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# InBr<sub>3</sub>-Catalyzed Coupling Reaction between Electron-deficient Alkenyl Ethers with Silyl Enolates for Stereoselective Synthesis of 1,5-Dioxo-alk-2-enes

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**Abstract:** A coupling reaction of electron-deficient alkenyl ethers with silyl enolates catalyzed by InBr<sub>3</sub> was achieved. Various silyl enolates and 2-carbonylalkenyl ethers were applicable, giving the corresponding 1,5-dioxo-alk-2-enes with perfect stereoselectivity of the alkene moieties. The present coupling reaction proceeds via the 1,4-addition of silyl enolates to alkenyl ethers followed by elimination of silyl alkoxides, in which moderate-Lewis acidic InBr<sub>3</sub> performs both the activation of alkenyl ethers and the elimination of alkoxy groups regardless of the presence of various coordinative functional groups.

Catalytic cross-coupling via the transformation of C-O bonds to C-C bonds has been an important pursuit of organic chemists for the past twenty years in attempts to replace organic halides with more environmentally benign oxygen-based electrophiles such as alcohol, arenol, and enol derivatives.<sup>[1,2]</sup> In particular, the coupling between enol derivatives and enolate nucleophiles is one of the most significant of these reactions, because the *a*-alkenyl carbonyl compounds produced in this process are recognized as valuable building blocks for pharmaceuticals, natural products, and organic materials (Scheme 1A),<sup>[3]</sup> but robust C-O bonds make this catalytic reaction a challenge.<sup>[4]</sup> Thus far, the report of GaBr<sub>3</sub>catalyzed coupling reactions of enol derivatives with ketene silvl acetals that were established by our group remains the only description of the availability of electron-rich enol derivatives (Scheme 1B).<sup>[5]</sup> As far as electron-deficient enol derivatives are concerned, the Michael addition/elimination reaction system using 2-carbonylalkenyl ethers is the sole methodology (Scheme 1C).<sup>[6,7,8]</sup> A severely narrow scope of substrates, however, restricts both the generality and the diversity of this reaction system. In fact, either a polyhalogenated acyl group or two electron-withdrawing groups on enol derivatives is necessary, and enolate nucleophiles are limited to stabilized alkali metal enolates such as those from 1,3-diketone and  $\beta$ -keto ester phosphoranylideneacetates<sup>[7]</sup>. derivatives,<sup>[6]</sup> 2and oxoethylpyridinium salts.<sup>[8]</sup> Therefore, a strategy that could achieve more versatile reactions is highly desirable. In this study, we overcame these limitations and developed an InBr<sub>3</sub>-catalyzed coupling reaction between 2-carbonylalkenyl ethers and silyl

enolates (Scheme 1D). Various alkenyl ethers substituted by only one carbonyl group are applicable to this reaction. The availability of useful silyl enolates is a notable advantage over previously reported reactions. It is noteworthy that the corresponding alk-2ene-1,5-diones were produced with alkene moieties that have perfect stereoselectivity.

(A)  $\alpha$ -alkenylation of carbonyl compounds



Scheme 1. Coupling reaction between enol derivatives and enolate nucleophiles.

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The electron-donating effect of an alkoxy group reduces electrophilicity of enol derivatives. Therefore, reported reactions require quite strong or two electron-withdrawing groups on enol derivatives and high-nucleophilic enolate species. A simple and promising strategy to solve this problem would be the enhancement of electrophilicity of electron-withdrawing group by Lewis acids. However, there is no report for Lewis acid-catalyzed system because typical Lewis acids are deactivated by substrates (2-carbonylalkenyl ethers and enolate nucleophiles), products, and by-products due to their coordinating sites which interacts with the strong Lewis acids. Our and other groups have revealed that moderate-Lewis acidic indium and gallium salts have an important property of fast ligand exchange to be not tightly trapped by one substrate but to flexibly interact with various coordinating sites in the reaction system.<sup>[5,9,10]</sup> Therefore, indium and gallium catalysts have a possibility to achieve a desired reaction course when a suitable reaction system is designed. In Table 1, we started from investigation of indium and gallium salts in the reaction of alkenvl ether **1a** with ketene silvl acetal **2a**.<sup>[11]</sup> To our delight, indium halides exhibited the effective catalytic activity (Entries 1-3). InBr<sub>3</sub> was the best catalyst to give an excellent yield of the desired product 3aa (Entry 2). Gallium halides possessed slightly less activity than indium halides (Entries 4-6). The use of In(OTf)<sub>3</sub> and Ga(OTf)<sub>3</sub> resulted in low yields (Entries 7 and 8). Typical group 13 Lewis acids, BF<sub>3</sub>·OEt<sub>2</sub> and AlCl<sub>3</sub>, hardly gave 3aa (Entries 9 and 10). Transition metal salts such as zinc, scandium, iron, palladium, gold salts were less effective to give sluggish results (Entries 11-17). The cationic Inl<sub>2</sub> catalyst generated from InI<sub>3</sub> and AgSbF<sub>6</sub> was less effective in the present coupling reaction (Entry 18).<sup>[12]</sup> The catalyst-free conditions afforded no products (Entry 19).

