**Table 1**, entry 3).

However, the observed enantiomeric excess of 55–74% in the reaction catalyzed by **2a** varied in the individual experiments. The addition of 0.15 equiv of iodine did not enhance the selectivity (entry 4). Employing the adduct **2b**, with the more bulky *iso*-propyl group, afforded iodolactone **4a** with improved yield, but with lower ee values. Again, low reproducibility was observed (entry 5). Our first concern was the lack of a strict control of moisture content. Surprisingly, the addition of 4 Å molecular sieves to the reaction mixture caused a drop in enantioselectivity (entries 6 and 7). The reaction conditions were then investigated. A solvent screen revealed that toluene was the best solvent (entries 2, 8–11). Further changes in the reaction conditions in terms of catalyst loadings, variations in concentration, amount of iodine added, the use of sodium bicarbonate as base, or altering the reaction times, did not enhance the enantioselectivity. To our surprise, the complex **2a** showed catalytic activity even after slow evaporation of the solvent and storage of the residue without any precautions against moisture and air. However, significant improvement in the reproducibility of the results was observed (**Table 1**, entry 12). This reaction was performed three times with the same results with respect to the yield and enantiomeric excess. These data suggest that in situ generated complex **2a** might act as a precatalyst with the formation of an even more active catalyst by contact with air and/or moisture. This was also supported by the above-mentioned observation that the addition of 4 Å molecular sieves gave a drop in the enantioselectivity. Unfortunately, our attempts to isolate crystals suitable for X-ray analysis were not successful. The nature of the active catalytic species therefore remains unknown. However, it has been reported that **2a** might form oxo-bridged dimers, such as **5** (**Fig. 1**), in the presence of adventitious amounts of water.¹¹ The addition of ethanol to the in situ generated complexes **2a** has been reported to alter the formation of the alkoxy-bridged dinuclear zinc species **6** as a result of exchange of the labile alkyl group.¹¹ We then performed the enantioselective iodolactonization reaction with the addition of ethanol to complex **2a**. These experiments yielded similar and results reproducible with those obtained in the absence of ethanol using the obtained solid (entry 13).

Table 1
Investigation of the reaction conditions



Entry ^a	Catalyst	Solvent	Additive	$^{\circ}\text{C}$	Time (h)	Yield ^b (%)	ee ^c (%)
1	1	PhMe	—	-20	72	30	Racemic
2	1	PhMe	0.15 equiv I_2	-20	24	48	Racemic
3	2a^d	PhMe	—	-20	70	70	55–74
4	2a^d	PhMe	0.15 equiv I_2	-20	24	68	50
5	2b^d	PhMe	—	-20	24	80	57–62
6	2a^d	PhMe	4 Å MS	-20	70	62	44
7	2a^d	THF	4 Å MS	-20	70	71	27
8	2a^d	THF	—	-20	70	72	31
9	2a^d	Et_2O	—	-20	70	66	57
10	2a^d	CH_2Cl_2	—	-20	70	84	31
11	2a^d	Me_2CO	—	-20	70	65	30
12	2a^e	PhMe	—	-20	48	70	76
13 ^f	2a^e	PhMe	EtOH	-20	48	71	74
14	2a^e	PhMe	—	-40	48	70	82
15	2a^e	PhMe	—	0	24	74	72

^a The reactions were carried out with acid **3a** (0.2 mmol), catalyst (0.02 mmol), and NIS (0.22 mmol) in solvent (4 mL) in the absence of light.

^b Isolated yield as an average of at least two experiments.

^c Determined by using HPLC with a chiral stationary phase (see supporting data for details).

^d In situ generated solution. The reactions were run under protection from air and moisture.

^e Solid residue after evaporation of THF from the catalyst solution.

^f The catalyst was obtained by addition of a stoichiometric amount of ethanol to an in situ generated solution of **2a**.

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