Tetrahedron Letters 50 (2009) 3547–3549

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Allylic substitution on the pyran ring

Tomonori Hyodo, Yuji Katayama, Yuichi Kobayashi *

Department of Biomolecular Engineering, Tokyo Institute of Technology, Box B52, Nagatsuta-cho 4259, Midori-ku, Yokohama 226-8501, Japan

ARTICLE INFO

Article history:
Received 12 January 2009
Revised 2 March 2009
Accepted 5 March 2009
Available online 9 March 2009

ABSTRACT

Allylic substitution of pyrans **10** and **15** possessing the picolinoxy leaving group with several alkyl and aryl copper reagents derived from RMgBr and CuBr·Me_2S was studied. First, reaction of **10** with three copper reagents derived from EtMgBr (2 equiv) and different equivalents of CuBr·Me_2S (2, 1, and 0.5 equiv, respectively) was examined in THF at −20 °C for 1 h to afford *anti* S_N2' product **16a** in high yields in all cases. Under these reaction conditions Me, *i*-Pr, Ph, *o*-MeC_6H_4, and *o*-$MeOC_6H_4$ were installed on the pyran ring of **10** successfully. Similar results were also obtained with pyran **15**.

© 2009 Elsevier Ltd. All rights reserved.

Substituted pyrans are a class of biologically active compounds,[1] while such a structure has been used as a mimic of specific amino acids in peptides.[2] To install substituent on the pyran ring Claisen rearrangement,[3] BF_3-catalyzed allylation,[4] Indium-mediated reaction with carbonyl compounds,[5] Pd-catalyzed [3+2] cyclization,[6] Pd-catalyzed allylic substitution with soft nucleophiles,[7] allylic substitution with copper reagents as hard nucleophiles,[8] etc.[9] have been studied so far. Among these reactions we were attracted by the last type because various types of alkyl and aryl groups are installed in principle.[10] This possibility, however, has limitedly been studied using pyrans possessing the acetoxy and pivaloxy (*t*-$BuCO_2$) leaving groups and organocopper reagents derived from RLi and CuX to afford *anti* S_N2' products **2** in moderate to good yields[8b,c] (Fig. 1). In contrast, reaction of BTZ ethers with copper reagents derived from Grignard reagents produces *syn* or *anti* S_N2' products depending on the nature of R in $(R_2Cu)MgBr$: that is, *syn* products **3** from Me, *n*-Bu, *i*-Pr cuprates; *anti* product **2** from the Ph cuprate.[8d,e] Interestingly, the corresponding thio ethers afford *syn* S_N2' products independent of the R group in $(R_2Cu)MgBr$.

Recently, (2-Py)CO_2 has been reported by us as a new leaving group for allylic substitution with copper reagents as illustrated in Scheme 1.[11,12] Although the leaving group is quite stable for purification by chromatography, $MgBr_2$ formed in situ from R^3MgBr and CuBr·Me_2S or added from outside activates this group through chelation, thus attaining high *anti* S_N2' selectivity even with aryl and alkenyl coppers, which are less selective in the reaction with allylic esters such as acetates and pivalates due to the low reactivity.[10] With these findings in mind, we studied the allylic substitution shown in Figure 1 with a hope that the picolinates will

