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# Synthesis of (Z)- $\beta$ -(carbonylamino)alkenylindium via Regioselective Anti-carboindation of Ynamides and Its Transformation to Multisubstituted Enamides

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Abstract: The regioselective anti-carboindation of ynamides using InBr<sub>3</sub> and silvlated nucleophiles was developed to synthesize (Z)- $\beta$ -(carbonylamino)alkenylindiums. The X-ray crystallographic analysis of an alkenylindium suggested the reaction proceeded in an antiaddition fashion. In contrast to reported syn-carbometalations of ynamides using organometallics, a cooperation of InBr<sub>3</sub> and silylated nucleophiles to ynamides achieved an anti-addition, which was supported by DFT calculation. The scope of substrates included various ynamides and silvlated nucleophiles such as silvl ketene acetals and silvl ketene imines. The transformation of synthesized alkenylindiums by iodination, radical coupling, and Pd-catalyzed cross-coupling successfully afforded trisubstituted enamines with high regio- and stereoselectivities.

Enamides are versatile building blocks for valuable nitrogencontaining compounds.<sup>[1]</sup> A combination of carbometalations of ynamides and transformations of the formed metalated enamides is one of the most reliable synthetic methods for multisubstituted enamides.<sup>[2]</sup> In this strategy, establishment of regio- and stereoselective carbometalation is necessary for selectively synthesizing a desired enamide among possible isomers. Syncarbometalation of ynamides of organometallic compounds has been widely studied (Scheme 1a). For example,  $\alpha$ -(carbonylamino)alkenylmetals are obtained via the syn-addition of organocoppers, -zincs, and -lithiums to ynamides.<sup>[3,4]</sup> In contrast,  $\beta$ -(carbonylamino)alkenylmetals are obtained by svncarbopalladion of ynamides using organopalladiums.<sup>[5]</sup> However, anti-carbometalation of ynamides remains underdeveloped, although the intramolecular carbometalations of ynamides have been reported (Scheme 1b).<sup>[6]</sup> We recently reported intermolecular anti-carbometalations of carbon-carbon triple bonds using silylated nucleophiles and metal salts such as InBr<sub>3</sub>, GaBr<sub>3</sub>, AlBr<sub>3</sub>, BiBr<sub>3</sub>, and ZnBr<sub>2</sub>.<sup>[7]</sup> Therefore, we assumed our strategy could achieve anti-carbometalation of ynamides. Here, we report the anti-carbometalation of ynamides using InBr<sub>3</sub> and silyl ketene acetals to synthesize (Z)-β-(carbonylamino)alkenylindiums (Scheme 1c).

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a) syn-Carbometalation of ynamide





c) Intermolecular anti-carbometalation of vnamide (This work)



Scheme 1. Carbometalation of ynamide.

First, we surveyed metal halides for carbometalation of Nethynylpyrrolidone 1a using silyl ketene acetal 2a (Table 1). The reaction of ynamide 1a using InBr3 and 2a followed by the addition of MeOH exclusively gave the product 3aa in a 96% yield, where the carbon-carbon bond was formed at the carbon atom adjacent to a nitrogen atom (entry 1). This result showed that enamide 3aa protonation was produced by the of ß-(carbonylamino)alkenylindium (details are described below). regioisomers obtained Notably. from α-(carbonylamino)alkenylindiums were not found despite the existence of an amide moiety which often serves as a directing group in carbometalation using organometallic compounds.[3,4] In an examination of the influence of halogen atoms on an indium, Inl<sub>3</sub> gave a slightly higher yield than InBr<sub>3</sub> (entry 2). On the other hand, the use of InCl<sub>3</sub> resulted in only a 66% yield (entry 3). ZnBr<sub>2</sub>, Znl<sub>2</sub>, GaBr<sub>3</sub>, Gal<sub>3</sub>, and BiBr<sub>3</sub> afforded **3aa** in moderate yields (entries 4-8). Other Lewis acids such as CuBr and AlBr<sub>3</sub> were not effective (entries 9 and 10). After the investigation of other conditions such as solvents and temperatures, we chose the conditions listed in entry 1 as optimal.<sup>[8]</sup>

