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ASYMMETRIC SYNTHESIS OF γ-SILOXYENAMIDES *VIA* CHIRAL AUXILIARY-MEDIATED DIASETEROSELECTIVE COUPLING OF YNAMIDES, ALDEHYDES, AND SILANE BY NICKEL CATALYST

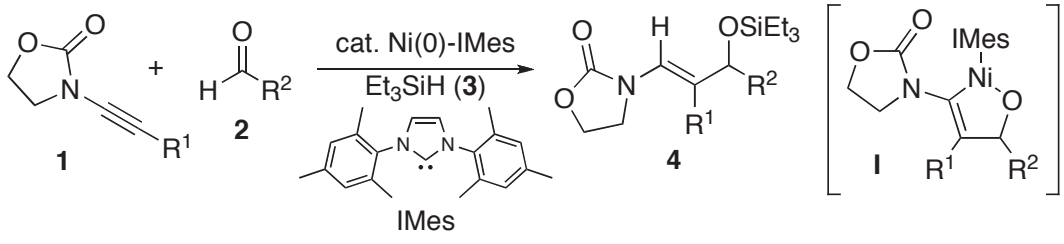
Nozomi Saito, Tomoyuki Katayama, and Yoshihiro Sato*

Faculty of Pharmaceutical Sciences, Hokkaido University, Sapporo 060-0812, Japan. E-mail: biyo@pharm.hokudai.ac.jp

Abstract – A nickel-catalyzed diastereoselective three-component coupling of optically active oxazolidinone-derived ynamides, aldehydes, and silane is described. The reaction proceeded *via* stereoselective formation of oxanickelacycle to give γ-siloxyenamide derivatives in a highly diastereoselective manner.

This paper is dedicated to Professor Albert Eschenmoser on the occasion of his 85th birthday.

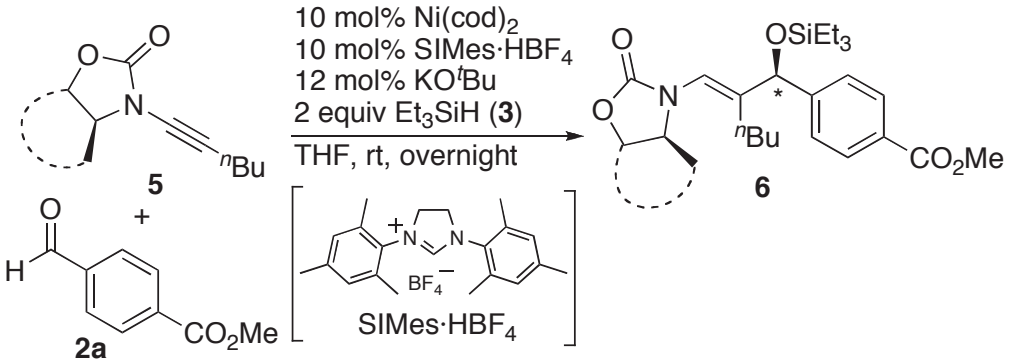
Ynamides, electron-rich alkynes, show unique reactivity and have been recognized as versatile synthetic units in recent organic chemistry.[1] Among the various reactions of ynamides, transformation of ynamides using transition metal catalysts has attracted much attention recently, and various excellent examples have been reported.[1,2] In this context, we demonstrated nickel-catalyzed multicomponent coupling of oxazolidinone-derived ynamides **1**, aldehydes **2**, and silane **3** (Scheme 1).[3] This reaction proceeded through oxanickelacycle **I** formed by oxidative addition of **1** and **2** to a zero-valent nickel complex to give γ-siloxyenamide derivative **4** in a highly regioselective manner.[4] Herein we report asymmetric synthesis of γ-siloxyenamide derivatives *via* diastereoselective three-component coupling of ynamides having a chiral auxiliary, aldehydes and silane.[5]

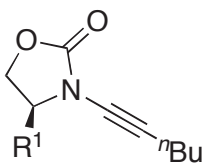
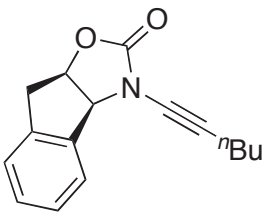


