residue was recrystallized from pentane at −40 °C to give **2** (34.7 mg, 58 %) as yellow crystals. m.p. 274–276 °C (decomp); ^{1}H NMR (300 MHz, C_6D_6): $\delta = 0.12$ (s, 18 H), 0.19 (s, 36 H), 1.49 (s, 1 H), 2.45 (br s, 1 H), 2.52 (br s, 1 H), 3.95 (d, ^3J(H,H) = 10.5 Hz, 2 H), 4.73 (t, ^3J(H,H) = 6.3 Hz, 1 H), 4.98 (dd, ^3J(H,H) = 6.3, 10.5 Hz, 2 H), 6.63 (br s, 1 H), 6.73 ppm (br s, 1 H); ^{13}C NMR (75 MHz, C_6D_6): $\delta = 0.61$ (q), 0.78 (q), 0.91 (q), 31.50 (d), 34.37 (d), 34.79 (d), 83.00 (d), 85.87 (d), 100.91 (d), 122.44 (d), 123.55 (s), 127.26 (d), 148.32 (s), 151.92 (s × 2), 235.05 ppm (s); IR (KBr): $\tilde{\nu} = 1867$, 1887, 1954 cm^{-1} (C=O); UV/Vis (*n*-hexane): λ_{max} (ε) = 225 (49 000), 279 (17 000), 340 nm (8000); LRMS (FAB): *m/z* (%) = 826 (8) [M^+], 691 (75) [{C_5H_5Ge(Tbt)}$^+$], 521 (100) [{(Tbt)−2 CH_3}$^+$]. Although we have tried to obtain the elemental analysis of **2** on several occasions, the results have not been commensurate with the calculated values for **2** because of its highly moisture-sensitive properties (elemental analysis calcd for $C_{35}H_{64}CrGeO_3Si_6$: C 50.89, H 7.81; found: C 49.16, H 7.87).

3: In a glove-box filled with argon, [Mo($CH_3CN)_3(CO)_3$] (16.3 mg, 0.054 mmol) was added to a solution of **1** (40.1 mg, 0.058 mmol) in THF (1 mL) at room temperature, and the mixture was stirred for 5 h. After the solvent was removed in vacuo, the residue was recrystallized from hexane at −40 °C to give **3** (31.4 mg, 67 %) as yellow crystals. M.p. 248–250 °C (decomp); ^{1}H NMR (300 MHz, C_6D_6): $\delta = 0.11$ (s, 18 H), 0.18 (s, 36 H), 1.47 (s, 1 H), 2.39 (br s, 1 H), 2.49 (br s, 1 H), 4.05 (d, ^3J(H,H) = 9.9 Hz, 2 H), 4.73 (t, ^3J(H,H) = 6.6 Hz, 1 H), 5.17 (dd, ^3J(H,H) = 6.6, 9.9 Hz, 2 H), 6.61 (br s, 1 H), 6.70 ppm (br s, 1 H); ^{13}C NMR (75 MHz, C_6D_6): $\delta = 0.57$ (q), 0.77 (q), 0.88 (q), 31.43 (d), 34.66 (d), 34.99 (d), 81.64 (d), 83.77 (d), 103.11 (d), 122.40 (d), 123.72 (s), 127.23 (d), 148.28 (s), 151.66 (s × 2), 222.19 ppm (s); IR (KBr): $\tilde{\nu} = 1865$, 1883, 1952 cm^{-1} (C=O); UV/Vis (*n*-hexane): λ_{max} (ε) = 228 (41 000), 287 (10 000), 344 nm (13 000); elemental analysis calcd for $C_{35}H_{64}GeMoO_3Si_6$: C 48.32, H 7.42; found: C 47.91, H 7.48.

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Synthesis of Amino Acid Derivatives

A Diversity-Oriented Synthesis of α-Amino Acid Derivatives by a Silyltelluride-Mediated Radical Coupling Reaction of Imines and Isonitriles**

Shigeru Yamago, Hiroshi Miyazoe,*
Takeyoshi Nakayama, Masaki Miyoshi, and
*Junichi Yoshida**

Development of new and practical methods for the synthesis of α-amino acids and their derivatives is of considerable interest to researchers, because the importance of these compounds in biological systems and their exceptional utility as building blocks in organic synthesis is well known.[1,2]