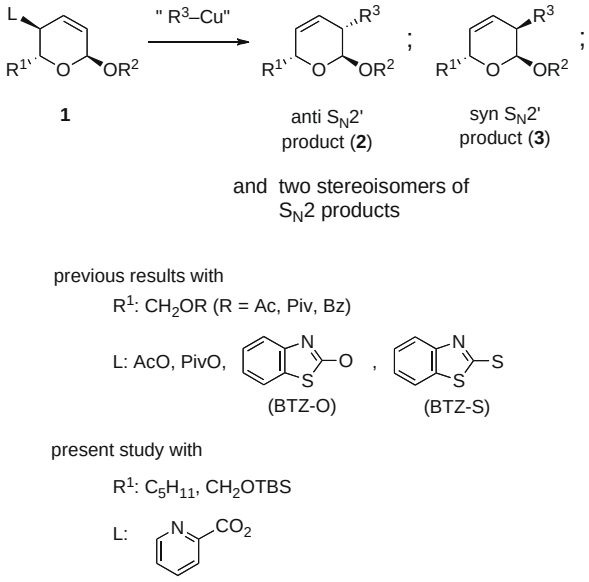
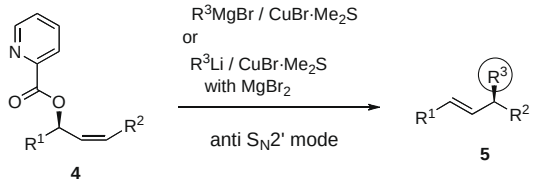


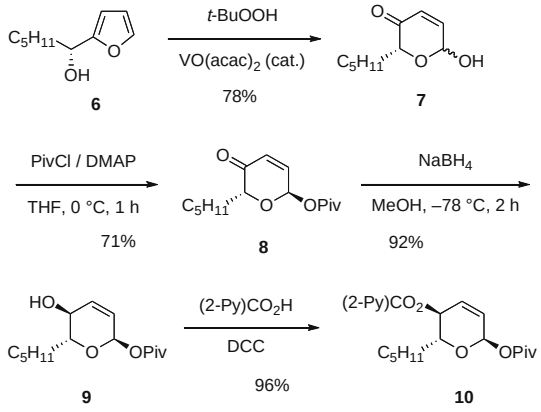
Figure 1. Allylic substitution of pyrans **1** and possible stereo- and regioisomers.



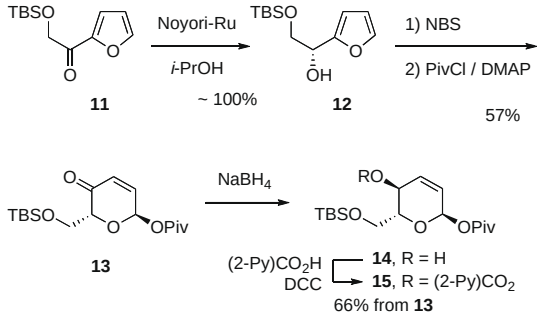
Scheme 1. Allylic substitution using (2-Py)CO_2 as a leaving group.

* Corresponding author. Tel./fax: +81 45 924 5789.
E-mail address: ykobayas@bio.titech.ac.jp (Y. Kobayashi).

0040-4039/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2009.03.018



Scheme 2. Synthesis of pyran **10**.



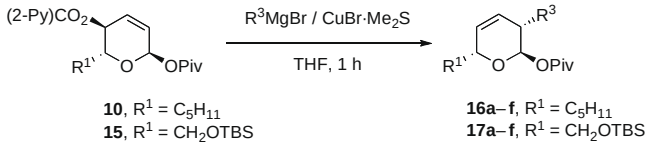
Scheme 3. Synthesis of pyran **15**.

expand the scope of the copper reagents. Herein, we present results of this study.