Scheme 1

First, the coupling reaction of phenylalanine-derived ynamide **5aa**, aldehyde **2a** and Et_3SiH (**3**) was carried out in the presence of a Ni(0)-SIMes catalyst generated from $Ni(cod)_2$, SIMes·HBF_4 and KO^{t}Bu in situ in THF overnight (Table 1, run 1). As a result, the γ-siloxyenamide derivative **6aaa** was obtained in 79% yield and with 66% de. Encouraged by these results, the effects of substituents on the oxazolidinone ring on the diastereoselectivity were examined (runs 2-6). The reaction of ynamide **5ba** prepared from phenylglycine with **2a** and Et_3SiH (**3**) gave **6baa** in 85% yield, 70% de (run 2). When ynamide **5ca** having an isobutyl group on the oxazolidinone was reacted with **2a** and **3**, the diastereoselectivity was increased to 84% (run 3). Surprisingly, the reaction of alanine-derived ynamide **5da** having the smallest methyl group on the oxazolidinone ring showed excellent diastereoselectivity, and the corresponding coupling product **6daa** was obtained in 98% yield, 91% de (run 4). On the other hand, the reaction of ynamide derived from valine **5ea** did not proceed probably due to the steric bulkiness of the isopropyl group (run 5). Moreover, when ynamide **5fa** prepared from aminoindanol was employed, γ-siloxyenamide **6faa** was obtained in 93% yield, 92% de (run 6).

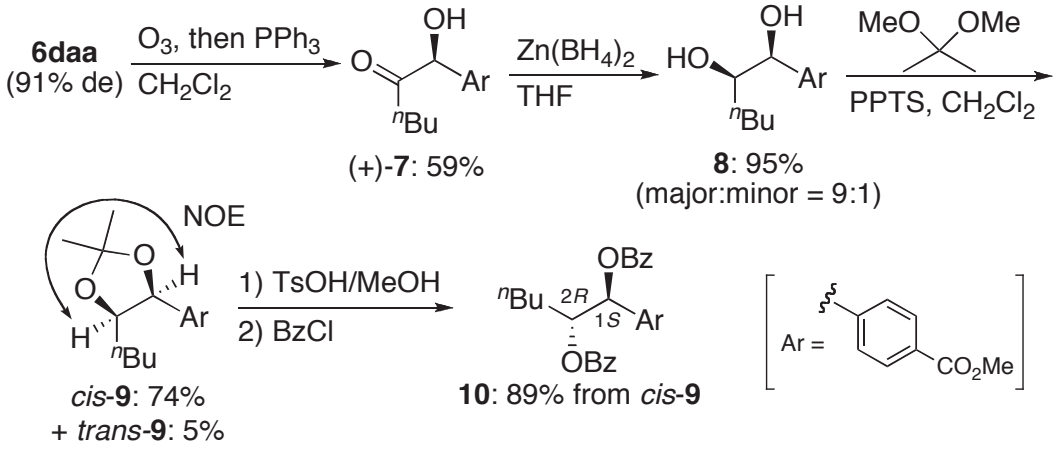
Table 1. Effect of Substituents on the Oxazolidinone Ring.[a]



run	ynamide		yield (%)	de (%)[b]
1		**5aa** (R^1 = Bn)	**6aaa**: 79	66
2		**5ba** (R^1 = Ph)	**6baa**: 85	70
3		**5ca** (R^1 = ^{i}Bu)	**6caa**: 86	84
4		**5da** (R^1 = Me)	**6daa**: 98	91
5		**5ea** (R^1 = ^{i}Pr)	**6eaa**: 0	-
6		**5fa**	**6faa**: 93	92

[a] Reaction procedure: A solution of ynamide **5** (0.50 mmol) in THF (3.0 mL) was added to a solution of aldehyde **2a** (3 equiv to **5**), Et_3SiH (**3**, 2 equiv to **5**), $Ni(cod)_2$ (10 mol% to **5**), SIMes·HBF_4 (10 mol% to **5**), and KO^{t}Bu (12 mol% to **5**) in THF (2.0 mL) over a period of 7 h by a syringe pump at room temperature. After the slow addition was finished, the reaction mixture was stirred overnight. The reaction mixture was concentrated, and the residue was purified by flash column chromatography on silica gel to give **6**. [b] Diastereomeric excess (de) was determined by ^{1}H-NMR (400 MHz or 500 MHz) analysis.

