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Introduction of Functionalized C1, C2, and C3 Units to Imines through the Dimethylzinc−Air-Initiated Radical Addition

Ken-ichi Yamada, Yasutomo Yamamoto, Masaru Maekawa, and Kiyoshi Tomioka*

Graduate School of Pharmaceutical Sciences, Kyoto University, Yoshida Sakyo-ku, Kyoto 606-8501, Japan

tomioka@pharm.kyoto-u.ac.jp

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Introduction of functionalized C1, C2, and C3 units to imines was achieved by using the dimethylzinc−air-initiated α-alkoxyalkyl radical addition as a key reaction. The addition to a $C=N$ double bond chemoselectively occurred in the presence of a $C=O$ double bond, which is one of the advantages of this radical addition reaction over ionic addition reactions.

Introduction

We have recently reported the radical addition of ethers to imines initiated by dimethylzinc−air.[1,2] In the presence of dimethylzinc and air oxygen,[3] α-alkoxyalkyl radicals are directly generated from ethers through hydrogen atom abstraction, and the resulting radicals undergo addition to imines in high yields.[4−7] We have also reported the distinctive chemoselectivity of this reaction: the addition to $C=N$ double bonds preferentially takes place rather than that to $C=O$ double bonds.[1b] As a part of continuing studies toward the synthetic utility of this reaction, we have examined the possibility of using this reaction for the introduction of versatile oxygen-functionalized carbon units to imine $C=N$ double bonds. The chemoselectivity as well as the mild conditions of this reaction are advantageous.

Results and Discussion

Direct C1 Unit Introduction. We first examined 4,4,5,5-tetramethyl-1,3-dioxolane (**2**) as a candidate for an oxygen-functionalized C1 unit (Scheme 1). The reaction of benzaldehyde tosylimine **1a** and **2** smoothly proceeded by the action of dimethylzinc (3 equiv) and air to give adduct **3** in satisfactorily high 81% yield after 18 h at room temperature. However, the hydrolysis of the tetramethylethylene acetal moiety under standard acidic conditions failed to proceed, resulting in quantitative recovery of **3**. Consumption of **3** was observed only in harsh refluxing 6 M HCl−dioxane conditions to give tosylamide (**4**) in 53% yield without the production of the desired product of hydrolysis of the acetal.[8]

tert-Butyl methyl ether (MTBE) was also examined as a candidate for a functionalized C1 unit.[4b,6i] A mixture

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* Corresponding author.

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(4) Addition of α-alkoxyalkyl radicals to $C=N$ double bonds: (a) Fernández, M.; Alonso, R. *Org. Lett.* **2003**, *5*, 2461−2464. (b) Torrente, S.; Alonso, R. *Org. Lett.* **2001**, *3*, 1985−1987. (c) Alves, M. J.; Gilchrist, T. L.; Sousa, J. H. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1305−1310. (d) Ishida, A.; Sugita, D.; Itoh, Y.; Takamuku, S. *J. Am. Chem. Soc.* **1995**, *117*, 11687−11694. (e) Citterio, A.; Filippini, L. *Synthesis* **1986**, *6*, 473−474.

(5) Addition of α-alkoxyalkyl radicals to $C=O$ double bonds: (a) Yoshimitsu, T.; Makino, T.; Nagaoka, H. *J. Org. Chem.* **2003**, *68*, 7548−7550. (b) Yoshimitsu, T.; Arano, Y.; Nagaoka, H. *J. Org. Chem.* **2003**, *68*, 625−627. (c) Yoshimitsu, T.; Tsunoda, M.; Nagaoka, H. *Chem. Commun.* **1999**, 1745−1746. (d) Mikolajczyk, M.; Graczyk, P.; Kabachnik, M. I.; Baranovt, A. P. *J. Org. Chem.* **1988**, *53*, 2859−2861.

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(7) Other reactions of α-alkoxyalkyl radicals: (a) Inoue, A.; Shinokubo, H.; Oshima, K. *Synlett* **1999**, 1582−1584. (b) Jung, J. C.; Choi, H. C.; Kim, Y. H. *Tetrahedron Lett.* **1993**, *34*, 3581−3584.