As typical examples we chose picolinates **10** and **15**, in which the anomeric hydroxyl group was protected as the pivaloxy group. Although the pivaloxy group constitutes another allylic moiety, we expected almost no allylic substitution at the allylic pivalate moiety because of the higher reactivity of the picolinoxy leaving group than the pivaloxy group and because of the low reactivity of this moiety to form *p*-allyl Pd complexes.[13] The picolinates were synthesized by the methods delineated in Schemes 2 and 3, respectively. In brief, alcohol **6** ($[\alpha]_D^{24}$ +14.3 (*c* 0.61, $CHCl_3$); lit. $[\alpha]_D^{25}$ +13.8 (*c* 1.07, $CHCl_3$)) was synthesized efficiently (45% yield) by the kinetic resolution of the racemic alcohol under the asymmetric epoxidation conditions according to the literature[14] (*t*-BuOOH, L-(+)-DIPT, $Ti(OPr)_4$) and oxidatively converted to pyranone hemiacetal **7** as a 2:1 anomeric mixture. The anomeric hydroxyl group of **7** was protected as a Piv ester with 93% stereoselectively under the conditions disclosed. The minor stereoisomer was separated easily by chromatography. Reduction of the ketone **8** with $NaBH_4$ in MeOH at −78 °C was stereoselective and subsequent esterification of the resulting alcohol **9** with (2-Py)CO_2H and DCC produced picolinate **10**[15] in high yield. As for picolinate **15**, asymmetric reduction of ketone **11** with the Ru diamine catalyst developed by Noyori[16] produced alcohol **12**,[17] which was 94% ee by chiral HPLC (chiral AD-H). NBS oxidation of **12** afforded an anomeric mixture of the pyranone (3:2 ratio). Subsequent Piv protection under the conditions reported[18] was quite slow (DMAP (cat.), Et_3N, CH_2Cl_2, −78 °C), whereas the conditions used above gave the Piv-protected pyranone **13** and its diastereoisomer in a 75:25 ratio. Fortunately, **13** was purified easily by chromatography. Further transformation was carried out successfully to afford picolinate **15**[15] in good yield.

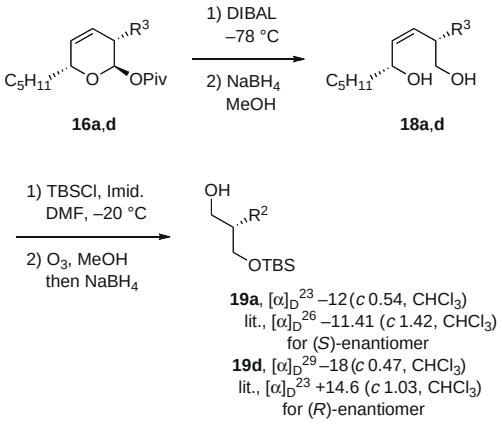
According to the previous success for *anti* S_N2' reaction with the three types of reagents derived from RMgBr and $CuBr{\cdot}Me_2S$ in the ratios of 1, 2, and 4:1, three reagents derived from EtMgBr (2 equiv) and $CuBr{\cdot}Me_2S$ (2, 1, or 0.5 equiv) at 0 °C for 30 min in THF were subjected to reaction with **10** at −20 °C for 1 h (Table 1, entries 1, 2, and 4). The product **16a** (*anti* S_N2' product) was obtained in high yields, whereas the stereoisomer of **16a** (*syn* S_N2' product), the regioisomer, and the product(s) that reacted at the α and/or γ position of the allylic pivalate moiety were not detected by ^1H NMR spectroscopy. For determination of the regio- and stereochemistries of **16a**, the product was transformed to the known compound **19a**[19] as shown in Scheme 4 since the coupling constants between the protons on the pyran ring were not decisive for determination. In another experiment at −40 °C, a mixture of **16a** and a small amount of alcohol **9** were produced (entry 3). On the basis of these results, following reactions were conducted at −20 °C for 1 h.[20] The Me and *i*-Pr copper reagents of the 2:1 ratio underwent smooth reaction to produce the desired *anti* S_N2'

Table 1
Allylic substitution of pyrans **10** and **15** with alkyl and aryl copper reagents[a]



