

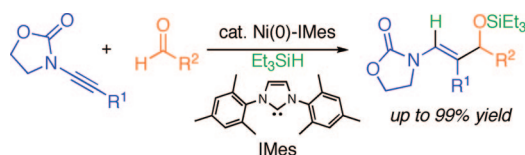
Nickel-Catalyzed Highly Regioselective Multicomponent Coupling of Ynamides, Aldehydes, and Silane: A New Access to Functionalized Enamides

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Received July 7, 2008

ABSTRACT



A new method for preparation of functionalized enamides by a nickel-catalyzed multicomponent coupling of ynamides, aldehydes, and silane has been developed. The coupling reaction proceeded in the presence of a nickel-IMes catalyst to give the corresponding γ -silyloxyenamide derivative, which has an allylic alcohol moiety in the molecule, in a highly stereoselective manner.

Enamide is recognized as one of the important fragments found in some biologically active natural products¹ as well as a valuable substrate for the synthesis of optically active amines via asymmetric hydrogenation.² Therefore, many protocols for enamide synthesis have been developed to date. Recently, enamides have been synthesized with transition metal catalysis including isomerization of *N*-allylamide,³ hydroamidation of alkynes,⁴ vinylation of amides,^{5,6} oxida-

tive amidation of alkenes,⁷ and co-oligomerization of *N*-vinylamides with alkenes or alkynes.⁸ Furthermore, enamides can be synthesized by transition metal-catalyzed ynamide transformation:⁹ hydrogenation,¹⁰ hydro-, carbo-, and bis-metalation,¹¹ as well as cycloaddition.¹² On the other hand, catalytic multicomponent coupling¹³ with ynamides as a

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platform could also be an attractive methodology for the synthesis of functionalized enamides.

We have demonstrated nickel-catalyzed multicomponent coupling of 1,3-dienes, aldehydes, and silanes, in which the stereoselectivity was controlled by the property of the ligands.^{14–16} With this as a background, we planned nickel-catalyzed multicomponent coupling of ynamides, aldehydes, and silanes as a new method for stereoselective synthesis of functionalized enamides (Scheme 1). Thus, oxidative cycloaddition of ynamides **1** and aldehydes **2** to a zerovalent nickel complex could proceed to give oxanickelacycle **I** or **II**. The reaction of the nickelacycle with silane would afford the corresponding three-component coupling product β -alkylated enamide **III** or α -alkylated enamide **IV**.^{17,18} In particular, γ -alkoxy enamide **III** is known as a useful substrate for the synthesis of some important organic molecules.¹⁹

First of all, the reaction of oxazolidinone-derived ynamide **1a**,²⁰ benzaldehyde (**2a**), and Et₃SiH (**3**) in the presence of Ni(0)-NHC catalyst, which was generated from Ni(cod)₂,

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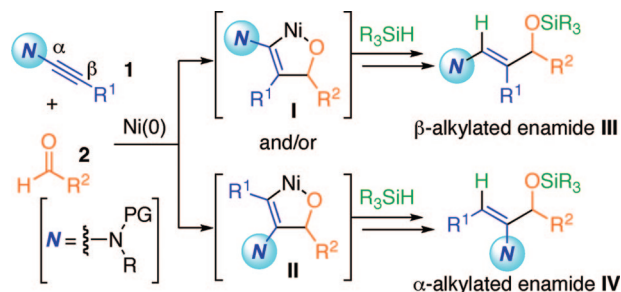
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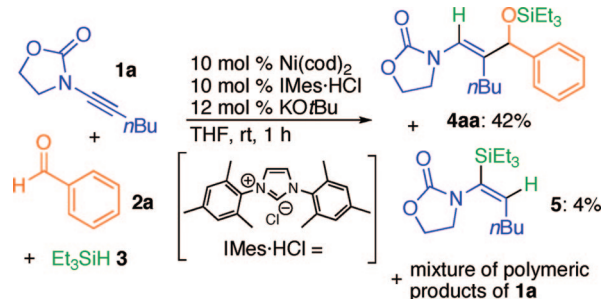
(20) In this work, the ynamides were synthesized by Hsung's Cu-catalyzed coupling reaction of haloalkynes and amides. Frederick, M. O.; Mulder, J. A.; Tracey, M. R.; Hsung, R. P.; Huang, J.; Kurtz, K. C. M.; Shen, L.; Douglas, C. J. *J. Am. Chem. Soc.* **2003**, *125*, 2368.