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Table 1. Optimizing the carbometalation of ynamide. <sup>[a]</sup>				
	$MtX_{n} + \begin{array}{ c c } H \\ MtX_{n} + \\ O \\ O \\ 1a \end{array} + \begin{array}{ c } O \\ OSIMe_{3} \\ O \\ $	Cl <sub>2</sub> , 2 h	MeOH, ON COOMe	
	Entry	MtX <sub>n</sub>	Yield <sup>[b]</sup> of <b>3aa</b>	
	1	InBr₃	96% (79%)	
	2	InI <sub>3</sub>	98%	
	3	InCl₃	66%	
	4	ZnBr <sub>2</sub>	42%	
	5	Znl <sub>2</sub>	50%	
	6	GaBr₃	35%	
	7	Gal₃	68%	
	8	BiBr <sub>3</sub>	35%	
	9	CuBr	0%	
	10	AlBr <sub>3</sub>	0%	

[a] MtX<sub>n</sub> (0.5 mmol), **1a** (0.5 mmol), **2a** (1.5 mmol), and CH<sub>2</sub>Cl<sub>2</sub> (1 mL). [b] The yields of **3aa** were measured via <sup>1</sup>H-NMR analysis of the crude mixture. The isolated yield is shown in parentheses.

Removal of the volatiles from the reaction mixture of InBr<sub>3</sub>, **1a** and **2a** followed by washing with hexane afforded a white solid. The obtained solid was recrystallized using CH<sub>2</sub>Cl<sub>2</sub>/hexane solvent to give a colorless crystal. X-ray crystallographic analysis revealed (*Z*)- $\beta$ -(carbonylamino)alkenylindium **4aa**. The *trans*-geometry between the InBr<sub>3</sub> group and a substituent derived from **2a** in the ORTEP drawing of **4aa** suggests an *anti*-addition mechanism (Scheme 2). The zwitterionic structure of **4aa** is composed of a formal negatively charged indium atom and a silyl oxocarbenium cation moiety. The length of the C-In bond (2.132(3) Å) is similar to that of In-C(sp<sup>2</sup>) (2.171(7) Å), as reported by our group for a zwitterion indium complex.<sup>[9]</sup> A chemical shift in the value of **4aa** ( $\delta$ (<sup>29</sup>Si-NMR) = 42 ppm) is reasonable for silyl oxocarbenium cations (36-44 ppm).<sup>[10]</sup>



Scheme 2. anti-Carboindation of ynamide 1a.

We investigated a reaction mechanism by DFT calculation to reveal the origin of the stereo- and regioselectivities.<sup>[11]</sup> The reaction profiles giving  $\beta$ -(carbonylamino)alkenylindium **E1** (4aa) (red line) and  $\alpha$ -(carbonylamino)alkenylindium **E2** (blue line) are shown in Figure 1. Two types of the interaction between InBr<sub>3</sub> and

the alkyne moiety of ynamide 1a (A and B) were expected.<sup>[12]</sup> Two complexes constructed by the coordination of an alkyne moiety to InBr<sub>3</sub> (A) and the chelation of carbonyl and alkyne moieties (B) were optimized. Although complex B is more thermodynamically favorable than complex A, IRC calculation<sup>[13]</sup> of the transition states suggests the carboindation starts from complex A because the alkyne moiety in A is more activated than that in B. In complex A, the indium atom effectively interacts with the C<sup>2</sup>-carbon atom of the ynamide because the electron density of the C2-carbon atom is enhanced by an electron-donation from the nitrogen atom.[11] NBO analysis of complex A shows that the positive charge is increased on the C1-carbon atom rather than on the C2carbon atom.<sup>[11]</sup> The two transition states TS1 and TS2 give D1 and D2, respectively, in which the carbonyl group on the nitrogen atom does not work as a directing group. The activation energy of TS2 (27.4 kcal/mol) is much higher than that of TS1 (18.5 kcal/mol) because there is less effective coordination by the  $\pi$ electrons with InBr<sub>3</sub>.<sup>[11]</sup> Migration of the Me<sub>3</sub>Si group in D1 is a thermodynamically favorable path to give the observed zwitterionic species E1(4aa).