Entry	Substrate	Reagent	R^3/Cu ratio	Temp (°C)	Major product	R^3	Isolated yield (%)
1	**10**	$EtCu{\cdot}MgBr_2$	1:1	−20	**16a**	Et	93
2	**10**	$Et_2CuMgBr{\cdot}MgBr_2$	2:1	−20	**16a**	Et	97
3	**10**	$Et_2CuMgBr{\cdot}MgBr_2$	2:1	−40	**16a**	Et	80
4	**10**	$EtMgBr/CuBr{\cdot}Me_2S$	4:1	−20	**16a**	Et	93
5	**10**	$Me_2CuMgBr{\cdot}MgBr_2$	2:1	−20	**16b**	Me	93
6	**10**	$i\text{-}Pr_2CuMgBr{\cdot}MgBr_2$	2:1	−20	**16c**	*i*-Pr	92
7	**10**	$PhCu{\cdot}MgBr_2$	1:1	−20	**16d**	Ph	94
8	**10**	$Ph_2CuMgBr{\cdot}MgBr_2$	2:1	−20	**16d**	Ph	95
9	**10**	$(o\text{-}MeC_6H_4)_2CuMgBr{\cdot}MgBr_2$	2:1	−20	**16e**	$o\text{-}MeC_6H_4$	95
10	**10**	$(o\text{-}MeOC_6H_4)_2CuMgBr{\cdot}MgBr_2$	2:1	−20	**16f**	$o\text{-}MeOC_6H_4$	92
11	**15**	$Et_2CuMgBr{\cdot}MgBr_2$	2:1	−20	**17a**	Et	80
12	**15**	$Me_2CuMgBr{\cdot}MgBr_2$	2:1	−20	**17b**	Me	94
13	**15**	$Ph_2CuMgBr{\cdot}MgBr_2$	2:1	−20	**17d**	Ph	71
14	**15**	$(o\text{-}MeC_6H_4)_2CuMgBr{\cdot}MgBr_2$	2:1	−20	**17e**	$o\text{-}MeC_6H_4$	91
15	**15**	$(o\text{-}MeOC_6H_4)_2CuMgBr{\cdot}MgBr_2$	2:1	−20	**17f**	$o\text{-}MeOC_6H_4$	89

[a] Reactions were carried out with the indicated reagent (2 equiv) at −20 °C for 1 h in THF.



Scheme 4. Transformation of **16a** and **16d** to the known compounds. R^3 for **16**, **18**, **19**: **a**, Et; **d**, Ph.

products **16b** and **16c**, respectively, in high yield (entries 5 and 6). No isomers were detected as well. However, *t*-$Bu_2CuMgBr{\cdot}MgBr_2$ afforded a complex mixture (no entry given). Next, the Ph reagents of $PhCu{\cdot}MgBr_2$ and $Ph_2CuMgBr{\cdot}MgBr_2$ were subjected to the reaction to afford **16d** in good yields (entries 7 and 8). The structure of **16d** was confirmed by transformation to the known alcohol **19d**[21] as shown in Scheme 4. Reaction with sterically more hindered reagents given in entries 9 and 10 proceeded without a hitch to afford **16e** and **16f**, respectively.

In a similar way, reaction of the other picolinate **15** with the Me, Et, and Ph copper reagents at −20 °C in THF was examined under the conditions established above to afford the corresponding products **17a**,**b**,**d** regio- and stereoselectively in high yields: cf. 50–74% yields for the BTZ ether **1**.[8e] Further experimentation with *o*-MeC_6H_4 and *o*-$MeOC_6H_4$ reagents furnished the products **17e** and **17f** efficiently.

In summary, allylic substitution with the picolinoxy leaving group was established to be an efficient method to install alkyl and aryl groups on the pyran ring. The groups investigated were Me, Et, *i*-Pr, Ph, *o*-MeC_6H_4, and *o*-$MeOC_6H_4$, and these results would be a good guideline for designing substituted pyrans.

Acknowledgments

This work was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, Sports, and Culture, Japan.

