

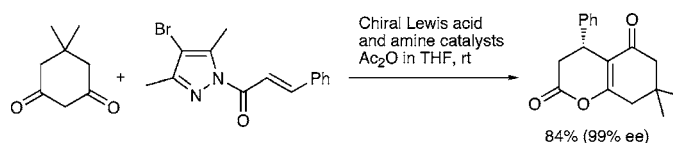
Enantioselective Enol Lactone Synthesis  
under Double Catalytic ConditionsKennosuke Itoh,<sup>†</sup> Masayuki Hasegawa,<sup>†</sup> Junji Tanaka, and Shuji Kanemasa\*

Institute for Materials Chemistry and Engineering, CREST of JST (Japan Science and Technology Agency), Kyushu University, 6-1 Kasugakoen, Kasuga 816-8580, Japan, and Department of Molecular and Material Sciences, Graduate School of Engineering Sciences, Kyushu University, 6-1 Kasugakoen, Kasuga 816-8580, Japan

kanemasa@cm.kyushu-u.ac.jp

Received October 14, 2004 (Revised Manuscript Received February 11, 2005)

## ABSTRACT

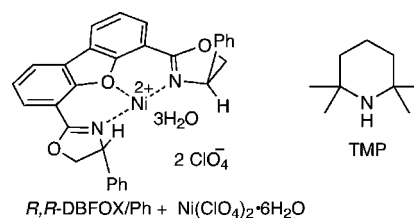


The reaction of dimedone with 1-(2-alkenyl)-4-bromo-3,5-dimethylpyrazoles in THF, catalyzed by catalytic amounts of both DBFOX/Ph-nickel-(II) perchlorate trihydrate and 2,2,6,6-tetramethylpiperidine, in the presence of acetic anhydride in THF produces the corresponding enol lactones in high enantioselectivities through enantioselective Michael additions followed by cyclization with removal of the pyrazole auxiliary. Other related nucleophile precursors can be successfully applied in the enantioselective enol lactone synthesis under the double catalytic conditions.

We have recently developed a new enantioselective Michael addition of nitromethane<sup>1</sup> or malononitrile<sup>2</sup> to  $\alpha,\beta$ -unsaturated carbonyl compounds such as 3-(2-alkenyl)-2-oxazolidinones and 1-(2-alkenyl)-3,5-dimethylpyrazoles where the reaction was highly activated under the so-called double catalytic conditions using catalytic amounts of both amine and chiral Lewis acid. For example, the reaction of malononitrile with 4-bromo-1-crotonyl-3,5-dimethylpyrazole was successfully performed in the presence of 10 mol % each of 2,2,6,6-tetramethylpiperidine (TMP) and the *R,R*-DBFOX/Ph complex of nickel(II) perchlorate hexahydrate, affording 4-bromo-1-(4,4-dicyano-3-methylbutanoyl)-3,5-dimethylpyrazole as Michael adduct in a high yield and high enantioselectivity.<sup>2</sup>

When cyclic  $\beta$ -diketones or  $\beta$ -keto lactones are employed as nucleophile precursors in the reactions with 1-(2-alkenyl)-4-bromo-3,5-dimethylpyrazoles under the double catalytic conditions using catalytic amounts of both nickel(II) perchlorate hexahydrate and TMP, the products obtained were not the corresponding Michael adducts but the enol lactones.<sup>3</sup>

However, a catalyzed enantioselective version of this new reaction is so far unknown.

