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

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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 products[1] 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] oxidative 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 bismetalation,[11] as well as cycloaddition.[12] On the other hand, catalytic multicomponent coupling[13] with ynamides as a

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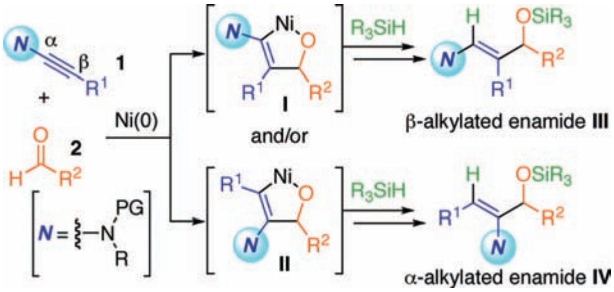
10.1021/ol801534e CCC: $40.75

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

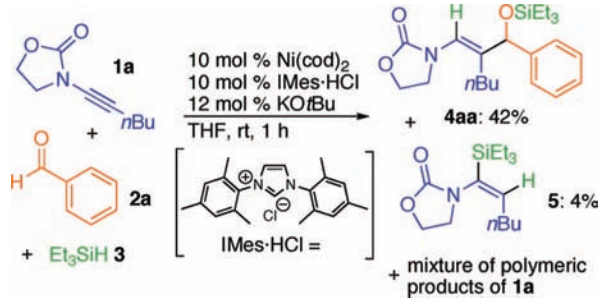
We have demonstrated nickel-catalyzed multicomponent coupling of 1,3-dienes, aldehydes, and silanes, in which the stereoselectivity was controlled by the property of the ligands.[14−16] With this as a background, we planned nickel-catalyzed multicomponent coupling of ynamides, aldehydes, and silanes 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]

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



First of all, the reaction of oxazolidinone-derived ynamide **1a**,[20] benzaldehyde (**2a**), and Et_3SiH (**3**) in the presence of Ni(0)-NHC catalyst, which was generated from $Ni(cod)_2$, IMes·HCl, and KO*t*Bu, 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 alkenylsilane **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 Et_3SiH (**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).

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

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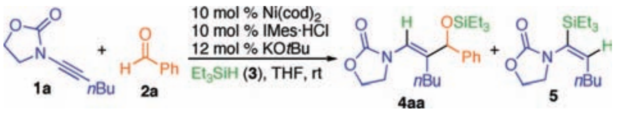
Table 1. Optimization of the Reaction Procedure

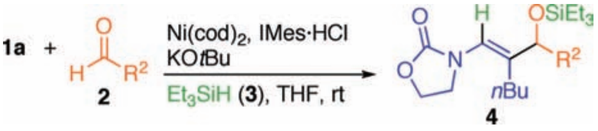


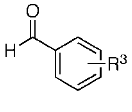
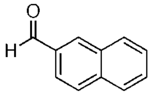
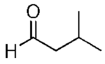
method[a]	4aa	yield (%) 5	1a
A	69	26	
B	73		19
C	91		

[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).

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

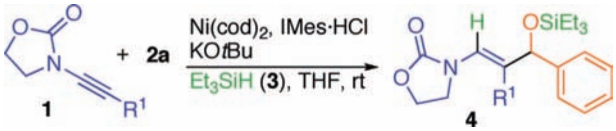


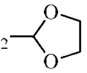
run	aldehyde 2		product 4 (%)
1[b]		**2b**: R^3 = 4-CH_3	**4ab**: 31
2[b]		**2c**: R^3 = 4-OCH_3	**4ac**: 25
3		**2d**: R^3 = 4-CO_2Me	**4ad**: 99
4		**2e**: R^3 = 4-CF_3	**4ae**: 94
5[b]		**2f**: R^3 = 4-Cl	**4af**: 61
6[b]		**2g**: R^3 = 4-F	**4ag**: 64
7		**2h**: R^3 = 3-F	**4ah**: 96
8		**2i**	**4ai**: 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), Et_3SiH (5 equiv), Ni(cod)$_2$ (10 mol %), IMes•HCl (10 mol %), and KO*t*Bu (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.

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 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).

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_2OTBS	**4ca**: 89
3[b]	**1d**:	CH_2CH_2OTBS	**4da**: 52
4	**1e**:	CH_2CH_2OMOM	**4ea**: 84
5[b]	**1f**:	$CH_2CH_2CH_2$— 	**4fa**: 50
6[b]	**1g**:	$CH_2CH_2CH_2CH_2OAc$	**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), Et_3SiH (5 equiv), Ni(cod)$_2$ (10 mol %), IMes•HCl (10 mol %), and KO*t*Bu (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.

Next, we turned our attention to investigation of the three-component coupling using various ynamides (Table 3). When 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 **4g** 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

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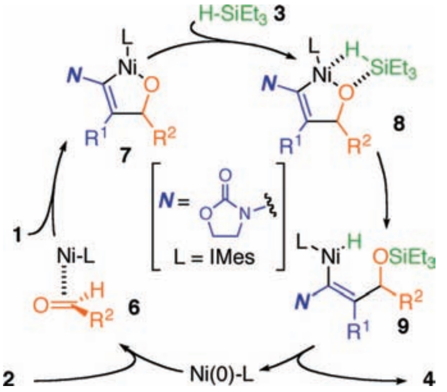
(23) For examples of the formation of η^2-arylaldehydenickel complexes from zerovalent nickel complex and aldehyde, see: (a) Walther, D. *J. Organomet. Chem.* **1980**, *190*, 393. (b) Ogoshi, S.; Kamada, H.; Kurosawa, H. *Tetrahedron* **2006**, *62*, 7583.

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

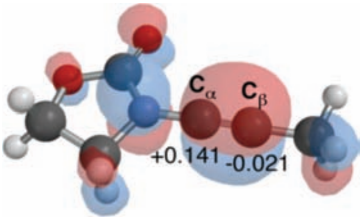
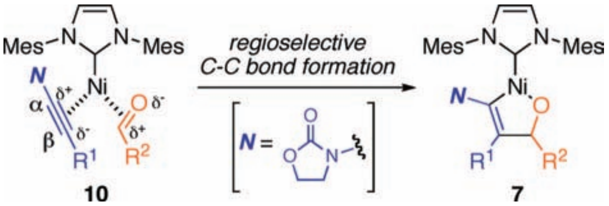


Figure 1. HOMO of geometrically optimized ynamide **1b**. The values show natural charge at C_α and C_β positions.

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 though 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.

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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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[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.

[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.