References and notes

1. (a) Thorn, S. N.; Gallagher, T. *Synlett* **1996**, 185–187; (b) Nelson, T. D.; Rosen, J. D.; Smitrovich, J. H.; Payack, J.; Craig, B.; Matty, L.; Huffman, M. A.; McNamara, J. *Org. Lett.* **2005**, *7*, 55–58; (c) Canac, Y.; Levoirier, E.; Lubineau, A. *J. Org. Chem.* **2001**, *66*, 3206–3210, and references cited therein.
2. (a) Gruner, S. A. W.; Locardi, E.; Lohof, E.; Kessler, H. *Chem. Rev.* **2002**, *102*, 491–514; (b) Montero, A.; Mann, E.; Herradón, B. *Tetrahedron Lett.* **2005**, *46*, 401–405.
3. Montero, A.; Mann, E.; Herradón, B. *Eur. J. Org. Chem.* **2004**, 3063–3073.
4. Sugawara, K.; Hashiyama, T. *Tetrahedron Lett.* **2007**, *48*, 3723–3726.
5. Norsikian, S.; Lubineau, A. *Org. Biomol. Chem.* **2005**, *3*, 4089–4094.
6. Trost, B. M.; King, S. A.; Schmidt, T. *J. Am. Chem. Soc.* **1989**, *111*, 5902–5915.
7. (a) RajanBabu, T. V. *J. Org. Chem.* **1985**, *50*, 3642–3644; (b) Dunkerton, L. V.; Euske, J. M.; Serino, A. J. *Carbohydr. Res.* **1987**, *171*, 89–107; (c) Curran, D. P.; Suh, Y.-G. *Carbohydr. Res.* **1987**, *171*, 161–191; (d) Brakta, M.; Lhoste, P.; Sinou, D. *J. Org. Chem.* **1989**, *54*, 1890–1896; (e) Engelbrecht, G. J.; Holzapfel, C. W. *Heterocycles* **1991**, *32*, 1267–1272; (f) Brescia, M. R.; Shimshock, Y. C.; DeShong, P. *J. Org. Chem.* **1997**, *62*, 1257–1263.
8. (a) Dorgan, B. J.; Jackson, R. F. W. *Synlett* **1996**, 859–861; (b) Chapleur, Y.; Grapsas, Y. *Carbohydr. Res.* **1985**, *141*, 153–158; (c) Danishefsky, S. J.; Armistead, D. M.; Wincott, F. E.; Selnick, H. G.; Hungate, R. *J. Am. Chem. Soc.* **1989**, *111*, 2967–2980; (d) Valverde, S.; Bernabé, M.; Garcia-Ochoa, S.; Gómez, A. M. *J. Org. Chem.* **1990**, *55*, 2294–2298; (e) Valverde, S.; Bernabé, M.; Gómez, A. M.; Puebla, P. *J. Org. Chem.* **1992**, *57*, 4546–4550.
9. Bussolo, V. D.; Caselli, M.; Pineschi, M.; Crotti, P. *Org. Lett.* **2003**, *5*, 2173–2176.
10. (a) Negishi, E.; Liu, F. In *Metal-catalyzed Cross-coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, 1998. Chapter 1; (b) Negishi, E.. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Wiley-VCH: Weinheim, 2002; Vol. 1; (c) Kar, A.; Argade, N. P. *Synthesis* **2005**, 2995–3022.
11. Kiyotsuka, Y.; Acharya, H. P.; Katayama, Y.; Hyodo, T.; Kobayashi, Y. *Org. Lett.* **2008**, *10*, 1719–1722.
12. Kiyotsuka, Y.; Kobayashi, Y. *Tetrahedron Lett.* **2008**, *49*, 7256–7259.
13. (a) Comely, A. C.; Eelkema, R.; Minnaard, A. J.; Feringa, B. L. *J. Am. Chem. Soc.* **2003**, *125*, 8714–8715; (b) Babu, R. S.; O'Doherty, G. A. *J. Am. Chem. Soc.* **2003**, *125*, 12406–12407.
14. (a) Kobayashi, Y.; Kusakabe, M.; Kitano, Y.; Sato, F. *J. Org. Chem.* **1988**, *53*, 1586–1587; (b) Kusakabe, M.; Kitano, Y.; Kobayashi, Y.; Sato, F. *J. Org. Chem.* **1989**, *54*, 2085–2091.