Scheme 1. Plan for Multicomponent Coupling of Ynamides, Aldehydes, and Silane by Ni(0) Catalyst



IMes·HCl, and KOtBu, was carried out in THF at room temperature for 1 h. As a result, an enamide derivative **4aa** was obtained in 42% yield as a single isomer,²¹ and no other regio- and stereoisomer was observed. However, the alkynylsilane **5**, which might be formed by hydrosilylation of **1a**,²² and significant amounts of the complex mixture of polymeric products of **1a** were also produced at the same time (Scheme 2).

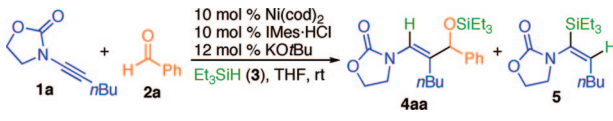
Scheme 2. Coupling of **1a**, **2a**, and **3** with Use of Ni(0)-IMes Catalyst



It was thought that suppression of the formation of the above byproduct was necessary to improve the yield of **4aa**. Therefore, we next investigated the impact of the reaction procedure on byproduct formation (Table 1). First, a THF solution of ynamide **1a** and **2a** was slowly added to a mixture of Ni-IMes complex and Et₃SiH (**3**) in THF over a period of 14 h by a syringe pump (Method A). As a result, the yield of the coupling product **4aa** was improved to 69%, and no polymeric product of **1a** was observed. However, hydrosilylation compound **5** was also obtained in 26% yield. Next, slow addition of a THF solution of **1a** to the mixture of Ni-IMes catalyst, **2a**, and **3** in THF was carried out over a period of 14 h, giving the coupling product **4aa** in 73% yield along with starting ynamide **1a** in 19% recovery (Method B).

(21) Olefinic geometry was determined by an NOE experiment. See the Supporting Information.

(22) For a hydrosilylation of alkyne with Ni-NHC catalyst, see: Chaulagain, M. R.; Mahandru, G. M.; Montgomery, J. *Tetrahedron* **2006**, *62*, 7560.

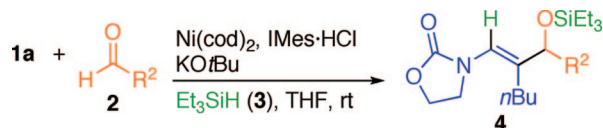
Table 1. Optimization of the Reaction Procedure


method ^a	yield (%)		
	4aa	5	1a
A	69	26	
B	73		19
C	91		

^a Method A: Slow addition of **1a** and **2a** in THF over a period of 14 h. Method B: Slow addition of **1a** in THF over a period of 14 h. Method C: Slow addition of **1a** in THF over a period of 7 h.

Finally, the only desired enamide derivative **4aa** was obtained in 91% by slow addition of the solution of **1a** in THF over a period of 7 h (Method C).

Using the optimal reaction procedure (Method C), study of the scope and limitations of aldehyde structure in the three-component coupling was conducted (Table 2). The reaction

Table 2. Scope of Aldehyde Structure in the Three-Component coupling.^a

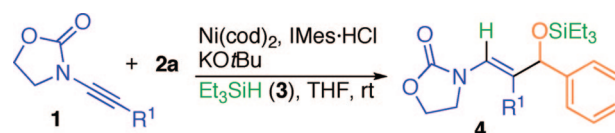
run	aldehyde 2	product 4 (%)
1 ^b	2b : R ¹ = 4-CH ₃	4ab : 31
2 ^b	2c : R ¹ = 4-OCH ₃	4ac : 25
3	2d : R ¹ = 4-CO ₂ Me	4ad : 99
4	2e : R ¹ = 4-CF ₃	4ae : 94
5 ^b	2f : R ¹ = 4-Cl	4af : 61
6 ^b	2g : R ¹ = 4-F	4ag : 64
7	2h : R ¹ = 3-F	4ah : 96
8	2i	4ai : 91
9 ^b	2j	4aj : 48

^a Reaction procedure (Method C: for details, see the Supporting Information): A solution of aldehyde **2** (3 equiv) in THF was added to a solution of ynamide **1a** (1 equiv), Et₃SiH (5 equiv), Ni(cod)₂ (10 mol %), IMes-HCl (10 mol %), and KOtBu (12 mol %) in THF over a period of 7 h by a syringe pump at room temperature. After the addition was finished, the reaction mixture was stirred for an additional 0.5 h. ^b After the slow addition was finished, the reaction mixture was stirred overnight.