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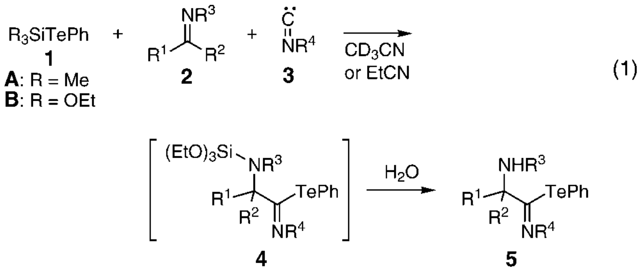
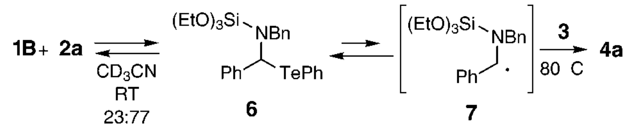
Because imines are excellent acceptors for various carbon nucleophiles, numerous synthetic routes from imines to amino acids have been developed under ionic conditions as exemplified by the Ugi reaction[3] and the Strecker reaction.[4,5] However, because of the unfavorable thermodynamics in the addition of carbon-centered radicals to imines, only a few examples of radical-mediated synthesis have been reported.[6–8] We report here a new synthesis of α-amino acid derivatives that relies on a silyltelluride-mediated radical coupling[9] strategy of imines and isonitriles followed by transformation of the resulting imidoyl tellurides [Eq. (1)].[10]



(1)

We initially examined the trimethylsilyl phenyl telluride (**1A**) mediated coupling reaction of imines and isonitriles. However, in sharp contrast to the reaction of **1A** and carbonyl compounds,[9] **1A** was totally unreactive toward imines. After screening several silyltellurides and group 14 metal tellurides, we were pleased to find that triethoxysilyl phenyl telluride (**1B**) was sufficiently reactive, providing the desired coupling product **4** with high efficiency. Thus, the reaction of **1B** (1.3 equiv), the imine **2a** ($R^1 = Ph$, $R^2 = H$, $R^3 = Bn$; Bn = benzyl; 1.0 equiv), and 2,6-xylylisonitrile (**3**, $R^4 = 2,6\text{-}Me_2C_6H_3$; 2.0 equiv) in CD_3CN was complete within 4 h at 80 °C and afforded the coupling product **5a** in 92 % yield after flash column chromatography (Table 1, entry 1). ^1H NMR spectroscopy indicated that the reaction initially afforded the silylated amine **4a**, which was hydrolyzed to **5a** during column chromatography. The NMR spectroscopic experiment also revealed the profile of the reaction (Scheme 1). The reaction of **1** and **2a** gave a 23:77 equilibrium mixture of the starting materials and the α-silylaminotelluride **6** after 0.5 h at room temperature in the absence of isonitrile, and the ratio did not change upon prolonged heating at 80 °C. However, addition of **3** (2 equiv) to the reaction mixture smoothly and completely converted **1**, **2a**, and **6** into **4a**. Because the imidoylation proceeds virtually irreversibly,[11] trapping of the α-amino radical **7**, which is reversibly generated from **6**,[12] by **3** shifted the equilibrium from the starting materials to the product.

As shown in Table 1, the current reaction is extremely versatile, and a variety of diversely substituted R^1 and R^2 groups of imines can participate in the coupling reaction. Thus, aromatic and aliphatic imines with acyclic and cyclic structures were coupled with **1B** and **3** within 4–24 h at 20–80 °C to give **4** in good to excellent yields. It is worth mentioning that the quaternary carbon center was effectively constructed by employing trisubstituted imines (entries 13 and 14). It is also interesting to observe that C–C multiple bonds were unaffected by the radical intermediates (entries 9 and 10). Because α-amino radicals undergo intermolecular addition to C–C multiple bonds only when electron-withdrawing groups are attached to the nitrogen atom,[13] the current results clearly indicate that the triethoxysilyl group is not a strong electron-withdrawing group. Moderate *anti* selectivity was observed in the reaction of the α-alkoxy imine **2c** (entry 11). Although we also examined several α-alkoxy imines with different α-alkyl substituents, such as the *iso*-propyl group, and/or a protecting group (results not shown), such as *tert*-butyldimethylsilyl (TBDMS), we could not increase the selectivity.

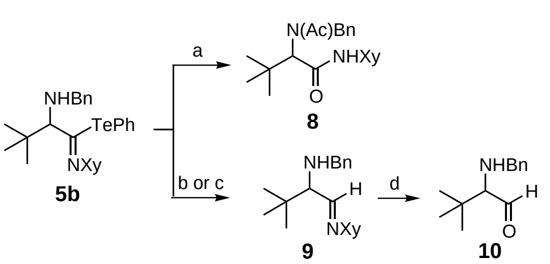


Scheme 1. The course of the coupling reaction.

Not only do the R^1 and R^2 substituents of the imines allow for diversity, but the R^3 moiety also serves as a diversification site. Thus, the reaction of a variety of *N*-alkyl benzylidene imine derivatives ($R^1 = Ph$, $R^2 = H$), afforded the desired coupling reaction ($R^3 = n$Bu; 94 %, $R^3 = (CH_2)_2OMe$; 78 %, $R^3 =$ allyl; 95 %), while the imines possessing electron-withdrawing groups, for example, SO_2Tol (Tol = toluyl), did not react under identical conditions.