*R,R*-DBFOX/Ph + Ni(ClO<sub>4</sub>)<sub>2</sub>·6H<sub>2</sub>O

Catalysts used in the double catalytic reactions

Some of the enol lactone family including coumarins, flavonoids, and neoflavonoids are known to show potent biological activity.<sup>4–6</sup> However, only limited numbers of effective synthetic methodologies are available for the synthesis of enol lactone derivatives.<sup>6a–c,7</sup> Our catalytic

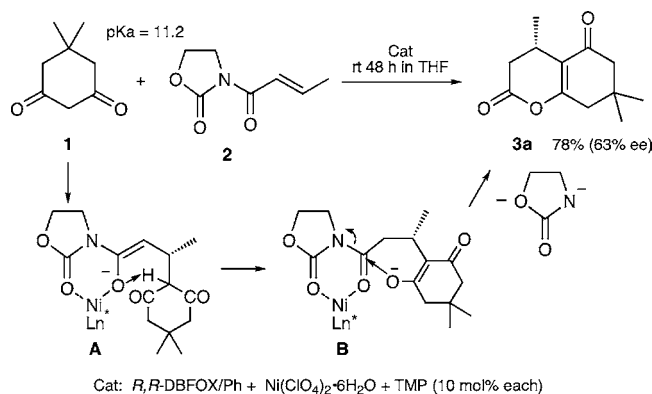
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reaction described above<sup>3</sup> is a rare successful example that can be performed at room temperature, giving quantitative yields of enol lactones.

In this communication, we present the highly efficient catalyzed enantioselective enol lactone synthesis through the Michael addition/lactonization sequence under double catalytic conditions.

Under the reaction conditions using TMP and the enantiopure complex catalyst derived from the *R,R*-DBFOX/Ph ligand and nickel(II) perchlorate hexahydrate (10 mol % each),<sup>8</sup> the reaction of 5,5-dimethyl-1,3-cyclohexanedione (**1**, named dimedone) with 3-crotonoyl-2-oxazolidinone (**2**), in THF at room temperature for 48 h, produced 4,7,7-trimethyl-3,4,5,6,7,8-hexahydrobenzopyran-2(*H*),5-dione (**3a**) as enol lactone in 78% yield with the enantioselectivity of 63% ee (Scheme 1). The reaction mechanism proposed involves the

**Scheme 1.** Nickel(II)-Catalyzed Enantioselective Enol Lactone Formation

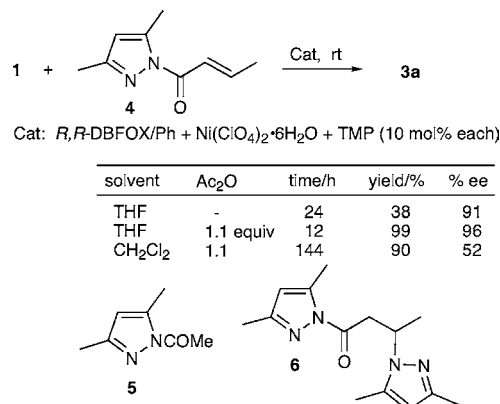


initial formation of the Michael adduct anion **A**, the subsequent intramolecular protonation of **A** generating enol **B**, and the final step of cyclization of **B** with the removal of 2-oxazolidinone auxiliary giving enol lactone **3a**.<sup>3</sup> Although lactonization of the enol **B** derived from the 2-oxazolidinone substrate **2** is generally not an easy process, the nickel(II) catalysis in the above reaction activates the imide carbonyl group of **B** and at the same time the leaving ability of 2-oxazolidinone auxiliary is enhanced.

When 3-crotonoyl-2-oxazolidinone (**2**) was replaced with 1-crotonoyl-3,5-dimethylpyrazole (**4**), not only the reactivity but also the selectivity was found to depend sharply upon the nature of reaction solvent. The reaction of dimedone (**1**)

was much faster in THF than in dichloromethane, and a higher enantioselectivity was observed. Although the pyrazole acceptor **4** as one of the substrates was rapidly consumed in a few hours at room temperature in the reaction in THF, the yield of enol lactone **3a** was disappointingly low (38%, Scheme 2). The side product was **6**, which was proposed to