(8) Benzylidene-4,4,5,5-tetramethyl-1,3-dioxolane, which would be formed by the elimination of **4**, was not detected in the crude product.

10.1021/jo035496s CCC: $27.50

SCHEME 1. Introduction of C1 Units to Imine 1a and Conversion of Adduct 5 to Alcohol 6

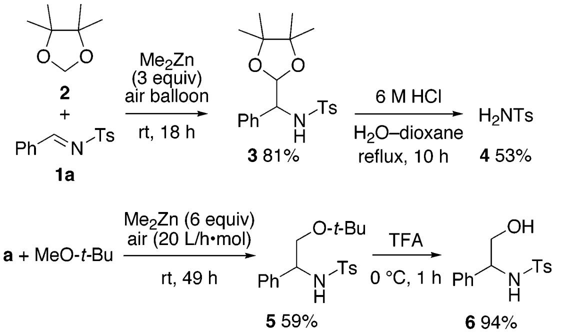
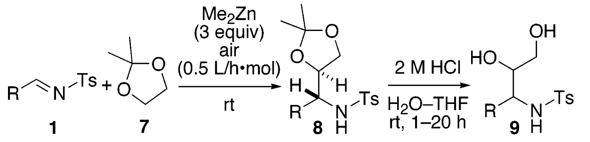


TABLE 1. Introduction of C2 Unit 7 to Imines 1 and Conversion of Adducts 8 to Diols 9



entry	1	R	8	time, h	yield, %	dr[a]	9	yield,[b] %
1	**1a**	Ph	**8a**	1	91	4:1	(*RS,RS*)-**9a** (*RS,SR*)-**9a**	quant 99
2	**1b**	4-ClC_6H_4	**8b**	1	91	4:1	**9b**	93
3	**1c**	4-$MeOC_6H_4$	**8c**	15[c]	94	4:1	**9c**	93
4	**1d**	4-MeC_6H_4	**8d**	20	84	4:1	**9d**	95
5	**1e**	2-MeC_6H_4	**8e**	20	88	9:1	**9e**	94
6	**1f**	3-pyridyl	**8f**	1.5	87	3:1	**9f**	98
7	**1g**	2-furyl	**8g**	2.5	52	7:3	**9g**	86
8	**1h**	$Ph(CH_2)_2$	**8h**	1	78	1:1		
9	**1i**	*c*-C_6H_{11}	**8i**	1	81	3:2		

[a] Determined by ^1H NMR of the crude products. See ref 9. [b] The dr of **9** was the same as that of the starting **8** (entries 2–7). [c] Me_2Zn (6 equiv) was used.

of dimethylzinc (6 equiv) and *N*-tosylimine **1a** in MTBE was stirred for 49 h at room temperature under continuous air stream through a syringe needle (20 L/(h•mol)). Adduct **5** was obtained in 59% yield, and the conversion to alcohol **6** was successfully achieved in 94% yield by treatment of TFA. Thus, MTBE was found to be the best ether for the direct introduction of a C1 unit, though the C1 unit introduction was also realized in higher yield by the transformation of C2-unit-introduced products (vide infra).

Direct C2 Unit Introduction. We then examined introduction of a C2 unit and found that 2,2-dimethyl-1,3-dioxolane (**7**)[5d,6j] was an excellent functionalized C2 unit for this purpose. The reaction of **1a** and **7** was completed for 1 h with dimethylzinc (3 equiv) and air (0.5 L/(h•mol)) to give adduct **8a** in 91% yield with a diastereomer ratio (dr)[9] of 4:1 (Table 1, entry 1). The diastereomers were separated by silica gel column chromatography and each was hydrolyzed in 2 M HCl–THF at room temperature to give a quantitative amount of diols (*RS*,*RS*)- and (*RS*,*SR*)-**9a**[10] with the established stereochemistry from the major and minor isomer of **8a**, respectively. Consequently, the stereochemistry of the major isomer was assigned to be (*RS*,*RS*), whose structure is illustrated as structure **8** in Table 1.