Table 1. Investigation of metal salt catalysts in coupling reaction of alkenyl ether 1a with ketene silyl acetal  $2a^{\rm [a]}$ 

MeO´	O OMe 1a	OSiMe <sub>3</sub> + OR - 2a (R = CH <sub>2</sub> CH <sub>2</sub> Ph	Catalyst (5 mol%) CH <sub>2</sub> Cl <sub>2</sub> RT, 4 h	O MeO (R	$\frac{O}{OR}$ $\frac{3aa}{C} = CH_2CH_2Ph)$
Entry	Catalyst	Yield of 3aa <sup>[b]</sup>	Entry	Catalyst	Yield of <b>3aa</b> <sup>[b]</sup>
1	InCl <sub>3</sub>	4%	10	AICI <sub>3</sub>	0%
2	InBr <sub>3</sub>	93% (84%)	11	ZnCl <sub>2</sub>	0%
3	Inl <sub>3</sub>	63%	12	ZnBr <sub>2</sub>	0%
4	GaCl <sub>3</sub>	0%	13	Sc(OTf) <sub>3</sub>	21%
5	$GaBr_3$	84%	14	FeCl <sub>3</sub>	0%
6	Gal <sub>3</sub>	72%	15	PdCl <sub>2</sub>	0%
7	In(OTf) <sub>3</sub>	10% <sup>[c]</sup>	16	AuCl	0%
8	Ga(OTf) <sub>3</sub>	8%	17	AuCl <sub>3</sub>	0%
9	BF <sub>3</sub> •OEt <sub>2</sub>	10%	18 <sup>[d]</sup>	InI <sub>3</sub> + AgSbF <sub>6</sub> 16%	
			19	none	0%

[a] **1a** (0.5 mmol), **2a** (0.75 mmol), Catalyst (0.025 mmol), CH<sub>2</sub>Cl<sub>2</sub> (1 mL), room temperature, 4 h. [b] The yields of **3aa** were measured by <sup>1</sup>H NMR analysis of the crude mixture. The isolated yield is shown in a parenthesis. [c] 24 h. [d] Inl<sub>3</sub> (5 mol%) and AgSbF<sub>6</sub> (5 mol%) were used.

We used typical methods to compare the InBr<sub>3</sub>-catalyzed reaction (Scheme 2). As mentioned above, a catalytic amount of InBr<sub>3</sub> gave **3aa** in an excellent yield in the reaction of **1a** with **2a** (Scheme 2A). A typical Mukaiyama-type reaction with TiCl<sub>4</sub><sup>[13]</sup> resulted in the recovery of **1a** without the formation of **3aa** 

(Scheme 2B). A fluoride anion<sup>[14]</sup> is known to mediate the addition of silyl enolates to  $\alpha$ , $\beta$ -unsaturated carbonyl compounds, but tetrabutylammonium fluoride was ineffective in this reaction (Scheme 2C). The use of lithium enolate **4** also gave a poor result (Scheme 2D).<sup>[15]</sup> Under Reformatsky-type reaction conditions, product **5** was obtained neither at room temperature nor at 50 °C, although an over-reaction of **5** with the zinc enolate proceeded at 50 °C to give undesired product **7** in 32% yield (Scheme 2E).<sup>[16]</sup> A comparison study revealed that, rather than strong Lewis acidi catalysts and highly nucleophilic enolates, moderate Lewis acidic InBr<sub>3</sub> and moderate nucleophilic silyl enolates efficiently achieved the desired coupling reaction.