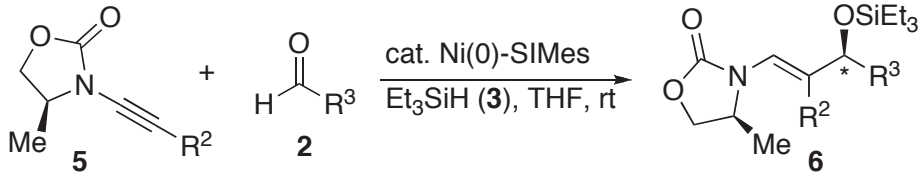
All absolute configurations of the methyne carbon in the predominant diastereomer of the coupling products **6** were determined through derivation of **6daa**, as shown in Scheme 2. Thus, treatment of the coupling product **6daa** (91% de) with O_3 gave α-hydroxyketone (+)-**7**, which was reduced by $Zn(BH_4)_2$ to give diol **8** as an inseparable mixture of diastereomers. The diol **8** was treated with 2,2-dimethoxypropane to give the corresponding acetonides *cis*-**9** and *trans*-**9** in 74% and 5% yields, respectively. After confirmation of the stereochemistry of *cis*-**9** by NOE experiments, *cis*-**9** was transformed into dibenzoate of 1-arylhexane-1,2-diol **10**, whose absolute configurations were determined to be 1*S* and 2*R*-configurations by the CD exciton chirality method.[6] Therefore, it was found that the major diastereomer in **6daa** has an *S*-configuration at the methyne carbon. Furthermore, all other coupling products **6aaa**-**6caa** and **6faa** could be also converted into (+)-**7** in a manner similar to that for **6daa**. These result indicate that the predominant diastereomer of **6aaa**-**6caa** and **6faa** also has an *S* configuration at the methyne carbon.



Scheme 2

Coupling reactions of various alanine-derived ynamides and aldehydes were investigated and the results are summarized in Table 2. The reaction of **5da** and aromatic aldehydes **2b-d** with Et_3SiH (**3**) in the presence of a Ni(0)-SIMes catalyst afforded the coupling products **6dab**-**6dad** in high yields and in high diastereoselectivity (runs 1-3). An aliphatic aldehyde **2e** was also applicable to the coupling with **5da** and **3**, giving **6dae** in 75% yield as a single diastereomer (run 4). On the other hand, ynamides **5db**-**5de** having various substituents on the alkyne part were reacted with **2a** and Et_3SiH (**3**) by Ni(0)-SIMes to give the corresponding γ-siloxyenamides **6dba**-**6dea**, respectively in good yields and in a highly diastereoselective manner (runs 5-8).[7]

Table 2. Coupling of Various Ynamides and Aldehydes.[a]