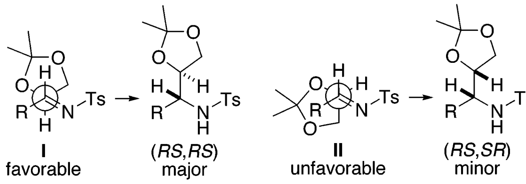
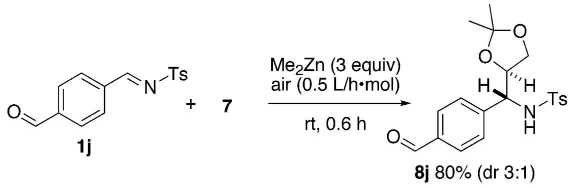


FIGURE 1. Rationale of the observed diastereoselectivity.

SCHEME 2. Chemoselective Addition of C2 Unit 7 to Imino-aldehyde 1j



Various tosylimines **1** are compatible with the reaction. The reaction with **1b** having an electron-withdrawing chloro group at the 4-position of the phenyl ring (entry 2) or **1c** and **1d** having electron-donating 4-methoxy and 4-methyl groups (entries 3 and 4) gave the corresponding adducts **8b**–**d** with a dr of 4:1 in 91%, 94%, and 84% yields, respectively. The reaction with sterically hindered 2-methylbenzaldehyde tosylimine **1e** proceeded without problem, giving **8e** in 88% yield with a dr of 9:1 (entry 5). 2-Pyridyl and 2-furyl imines **1f** and **1g** with arylheterocycles were also applicable to the reaction, giving adducts **8f** and **8g** in 87% and 52% yields with a dr of 3:1 and 7:3, respectively (entries 6 and 7). It is worthy to note that linear and cyclic aliphatic imines **1h** and **1i** were also good substrates for this reaction to provide the corresponding adducts **8h** and **8i** with a dr of 1:1 and 3:2 in 78% and 81% yields, respectively (entries 8 and 9). The acetals **8a**–**g** were hydrolyzed to the corresponding diols **9a**–**g** in high yields (86% to quantitative).

Diastereoselectivity in the reaction with cyclohexyl imine **1i** having a tertiary carbon at the α-position was better (3:2, entry 9) than that with linear aliphatic imine **1h** having a methylene carbon at the α-position (1:1, entry 8), and that with **1e** having an ortho-substituted phenyl group (9:1, entry 5) was better than those with other aromatic imines **1** (7:3–4:1, entries 1–4, 6, and 7), suggesting that the bulkiness of substituents on imines is one of the stereocontrolling factors. One plausible explanation for these results is illustrated in Figure 1. The reaction would proceed via transition state **I** or **II** where the dipole–dipole repulsion is minimized. Transition state **I** leading to the major (*RS*,*RS*)-isomer is preferred to transition state **II** because of the absence of the repulsion between the substituent R and the overlapping cyclic ether. Bulkier R makes transition state **II** more unfavorable to result in higher selectivity.

One of the advantages of this radical addition reaction over polar nucleophilic addition is the chemoselective preference for a C=N double bond to a C=O double bond (Scheme 2). Thus, imino-aldehyde **1j** having both C=O

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[9] The diastereomer ratios were determined by ^1H NMR analysis of the crude products, comparing integral areas of the amine α-proton signals of both isomers which usually appear in 4.0–5.0 ppm in $CDCl_3$.

[10] The relative configuration of **9a** was determined by the comparison of their melting points, 126–127 °C for the major isomer and 120–120.5 °C for the minor isomer, to that reported for (*RS*,*SR*)-**9a**, 118–120 °C, in: Sharpless, K. B.; Chong, A. O.; Oshima, K. *J. Org. Chem.* **1976**, *41*, 177–179.