**Scheme 2.** Solvent and Additive Effect in the Enol Lactone Formation

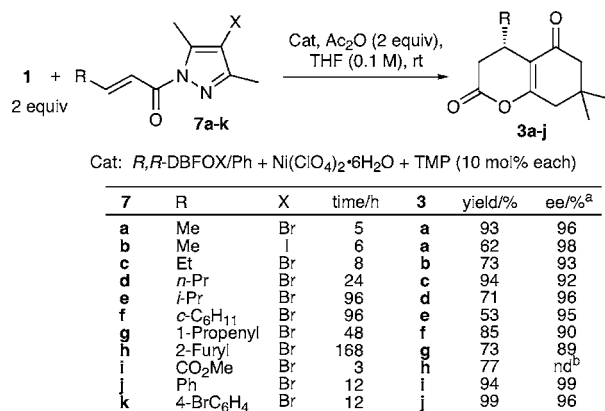


form through conjugate addition of the 3,5-dimethylpyrazole removed in the lactonization step.<sup>3</sup>

Use of acetic anhydride was highly effective to prevent formation of the undesired **6**, through the acetylation trapping of the liberated pyrazole giving 1-acetyl-3,5-dimethylpyrazole (**5**).<sup>9,10</sup> Thus, the reaction in THF was complete in 12 h in the presence of acetic anhydride (1.1 equiv) to give enol lactone **3a** with the improved yield of 99% and enantioselectivity of 96% ee.<sup>10</sup> However, the reaction in dichloromethane was very slow, even in the presence of acetic anhydride, indicating that THF is the solvent of choice.

After efforts for the optimization of reaction conditions, we have found that use of 4-bromo-3,5-dimethylpyrazole chelating auxiliary gives better results (Scheme 3). Thus,

**Scheme 3.** Nickel(II)-Catalyzed Enantioselective Synthesis of a Variety of Enol Lactones



<sup>a</sup>Determined by chiral HPLC, <sup>b</sup>nd: not determined.

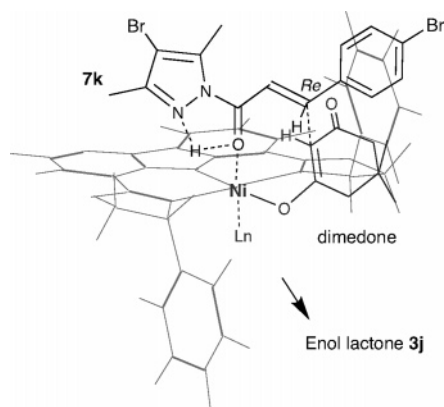
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(8) The double catalytic conditions using 10 mol % each of TMP and the *R,R*-DBFOX/Ph complex of nickel(II) perchlorate hexahydrate is called “the standard double-catalytic conditions” in the present communication.

reactions of dimedone **1** (2 equiv) with 1-(2-alkenyl)-4-bromo-3,5-dimethylpyrazoles **7a** and **7c–k** having a variety of  $\beta$ -substituents and 1-crotonyl-4-iodo-3,5-dimethyl-pyrazole (**7b**), in THF at room temperature under the standard double catalytic conditions in the presence of 2 equiv of acetic anhydride, gave 7,7-dimethyl-3,4,5,6,7,8-hexahydrobenzopyran-2(*H*),5-diones **3a–j** in high yields and excellent enantioselectivities as shown in Scheme 3.

The absolute configuration of enol lactones **3a–j** was determined as shown in Scheme 3 on the basis of the X-ray confirmed structure of 4-(*R*)-(p-bromophenyl)-7,7-dimethyl-3,4,5,6,7,8-hexahydrobenzopyran-2(*H*),5-dione (**3j**), which was derived from the reaction of **1** with 4-bromo-1-(p-bromocinnamoyl)-3,5-dimethylpyrazole (**7k**) under the double catalytic conditions using the aqua complex of *R,R*-DBFOX/Ph ligand. This indicates that the *re* face at the  $\beta$ -position of **7k** has been involved in the step of enantioselective Michael addition reaction. A possible transition structure for the highly enantioselective enol lactone formation reaction in the presence of the *R,R*-DBFOX/Ph complex catalyst is given in Figure 1.



**Figure 1.** Suggested transition model to rationalize the stereoselectivity observed in the *R,R*-DBFOX/Ph complex catalyzed reaction.