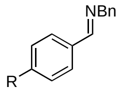
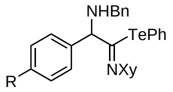
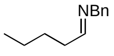
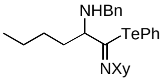
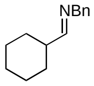
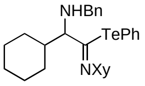
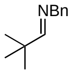
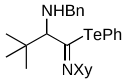
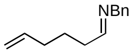
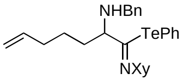
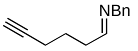
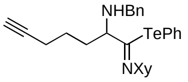
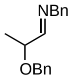
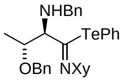
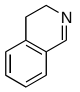
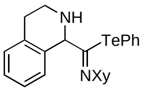
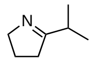
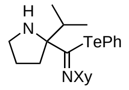
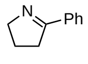
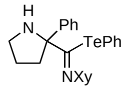
As the reaction proceeds in a group-transfer manner, the carbon-tellurium bond in the products can also be used for the diversity-oriented transformation to a variety of amino acid derivatives (Scheme 2). Thus, mercury-mediated oxidative hydrolysis of **5b** gave the *tert*-leucine amide **8** in good yield.[14] Treatment of **5b** with *n*BuLi followed by hydrolysis of the resulting imidoyl lithium afforded the α-amino imine **9**,[15] which was further hydrolyzed to the α-amino aldehyde **10**. The tributyltin hydride-mediated radical reduction of **5b** also afforded **9** in good yield.

In summary, the combination of the silyl telluride-mediated coupling reaction of imines and isonitriles and C–Te bond manipulations allows the diversity-oriented synthesis of α-amino acid derivatives. Further synthetic studies on mechanistic and synthetic aspects as well as combinatorial applications of the reaction are currently underway.



Scheme 2. Transformation of the coupling product into α-amino acids and their derivatives. Conditions: a) $Hg(OAc)_2$ (1.0 equiv), BSA (1.5 equiv), H_2O/THF, RT, 0.25 h, 94%; b) BuLi (2.2 equiv), THF, −72 °C, 0.2 h then H_3O^+, 76%; c) Bu_3SnH (1.2 equiv), AIBN (0.1 equiv), benzene, 80 °C, 2 h, 70% d) AcOH (1.2 equiv), THF, −72 °C, 78%. AIBN = azobisisobutyronitrile. Xy = 2,6-dimethylphenyl

Table 1: Three component coupling reactions with silyltelluride **1 A**, imine **2** and isonitrile **3 a**[a]

Entry	Imine	T [°C]	t [h]	Product	Yield [%]
					
1	R = H (**2 a**)	80	4	(**5 a**)	92
2	R = Me	80	4		93
3	R = OMe	80	4		88
4	R = NMe$_2$	80	4		91
5	R = CO$_2$Me	80	2		50
6		25	24		63
7		25	24		92
8		25	24		74 (72)[c]
9		25	24		67
10		25	24		68
11		25	24		77[b]
12		25	24		61
13		25	24		50
14		25	24		43

[a] The reaction was carried out by heating a solution of **1 a** (1.3 equiv), **2** (1.0 equiv) and **3 a** (2.0 equiv) in CD$_3$CN or MeCN. [b] A 76:24 mixture of the diastereomers was obtained. The major isomer is shown. [c] Yield using one equivalent of each reagent.

Experimental Section

Typical experimental procedure: Synthesis of **5 b**. A solution of **1 B** (3.69 g, 10.0 mmol), *N*-(*tert*-butylmethylidene)benzylamine (**2 b**) (1.76 g, 10.0 mmol), and **3** (1.31 g, 10.0 mmol) in acetonitrile (10.0 mL) was stirred at room temperature for 24 h. After removal of the solvent, purification of the crude mixture by flash column chromatography (silica gel: 270 g, elution with 3 % ethyl acetate in hexane) gave **5 b** in 72 % yield as a pale yellow solid (3.68 g, 7.20 mmol); m.p. 53.9–54.3 °C; IR (KBr): $\tilde{\nu} = 2950$, 1609, 1588, 1464, 847, 804, 764, 731, 695 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$): $\delta = 1.04$ (s, 9 H), 2.27 (s, 6 H), 2.39 (br s, 1 H), 3.26 (s, 1 H), 3.77 (d, $J = 12.9$ Hz, 1 H), 4.26 (d, $J = 12.9$ Hz, 1 H), 6.90–6.99 (m, 2 H), 6.99–7.05 (m, 1 H), 7.13 (t, $J = 7.5$ Hz, 2 H), 7.23–7.42 (m, 6 H), 7.70–7.77 ppm (m, 2 H); ^{13}C NMR (75 MHz, CDCl$_3$): $\delta = 18.94$, 19.11, 27.28, 35.99, 53.18, 71.43, 114.17, 124.55, 125.75, 126.09, 126.91, 128.00, 128.27, 128.65, 129.17, 140.80, 141.92, 150.59, 170.06 ppm; HRMS (FAB) m/z: calcd for $C_{27}H_{33}N_2Te$ $[M+H]^+$, 515.1706, found 515.1699; elemental analysis calcd for $C_{27}H_{32}N_2Te$: C 63.32, H 6.30, N 5.47, found: C 63.08, H 6.33, N 5.33.

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