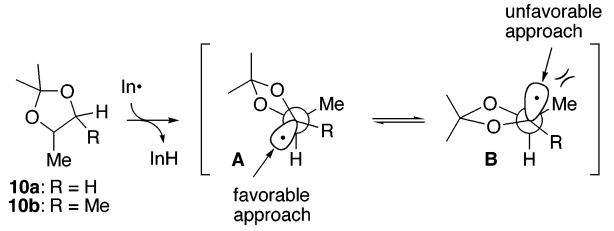
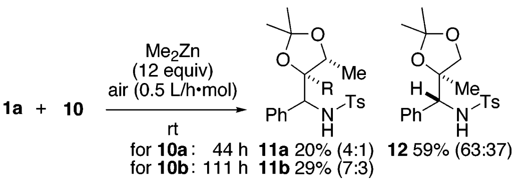


FIGURE 2. Basic strategy of the stereocontrolled reaction with chiral ethers **10**.

SCHEME 3. Diastereoselective Addition of Ethers 10 to Imine 1a



and C=N double bonds was subjected to the radical addition reaction of C2 unit **7** giving the C=N double bond selective reaction product, amino aldehyde **8j**, with a dr of 3:1 in 80% yield. No products derived from addition to the C=O double bond were observed.

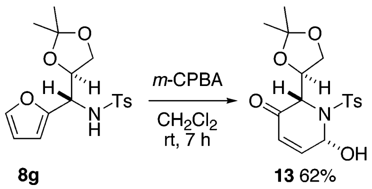
Attempts toward Asymmetric Synthesis. We directed our attention to a development of an asymmetric radical reaction employing ether **10** (Figure 2). The radical generated from **10** would exist as a mixture of two rapidly exchangeable conformers **A** and **B**.[11] Steric repulsion by the methyl group next to the carbon radical prefers the addition of **A** to that of **B**.

The reaction of **1a** with **10a** was slower than that with **7**, and required 12 equiv of dimethylzinc and 44 h for complete consumption of **1a** (Scheme 3). Product **11a** was obtained in 20% yield as a 4:1 mixture of two diastereomers arising from the stereochemistry of the benzylic carbon,[12] although the main product was regioisomer **12** (59%, dr 63:37). It is noteworthy that the addition of conformer **A** predominantly occurred and no product from conformer **B** was detected: the stereocontrol at the radical carbon was almost perfect. Furthermore, it is also remarkable that an oxygenated quaternary carbon was created in **12**.

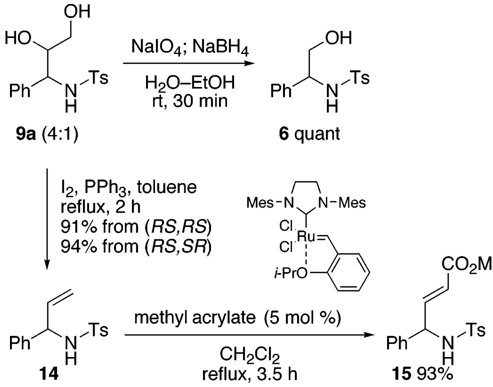
The reaction of **1a** with **10b** (a 3:2 mixture of *dl* and *meso*) for 111 h gave adduct **11b** in 29% yield with a 7:3 ratio of the diastereomers resulting from the stereochemistry of the benzylic carbon (Scheme 3).[12] Again, the addition of the ether radical to the imine C=N double bond took place so as to avoid the steric repulsion by the adjacent methyl group, indicating the possibility of stereoselective construction of contiguous three chiral carbon centers.

Transformation of C2 Addition Products 8. Conversion of C2 addition products **8** to several useful structures shows their versatility. Aza-Achmatowich rearrangement converted the major isomer of furan **8g** to dihydropyridone **13**[13] in a single step, providing a useful building block for nitrogen-containing compounds such as amino sugars[14] (Scheme 4).