with **1a** and aromatic aldehydes **2b** and **2c**, having an electron-donating group, gave the corresponding enamide derivatives **4ab** and **4ac** in low yield (runs 1 and 2). On the other hand, the reaction of **1a** and aldehyde **2d** and **2e**, which had an electron-withdrawing group at the para position on the aromatic ring, proceeded smoothly to give the coupling products **4ad** and **4ae** in 99% and 94% yield, respectively

(runs 3 and 4). When 4-chlorobenzaldehyde (**2f**) was used for the coupling reaction, the corresponding enamide **4af** was obtained in 61% yield (run 5). 4-Fluorobenzaldehyde (**2g**) reacted with **1a** and **3**, giving the enamide derivative **4ag** in 64% yield (run 6), and the reaction with 3-fluorobenzaldehyde (**2h**) provided the coupling product **4ah** in 96% yield (run 7). When 2-naphthaldehyde (**2i**) was reacted with **1a** under the same reaction conditions, the enamide product **4ai** was obtained in 91% yield (run 8). An aliphatic aldehyde such as isobutyraldehyde (**2j**) was also applicable to the three-component coupling, and the corresponding enamide derivative **4aj** was obtained in 48% yield as a single isomer (run 9).

Next, we turned our attention to investigation of the three-component coupling using various ynamides (Table 3). When

Table 3. Scope of Ynamide Structure in the Three-Component Coupling^a

run	ynamide 1 (R ¹ =)	product 4 (%)
1	1b : CH ₃	4ba : 91
2	1c : CH ₂ OTBS	4ca : 89
3 ^b	1d : CH ₂ CH ₂ OTBS	4da : 52
4	1e : CH ₂ CH ₂ OMOM	4ea : 84
5 ^b	1f : CH ₂ CH ₂ CH ₂ -[cyclohexane ring]	4fa : 50
6 ^b	1g : CH ₂ CH ₂ CH ₂ CH ₂ OAc	4ga : 53

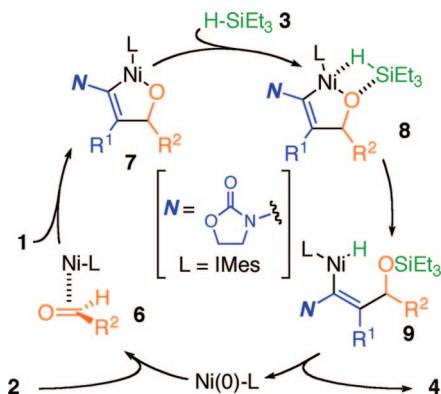
^a Reaction procedure (Method C: for details, see the Supporting Information): A solution of aldehyde **2** (3 equiv) in THF was added to a solution of ynamide **1a** (1 equiv), Et₃SiH (5 equiv), Ni(cod)₂ (10 mol %), IMes-HCl (10 mol %), and KOtBu (12 mol %) in THF over a period of 7 h by a syringe pump at room temperature. After the addition was finished, the reaction mixture was stirred for an additional 0.5 h. ^b After the slow addition was finished, the reaction mixture was stirred overnight.

methyl-substituted ynamide **1b** and **2a** were treated with **3**, coupling product **4ba** was obtained in 91% yield. The reaction of ynamides having a silylether tether (**1c** and **1d**) or acetal tether (**1e** and **1f**) with **2a** and **3** gave the corresponding γ -silyloxyenamide derivatives **4ca–4fa** in moderate to good yield (runs 2–5). Ynamides having an ester group **1g** reacted with **2a** and **3** to give the product **4ga** in 53% yield (run 6).

The possible reaction course of the regioselective three-component coupling of ynamides, aldehydes, and silane is shown in Scheme 3. Under the conditions using Method C, the aldehyde **2** coordinates to zerovalent Ni complex to give η^2 -aldehydenickel intermediate **6**.²³ Next, the reaction of ynamide **1** with the complex **6** would proceed to give oxaniceklacycle **7** regioselectively. Then cleavage of the

(23) For examples of the formation of η^2 -arylaldehydenickel complexes from zerovalent nickel complex and aldehyde, see: (a) Walther, D. J. *Organomet. Chem.* **1980**, 190, 393. (b) Ogoshi, S.; Kamada, H.; Kurosawa, H. *Tetrahedron* **2006**, 62, 7583.