Scheme 2. Comparison among InBr3-catalyzed reaction and typical methods

With the optimal conditions in hand (Entry 2, Table 1), we explored the scope of alkenyl ethers 1 (Scheme 3). Various 2carbonylalkenyl ethers were applicable to this reaction system, and the single stereoisomers for alkene moieties were selectively furnished in all cases. Acetyl and benzoyl groups were tolerated and the desired products **3ba** and **3ca** were obtained in 61 and 88% yields, respectively. The coupling reactions using 1- or 2alkylsubstituted alkenyl ethers occurred in moderate yields (**3da**, **3ea**, and **3fa**). Phenyl-substituted substrates reacted effectively (**3gj**). The halogen-substituted alkenyl ethers were also suitable substrates, affording the corresponding products **3ha** and **3ia**. In a reaction using a 2,2-di(methoxycarbonyl)-substituted substrate, GaBr<sub>3</sub> instead of InBr<sub>3</sub> worked as an efficient catalyst to afford a

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high yield of 3ja. The alkynyl group at the 2-position was compatible in this coupling reaction (3kj). It is noted that an E/Zmixture of alkenyl ether 11 led to the exclusive yield of E-isomer product 3la.[17]



Scheme 3. Scope of alkenyl ethers 1 in the coupling of 2a. Standard conditions: 1 (0.5 mmol), 2a (0.5-0.75 mmol), InBr<sub>3</sub> (0.025 mmol), CH<sub>2</sub>Cl<sub>2</sub> (1 mL), 4 h. Isolated yields are shown. [a] 0 °C, 2 h. [b] In(OTf)3 instead of InBr3. [c] InBr3 (10 mol%) was used. [d] Ketene silyl acetal 2j (R = Me) was used. [e] The NMR yield is shown. [f] GaBr3 instead of InBr3 was used. 2 h.

The scope of ketene silvl acetals 2 in the coupling reaction of alkenyl ether 1b was investigated (Table 2). Disubstituted ketene silyl acetals 2b, 2c and 2d afforded the corresponding α-alkenyl esters in yields that ranged from moderate to high (Entries 1-3). Butylketene silyl acetal 2e and unsubstituted ketene silyl acetal 2f were applicable to afford products 3be (Entry 4) and 3bf (Entry 5) in 49 and 97% yields, respectively, although the alkene moiety of 3bf was isomerized. The coupling with cyclic ketene silyl acetal 2g proceeded to give product 3bg in 52% yield (Entry 6). Silyl enol ethers acted as efficient nucleophiles. The desired products 3bh and 3bi were selectively obtained in the reactions using 2h and 2i, respectively (Entries 7 and 8).



[a] 1b (0.5 mmol), 2 (0.6 mmol), InBr<sub>3</sub> (0.025 mmol), CH<sub>2</sub>Cl<sub>2</sub> (1 mL), 0 °C, 2 h. Isolated yields are shown. [b] The yield and the ratio of products determined by <sup>1</sup>H NMR analysis in crude products is shown. [c] room temperature. [d] 6 h.

<sup>t</sup>Bu

3bi

<sup>t</sup>Bu

2i

We monitored the reaction progress via <sup>1</sup>H NMR spectroscopy to gain insight into the mechanism (Scheme 4A). In the reaction of alkenyl ether 1b with ketene silyl acetal 2j, the 1,4-addition of 2j to 1b readily proceeded at -60 °C to give silvl enol ether intermediate 8. Then, an elimination of the MeO group took place anuscr