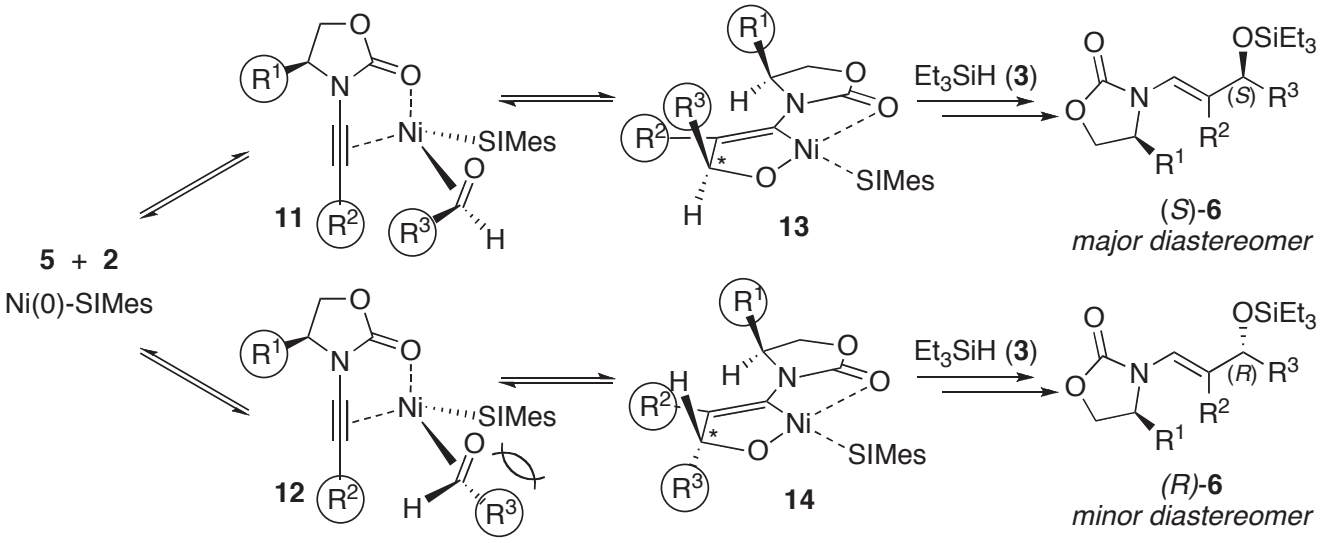


run	ynamide	aldehyde	yield (%)	de (%)[b]
1	**5da** (R^2 = ^{n}Bu)	**2b** (R^3 = C_6H_5)	**6dab**: 95	91
2	**5da**	**2c** (R^3 = 4-$CF_3CC_6H_4$)	**6dac**: 97	84
3	**5da**	**2d** (R^3 = 2-naphtyl)	**6dad**: 93	90
4	**5da**	**2e** (R^3 = CH_2CHMe_2)	**6dae**: 75	>99
5	**5db** (R^2 = Me)	**2a** (R^3 = 4-$MeO_2CC_6H_4$)	**6dba**: 88	85
6	**5dc** (R^2 = CH_2OTBS)	**2a**	**6dca**: 93	90
7	**5dd** (R^2 = CH_2CH_2OTBS)	**2a**	**6dda**: 83	94
8	**5de** (R^2 = CH_2CH_2OMOM)	**2a**	**6dea**: 73	91

[a] Reaction procedure: A solution of ynamide **5** (0.50 mmol) in THF (3.0 mL) was added to a solution of aldehyde **2a** (3 equiv to **5**), Et_3SiH (**3**, 2 equiv to **5**), $Ni(cod)_2$ (10 mol% to **5**), SIMes·HBF_4 (10 mol% to **5**), and KO^{t}Bu (12 mol% to **5**) in THF (2.0 mL) over a period of 7 h by a syringe pump at room temperature. After the slow addition was finished, the reaction mixture was stirred overnight. The reaction mixture was concentrated, and the residue was purified by flash column chromatography on silica gel to give **6**. [b] Diastereomeric excess (de) was determined by ^{1}H-NMR (400 MHz or 500 MHz) analysis. The absolute configuration at the methyne carbon of the coupling products **6** in Table 2 was tentatively assigned as *S*-configuration by the analogy to that of **6daa**.