Scheme 3. Possible Reaction Course



nickel–oxygen bond by σ -bond metathesis (depicted as **8**) of the nickelacycle **7** with Et_3SiH (**3**) would afford hydride-nickel intermediate **9**. Finally, the reductive elimination from **9** would occur to afford the γ -silyloxyenamide derivative **4** in a regio- and stereoselective manner.^{24,25}

To gain an insight into the high regioselectivity of the ynamide–aldehyde coupling, the structural and electronic properties of ynamide were investigated by DFT calculation at the B3LYP/6-31G* level utilizing Spartan'06 (Wavefunction, Inc., Irvine, CA). Figure 1 illustrates the highest occupied molecular orbital (HOMO) of geometrical

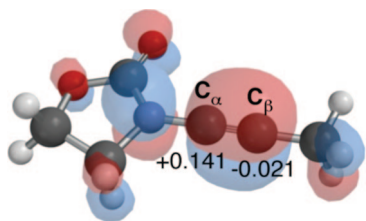


Figure 1. HOMO of geometrically optimized ynamide **1b**. The values show natural charge at C_α and C_β positions.

optimized ynamide **1b** along with the natural charge at C_α and C_β positions. The calculation results suggested that the

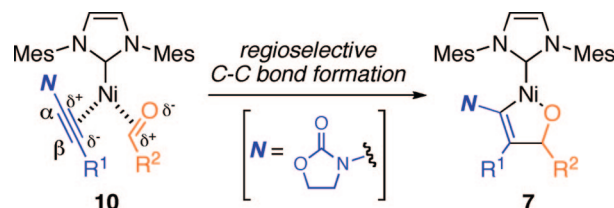
(24) Recently, oxanickelacyclopentene from zerovalent nickel, aldehyde, and alkyne was isolated and its structure was elucidated by X-ray analysis, see: Ogoshi, S.; Arai, T.; Ohashi, M.; Kurosawa, H. *Chem. Commun.* **2008**, 1347.

(25) Montgomery suggested the reaction mechanism via oxanickelacyclopentene formation followed by σ -bond metathesis with silane in his three-component coupling of alkynes, aldehydes, and silanes using Ni-NHC catalyst. See refs 17a and 17c.

HOMO of **1b** exists on the carbon–carbon triple bond and that β -carbon has a negative charge. This means that the β -carbon would be more nucleophilic than the α -carbon.

On the basis of the above insight from the calculation results, one reason for the highly regioselective formation of oxanickelacycle **7** in the possible reaction mechanism might be the electronic properties of ynamide (Scheme 4).

Scheme 4. Possible Reason for Regioselective Formation of Nickelacycle **7**



That is, at the oxanickelacycle formation stage, the reaction would proceed as the negatively polarized carbon at the β -position of ynamide **1** might interact with the positive carbonyl carbon of aldehyde **2** (illustrated as **10**) and carbon–carbon bond formation would occur between those two carbons.²⁶ Consequently, only oxanickelacycle intermediate **7** would be produced in a regioselective manner.

In summary, we have developed a new method for the synthesis of functionalized enamides by a nickel-catalyzed multicomponent coupling of ynamides, aldehydes, and silane. The coupling reaction proceeded through carbon–carbon bond formation between β -carbon of ynamides and carbonyl carbon of aldehydes to afford γ -silyloxyenamide derivatives in a highly regio- and stereoselective manner. Further studies along this line are now in progress.

Acknowledgment. A part of this work was supported by a Grant-in-Aid for Science Research on Priority Areas (No. 19027005, Synergy of Elements) from the Ministry of Education, Culture, Sports, Science and Technology, Japan and by a Grant-in-Aid for Scientific Research (B) (No. 19390001) from the Japan Society for the Promotion of Science (JSPS). N.S. acknowledges the Akiyama Foundation for financial support.

Supporting Information Available: Experimental details and spectral data of all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(26) Similar regioselectivity has been observed in Lewis acid-mediated coupling of ynamides and aldehydes or ketones demonstrated by Hsung, see: You, L.; Al-Rashid, Z. F.; Figueroa, R.; Ghosh, S. K.; Li, G.; Lu, T.; Hsung, R. P. *Synlett* **2007**, 1656.