The loading of catalysts can be reduced to 2%. Reaction time to completion under these conditions increases to 2 days, but product **3a** is formed quantitatively with an enantiomeric excess that is only slightly lower than those from reactions with 5% or 10% catalysts (Scheme 4).

3-Hydroxyperinaphthenone (**8**), 4-hydroxy-6-methyl-2-pyrone (**9**), and 4-hydroxycoumarin (**10**) can be applied as well in the reactions to pyrazole acceptors **7**, under the standard double-catalyzed conditions, to give the corresponding enol lactones **11a,b**, **12a–c**, and **13a–e**, respectively, in high to excellent enantioselectivities (Scheme 5). Although two cyclization modes are possible in the reactions of **9** and

(9) The reaction of 3,5-dimethylpyrazole with acetic anhydride (1.1 equiv) in THF is finished in 5 min at 0 °C producing **5** in 91% yield.

(10) Di-*tert*-butyl dicarbonate (65%, 91% ee), dimethyl pyrocarbonate (88%, 86% ee), and diethyl carbonate (63%, 75% ee) were also effective. However, trifluoroacetic anhydride did not work well.

#### Scheme 4. Catalytic Efficiency

*R,R*-DBFOX/Ph + Ni(ClO<sub>4</sub>)<sub>2</sub>·6H<sub>2</sub>O + TMP (X mol% each), Ac<sub>2</sub>O (1.1 equiv), rt in THF

X mol%	concentration	time/h	yield/%	% ee
10	0.1 M	5	93	96
5	0.33	24	93	96
2	0.42	48	quant	94

Concentration: referred to **7a**

**10**, enol lactones **12** and **13** derived from the ketone enols were produced selectively rather than those from the corresponding ester enols. Their structures were determined on the basis of the X-ray-based structure of **13d** produced from the reaction of **10** with **7l**.<sup>3</sup>

#### Scheme 5. Reactions of $\beta$ -Hydroxy Lactones

Donor **8–10** (2 equiv) + **7**  $\xrightarrow[\text{THF (0.1 M), rt}]{\text{Cat, Ac}_2\text{O (2 equiv)}}$  Enol Lactones **11–13**

Cat: *R,R*-DBFOX/Ph + Ni(ClO<sub>4</sub>)<sub>2</sub>·6H<sub>2</sub>O + TMP (10 mol% each)

donor	products	R	time/h	yield/%	ee/%
<b>8</b>	<b>11a,b</b>				
		a Me	h	%,	%ee
		b 5-Br-2-OMeC <sub>6</sub> H <sub>3</sub>	96	81	91
<b>9</b>	<b>12a–c</b>				
		a Me	12	85	98
		b 5-Br-2-OMeC <sub>6</sub> H <sub>3</sub>	166	23	84
		c 3,5-Br <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	24	60	96
<b>10</b>	<b>13a–e</b>				
		a Me	2.5	66	93
		b Ph	144	64	96
		c 4-BrC <sub>6</sub> H <sub>5</sub>	96	65	95
		d 5-Br-2-OMeC <sub>6</sub> H <sub>3</sub>	168	53	84
		e 3,5-Br <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	24	80	97

In conclusion, the first example has been achieved for highly enantioselective enol lactone synthesis through the reaction of a variety of nucleophile precursors, under double-catalytic conditions. The catalytic loadings can be minimized to 2 mol % and the highest enantioselectivity attained is 99% ee. The scope of reactions with other cyclic 1,3-dicarbonyl compounds is under investigation and will be detailed soon in a full paper.

**Acknowledgment.** Financial supports from the Grant-in-Aid for Scientific Researches on Scientific Research (B) 15350059 and on Exploratory Research 16655038 from the Ministry of Education, Culture, Sports, Science and Technology of Japan are acknowledged.

**Supporting Information Available:** Experimental procedure, spectral data of all new compounds, and X-ray crystallographic data of **3j** in CIF format. This material is available free of charge via the Internet at <http://pubs.acs.org>.

OL047872G