It is well known that nickel-catalyzed reductive coupling of alkyne and aldehyde proceeds *via* the formation of oxanickelacycle generated by oxidative cycloaddition of alkyne and aldehyde to a zero-valent nickel complex.[8,9] Moreover, Jamison and Houk recently reported that the oxidative cycloaddition is the rate-determining step of the alkyne-aldehyde coupling and controls the regioselectivity of formation of the oxanickelacycle.[10] Therefore, the most significant step for the diasteroselection of this coupling of chiral ynamides and aldehydes was also thought to be the oxidative cycloaddition stage (Scheme 3). First, both the π-orbital of the triple bond and lone-pair electrons of the carbonyl group in ynamide **5**, aldehyde **2** and ligand (SIMes) would coordinate to the nickel center, and two possible tetracoordinate complexes **11** and **12**, in which the R^1 group on the oxazolidinone ring should be oriented to avoid steric interaction with the bulky SIMes ligand, could be formed. Then oxidative cycloaddition from each tetracoordinate complex would occur to afford oxanickelacycle **13** or **14**. However, the formation of **14** from **12** seems to be less favorable than the formation of **13** because of steric repulsion between the R^3 group in the aldehyde and the bulky SIMes ligand. Thus, nickelacycle **13** would be formed preferably as compared with **14**. Therefore, the coupling reaction would predominantly proceed *via* oxanickelacycle **13**, and (*S*)-**6** was obtained as a major diastereomer through σ-bond metathesis of **13** with Et_3SiH (**3**) followed by reductive elimination. On the other hand, diastereoselectivity of the reaction of ynamides having a bulkier R^1 group such as **5aa**-**5ca** decreased in

contrast to that of **5da** having a methyl group as described above. It is thought that formation of **13** from **5aa**-**5ca** might be less favorable than the reaction of **5da** due to steric interaction between the hindered R^1 group and the R^3 group. Therefore, it is thought that contribution of the reaction pathway *via* **14** increased and the diastereoselectivity of the coupling diminished.



Scheme 3

In summary, nickel-catalyzed three-component coupling of chiral oxazolidinone-derived ynamides, aldehydes and silane was developed. The reaction proceeds through the formation of oxanickelacycle to afford γ-siloxyenamide derivatives in a highly regio- and stereoselective manner.

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7. **Typical Procedure for the Nickel-Catalyzed Coupling of Ynamide, Aldehyde, and Et_3SiH (Table 2, run 4).** To a solution of $Ni(cod)_2$ (14 mg, 0.050 mol), SIMes·HBF_4 (20 mg, 0.050 mmol), and KO^{t}Bu (6.8 mg, 0.061 mmol) in THF (3.0 mL) were added **2e** (0.16 mL, 1.5 mmol) and **3** (0.16 mL, 1.1 mmol) at 0 °C, and the mixture was stirred at the same temperature for 10 min. To the mixture was added a solution of **5da** (91 mg, 0.50 mmol) in THF (2.0 mL) over a period of 7 h by a syringe pump at room temperature. After the slow addition was finished, the reaction mixture was stirred at room temperature overnight. The mixture was concentrated, and the residue was purified by flash column chromatography on silica gel (hexane/AcOEt = 8/1) to give **6dae** (144 mg, 75%) as a colorless oil. $[\alpha]_D^{26}$ -37.8° (*c* 0.22, $CHCl_3$); IR (neat) 1761, 1236 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.58-062 (m, 6H), 0.89 (d, *J* = 4.0 Hz, 3 H), 0.91 (d, *J* = 4.6 Hz, 3 H), 0.91 (d, *J* = 3.4 Hz, 3 H), 0.95 (t, *J* = 8.0 Hz, 9 H), 1.25 (d, *J* = 6.3 Hz, 3H), 1.29-1.45 (m, 6H), 1.69 (m, 1H), 1.99-2.9 (m, 2H), 3.94 (dd, *J* = 8.0, 5.2 Hz, 1H), 4.07 (m, 1H), 4.17 (dd, *J* = 8.0, 4.6 Hz, 1H), 4.44 (t, *J* = 8.3 Hz, 1H), 5.97 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 4.7, (3C), 6.8 (3C), 13.8, 18.5, 22.2, 23.0, 23.3, 24.1, 26.7, 30.4, 46.5, 52.4, 68.8, 73.2, 117.9, 139.2, 156.0; EI-LRMS *m/z* 354 [$(M-Et)^+$], 326, 298, 251; EI-HRMS calcd for $C_{19}H_{36}NO_3Si$ [$(M-Et)^+$] 354.2464, found 354.2458.
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