Figure 1. Energy diagram of the *anti*-carboindation of 1a. B3LYP/6-31+G(d) for H, C, N, O and Si, and DGDZVP for In and Br.

We investigated the scope of silyl ketene acetals 2 via carboindation followed by Pd-catalyzed cross-coupling using alkenylindium 4 (Table 2).<sup>[14]</sup> After the carboindation of **1a** using InBr<sub>3</sub> and **2a**, an addition of *p*-iodotoluene, a catalyltic amount of Pd(PPh<sub>3</sub>)<sub>4</sub>, and DMF as an additional solvent into the reaction mixture gave trisubstituted enamide **5aa** in a 90% yield (entry 1).<sup>[7a]</sup> The (*Z*)-configuration of enamide **5aa** was confirmed via a <sup>1</sup>H nuclear Overhauser effect (NOE) experiment.<sup>[15]</sup> Also, **2b** bearing a phenoxy group afforded **5ab** (entry 2). The reaction using **2c** and **2d** with bulky substituents on nucleophilic carbons smoothly proceeded in sufficient product yields (entries 3 and 4).<sup>[16]</sup> Monosubstituted ketene silyl acetals (**2e**, **2f** and **2g**) were found to be facile nucleophiles (entries 5-7). Carboindation using thienyl-substituted ketene silyl acetal **2h** afforded product **5ah** (entry 8). Silyl ketene imine **2i** was applicable to the

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carboindation/cross-coupling process to give nitrile **5ai** in a 78% yield (entry 9).









[a] Ar = 4-Me-C<sub>6</sub>H<sub>4</sub>, InBr<sub>3</sub> (0.5 mmol), **1a** (0.5 mmol), **2** (1.5 mmol), CH<sub>2</sub>Cl<sub>2</sub> (1 mL), Pd(PPh<sub>3</sub>)<sub>4</sub> (5 mol%), *p*-iodotoluene (1.0 mmol), and DMF (1.5 mL). [b] Isolated yields.

Various aryl iodides were applicable to the present carboindation/cross-coupling process (Table 3). The coupling reaction using either electron-rich or electron-poor aryl iodides smoothly produced trisubstituted enamides **6a**, **6b** and **6c** (entries 1-3). Aryl iodides bearing *N*-phthaloylamino and nitro groups gave the corresponding products **6d** and **6e**, respectively (entries 4 and 5). A cross-coupling with benzyl bromide gave **6f** (entry 6). The use of *p*-bromotoluene instead of *p*-iodotoluene gave the desired product, although the yield was moderate (entry 7). A radical coupling in the presence of AIBN between diphenyl disulfide and alkenylindium **4aa** gave alkenyl sulfide **6g** in a 92% yield (entry 8).<sup>[7e]</sup> In all coupling reactions, the products were obtained as single isomers.<sup>[15]</sup>

alkenylindium **4** formed via carboindation (Table 4). Ynamide **1a** was transformed to iodinated enamide **7aa** in a 76% yield by treatment of the reaction mixture with  $I_2$  (entry 1). Alkynyl carbamates **1b** and **1c** were suitable substrates to give products **7ba** and **7ca**, respectively (entries 2 and 3). Carboindations of *N*-benzyl- or *N*-aryl-ynamides **1d**, **1e**, and **1e** smoothly occurred (entries 4-6).<sup>[16]</sup> *N*-ethynyl-*p*-toluenesulfonamides **1g** and **1h** were converted to the corresponding enamides **7ga** and **7ha**, respectively (entries 7 and 8).