SCHEME 4. Aza-Achmatowich Rearrangement of Furan 8g to Dihydropyridone 13



SCHEME 5. Conversion of Diols 9a to Alcohol 6, Olefin 14, and Butenoate 15



Although the direct introduction of a C1 unit was less satisfactory, C1-unit-introduced product **6** was easily derived from C2-addition product **9**. Diols **9a** (dr 4:1) were transformed to alcohol **6** in quantitative yield through the oxidative cleavage with sodium periodate followed by sodium borohydride reduction (Scheme 5). Thus, oxygen-functionalized C1-introduced product **6** was prepared from **1a** in 91% overall yield.

The deoxygenation[15] of both (*RS*,*RS*)- and (*RS*,*SR*)-**9a** gave olefin **14** in 91% and 94% yield, respectively. The cross olefin metathesis of **14** with methyl acrylate in the presence of the Hoveyda-Grubbs' catalyst[16] (5 mol %) afforded butenoate **15** (93%), which is a functionalized C3-unit-introduced product.

Direct C3 Unit Introduction. While introduction of a C3 unit was easily attainable by the manipulation of C2-unit-introduced product **9** as shown above, direct introduction of a functionalized C3 unit was also examined with 2,2-dimethyl-1,3-dioxane (**16**) as a radical precursor to give adduct **17** (dr 53:47) in 33% yield after

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[11] A carbon radical having a π-donor substituent, such as an α-alkoxyalkyl radical, favors a pyramidal structure: (a) Bernard, F.; Cherry, W.; Shaik, S.; Epiotis, N. D. *J. Am. Chem. Soc.* **1978**, *100*, 1352–1356. (b) Krusic, P. J.; Bingham, R. C. *J. Am. Chem. Soc.* **1976**, *98*, 230–232.

[12] The relative configuration (*RS*,*RS*) of the substituents on the dioxolane ring was confirmed by the nOe between the 5-methyl protons and the methine proton at the 4-position for **11a** or the 4-methyl protons for **11b**.

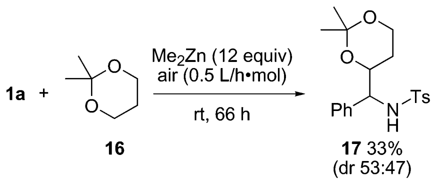
[13] The relative configuration of **13** was tentatively assigned as shown based on this precedent: Harris, J. M.; Padwa, A. *Org. Lett.* **2002**, *4*, 2029–2031.

[14] (a) Haukaas, M. H.; O'Doherty, G. A. *Org. Lett.* **2001**, *3*, 401–404. (b) Koulocheri, S. D.; Magiatis, P.; Skaltsounis, A.-L.; Haroutounian, S. A. *Tetrahedron* **2000**, *56*, 6135–6141. (c) Yang, C.-F.; Xu, Y.-M.; Liao, L.-X.; Zhou, W.-S. *Tetrahedron Lett.* **1998**, *39*, 9227–9228. For a review, see: (d) Ciufollini, M. A.; Hermann, A. Y. W.; Dong, Q.; Shimizu, T.; Swaminathan, S.; Xi, N. *Synlett* **1998**, 105–114. See also ref 13.

[15] (a) Garegg, P. J.; Samuelsson, B. *Synthesis* **1979**, 469–470. (b) Mereyala, H. B.; Gadikota, R. R.; Sunder, K. S.; Shailaja, S. *Tetrahedron* **2000**, *56*, 3021–3026.

[16] Kingsbury, J. S.; Harrity, J. P. A.; Bonitatebus, P. J., Jr.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1999**, *121*, 791–799.

SCHEME 6. Direct Introduction of the C3 Unit to Imine 1a



66 h (Scheme 6). High-yield formation of butenoate **15** from **9a** is thus superior to the direct introduction of **16**.

Conclusion

We have developed a new methodology to introduce oxygen-functionalized C1, C2, and C3 units to imines. The products were easily transformed to potential building blocks for nitrogen-containing compounds such as amino alcohols, aminoalkenoate, and a dihydropyridone derivative. The characteristic of this reaction is its preference for C=N to C=O double bonds. A substrate having both C=O and C=N double bonds undergoes chemoselective addition to the C=N double bond predominantly without protection of the C=O double bond.

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Supporting Information Available: Experiment procedure and the characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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