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at -20 °C with the formation of coupling product 9.[18] Based on these results, a plausible reaction mechanism is illustrated in Scheme 4B(i). InBr<sub>3</sub> activates alkenyl ether 1 via coordination of the carbonyl group of 1 to the indium center. The 1,4-addition of silvl enolate 2 to 1 activated by InBr<sub>3</sub> gives indium enolate 12. Then, silvl enol ether 13 is generated via the exchange of InBr<sub>3</sub> with Me<sub>3</sub>Si groups. Finally, InBr<sub>3</sub> mediates the elimination of the R<sup>5</sup>O group (14) to give coupling product 15. The explanation about the selective production of E-isomer 15 via the elimination of Me<sub>3</sub>SiOR<sup>5</sup> from the *E*/*Z*-mixture of intermediate **13** is shown in Scheme 4B(ii).<sup>[19]</sup> The elimination of Me<sub>3</sub>SiOR<sup>5</sup> from the Z-isomer of 13 proceeds via the six-membered ring transition state TS A to avoid the steric repulsion between the Br atom on the indium center and the substituent CR<sup>1</sup>R<sup>2</sup>(COR<sup>3</sup>), giving the Z-isomer of 15. In the case of the E-isomer of 13, the elimination occurs via acyclic transition state TS B to afford the Z-isomer of 15. As catalysts, strong Lewis acids such as TiCl<sub>4</sub> (Scheme 2B) and AlCl<sub>3</sub> (Table 1. Entry 10) suffer from a detrimental interaction with either silvl enolate 2 or product 9 so that the catalytic reaction hardly proceeds (Scheme 4C-1). On the other hand, lithium enolates could cause a 1.4-addition to 1 (Scheme 2D), but the alkoxy (R<sup>5</sup>O) group could not released without the assistance of Lewis acids. and an anionic polymerization of 1 would occur (Scheme 4C-2).<sup>[20]</sup> It is noteworthy that moderate Lewis acidic InBr<sub>3</sub> capably performs both the activation of alkenyl ethers (10) and the elimination<sup>[21]</sup> of the R<sup>5</sup>O group (14) in the presence of various coordinative functional groups.



Scheme 4. (A) Monitoring reaction progress and silyl enol intermediate by 1H NMR spectroscopy. (B) Plausible mechanism of the InBr<sub>3</sub>-catalyzed coupling of 2-carbonylalkenyl ethers with silyl enolates. (C) Problems of other reaction systems.

The reductive transformation of alk-2-ene-1,5-diones, which were endowed with alkene moieties that have perfect stereoselectivity via the present reaction, was demonstrated toward the construction of 1,5-hydroxyalk-2-ene structures that are important in molecules with biological relevance (Scheme

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5).<sup>[22]</sup> The InBr<sub>3</sub>-catalyzed coupling between alkenyl ether **1d** and ketene silyl acetal **2k** gave alk-2-ene-1,5-dione **3dk** with *E*-selectivity. Then, the reduction of **3dk** by LiAlH<sub>4</sub> afforded 1,5-hydroxyalk-2-ene **16** with the retention of the *E*-configuration. The structure of **16** is included in berkleasmins that are eremophilane sesquiterpenoids from a saprobic fungus, and these have exhibited cytotoxic activity against cancer cell lines as well as antimalarial activity.<sup>[23]</sup>



In conclusion, we established an InBr<sub>3</sub>-catalyzed coupling reaction of 2-carbonylalkenyl ethers with silyl enolates to give the corresponding alk-2-ene-1,5-diones that feature alkene moieties with perfect stereoselectivity. The scope of the substrates is wide, and various functional groups are compatible with this reaction system. The observation of the silyl enolate intermediate by in situ <sup>1</sup>H NMR study revealed that the present reaction proceeded via 1,4-addition of silyl enolates to alkenyl ethers and elimination of silyl alkoxides. The reductive transformation of the synthesized alk-2-ene-1,5-diones enabled ready access to valuable compounds in organic synthesis such as 1,5-dihydroxyalk-2-enes.

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# COMMUNICATION

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InBr<sub>3</sub> catalysis enable the coupling between 2-carbonylalkenyl ethers and silyl enolates to give alk-2-ene-1,5-diones featuring alkene moieties with perfect stereoselectivity. Various types of 2-carbonylalkenyl ethers and silyl enolates are applicable to the present reaction. InBr<sub>3</sub> with moderate Lewis acidity plays an important role in both the activation of alkenyl ethers and in the elimination of alkoxy groups regardless of the presence of various coordinative functional groups.