Various ynamides 1 were investigated via the iodination of

[a]  $InBr_3$  (0.5 mmol), **1a** (0.5 mmol), **2a** (1.5 mmol),  $CH_2Cl_2$  (1 mL),  $Pd(PPh_3)_4$  (5 mol%), R-X (1.0 mmol), and DMF (1.5 mL). [b]  $InBr_3$  (0.5 mmol), **1a** (0.5

mmol), 2 (1.5 mmol), CH<sub>2</sub>Cl<sub>2</sub> (1 mL), PhSSPh (1.0 mmol), AIBN





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#### Table 4. Scope of ynamides 1.[a]





[a] InBr<sub>3</sub> (0.5 mmol), 1 (0.5 mmol), 2a (1.5 mmol), CH<sub>2</sub>Cl<sub>2</sub> (1 mL),  $I_2$  (1.5 mmol), and DMF (1.5 mL). [b] Isolated yields.

The transformations of enamides obtained using the proposed form of carboindation were demonstrated as synthetic applications (Schemes 3 and 4). Enamide **3ia** was synthesized via the carboindation of ynamide **1i** using **2a** and InBr<sub>3</sub> in a 74% yield (Scheme 3A). The intramolecular Heck reaction<sup>[17]</sup> of **3ia** followed by Dieckmann cyclization<sup>[18]</sup> between ester and amide moieties accomplished the synthesis of a heterocyclic compound **8** including a benzo[*b*]quinolizidine structure that is often found in antibacterially active compounds.<sup>[19]</sup> Enamide **3aa** was treated with *N*-bromosuccinimide<sup>[20]</sup> to give *y*-bromo *β*-keto ester **9**, which is a useful building block for bioactive compounds,<sup>[21]</sup> in a 73% yield (Scheme 3B).



Scheme 3. Synthesis of 1,6-dihydrobenzo[b]quinolizine-2,4-dione 8 and  $\gamma$ -bromo  $\beta$ -keto ester 9.

The transformation of an enamide to an amine was examined using an enamide with removable protecting groups on the nitrogen atom (Scheme 4). Enamide **5ca** with benzyl and methylcarboxy groups was successfully synthesized by the sequential process of carboindation/cross-coupling using **1c**.<sup>[16]</sup> The reduction of **5ca** by H<sub>2</sub> using Pd(OH)<sub>2</sub>/C afforded amide **10**.<sup>[22]</sup> The carbamate group was removed by using Me<sub>3</sub>Sil to afford amine **11**.<sup>[23]</sup> Hydrogenation of **11** to remove the benzyl group gave the *β*-amino acid ester **12**.



Scheme 4. Synthesis of  $\beta$ -amino ester 12.

In conclusion, we developed a regioselective anticarboindation of ynamides using silylated nucleophiles and InBr<sub>3</sub> to synthesize (*Z*)- $\beta$ -(carbonylamino)alkenylindiums. Isolated zwitterionic alkenylindiums were characterized by X-ray diffraction analysis, which supported the use of an *anti*-addition mechanism. DFT calculation proved that the regioselectivity of carboindation depends on the polarization of a carbon-carbon triple bond by electron-donating nitrogen. The scope of nucleophiles involved various silyl ketene acetals and silyl ketene imines. The prepared alkenylindiums were successfully transformed to functionalized trisubstituted enamides through halogenation, radical coupling or Pd catalyzed cross-coupling.

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**Keywords:** Carbometalation • Indium • Lewis acids • Silicon • Ynamide

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#### Entry for the Table of Contents (Please choose one layout)

Layout 2:

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**Regioselective** *anti*-carboindation: The regioselective *anti*-carboindation of ynamides using InBr<sub>3</sub> and silyl ketene acetals was achieved to give  $\beta$ -(carbonylamino)alkenylindium. Superior  $\pi$ -electron affinity of InBr<sub>3</sub> efficiently activated the triple bond of an ynamide despite the existence of an amide moiety. The regioselectivity of the nucleophilic attack of a silyl ketene acetal was controlled via the polarization of a triple bond derived from a nitrogen atom.

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