15. *Spectral data*: *Compound* **10**: $[\alpha]_D^{23}$ +79 (*c* 0.65, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.85 (t, *J* = 6.5 Hz, 3H), 1.24 (s, 9H), 1.20–1.74 (m, 8H), 4.10 (dt, *J* = 9, 2 Hz, 1H), 5.54 (dq, *J* = 9, 1.5 Hz, 1H), 5.87 (ddd, *J* = 10, 3, 2 Hz, 1H), 6.12 (dt, *J* = 10, 1 Hz, 1H), 6.33 (br s, 1H), 7.53 (ddd, *J* = 8, 5, 1 Hz, 1H), 7.89 (dt, *J* = 8, 2 Hz, 1H), 8.17 (dt, *J* = 8, 1 Hz, 1 H), 8.81 (dm, *J* = 5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0 (−), 22.6 (+), 24.7 (+), 27.1 (−), 31.4 (+), 31.5 (+), 39.0 (+), 70.3 (−), 70.7 (−), 88.0 (−), 125.5 (−), 126.4 (−), 127.3 (−), 131.1 (−), 137.1 (−), 147.6 (+), 150.1 (−), 164.7 (+), 177.4 (+); HRMS (FAB) calcd for $C_{21}H_{30}NO_5$ [(M+H)$^+$] 376.2124, found 376.2128. *Compound* **15**: $[\alpha]_D^{25}$ +49 (*c* 1.20, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ −0.02 (s, 6H), 0.83 (s, 9H), 1.22 (s, 9H), 3.79–3.85 (m, 2H), 4.21 (dt, *J* = 10, 4 Hz, 1H), 5.72 (dq, *J* = 10, 1.5 Hz, 1H), 5.87 (ddd, *J* = 10, 3, 2 Hz, 1H), 6.14 (d, *J* = 10 Hz, 1H), 6.36 (br s, 1H), 7.51 (ddd, *J* = 8, 4.5, 1 Hz, 1H), 7.87 (dt, *J* = 1.5, 8 Hz, 1H), 8.16 (dt, *J* = 8, 1 Hz, 1H), 8.79 (dm, *J* = 4.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.4 (−), 5.3 (−), 18.4 (+), 25.9 (−), 27.1 (−), 39.0 (+), 62.7 (+), 66.5 (−), 71.7 (−), 88.1 (−), 125.1 (−), 126.4 (−), 127.2 (−), 130.5 (−), 137.1 (−), 147.7 (+), 150.1 (−), 164.5 (+), 177.3 (+).
16. Fujii, A.; Hashiguchi, S.; Uematsu, N.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1996**, *118*, 2521–2522.
17. (a) Li, M.; Scott, J.; O'Doherty, G. A. *Tetrahedron Lett.* **2004**, *45*, 1005–1009; (b) Zhou, M.; O'Doherty, G. A. *Org. Lett.* **2006**, *8*, 4339–4342; (c) Zhou, M.; O'Doherty, G. A. *J. Org. Chem.* **2007**, *72*, 2485–2493.
18. (a) Harris, J. M.; Keranen, M. D.; O'Doherty, G. A. *J. Org. Chem.* **1999**, *64*, 2982–2983; (b) Harris, J. M.; Keränen, M. D.; Nguyen, H.; Young, V. G.; O'Doherty, G. A. *Carbohydr. Res.* **2000**, *328*, 17–36.
19. Ihara, M.; Takahashi, M.; Taniguchi, N.; Yasui, K.; Fukumoto, K. *J. Chem. Soc., Perkin Trans. 1* **1989**, 897–903.
20. *Typical procedure*: To an ice-cold suspension of $CuBr{\cdot}Me_2S$ (252 mg, 1.23 mmol) in THF (10 mL) was added EtMgBr (2.34 mL, 1.05 M in THF, 2.46 mmol) dropwise. After 30 min of stirring, the resulting mixture was cooled to −20 °C, and a solution of **10** (230 mg, 0.613 mmol) in THF (5 mL) was added to the mixture dropwise. The resulting mixture was stirred at −20 °C for 1 h, and diluted with hexane and saturated NH_4Cl with vigorous stirring. The crude product thus obtained was purified by chromatography on silica gel (hexane/EtOAc) to afford **16a** (168 mg, 97%): $[\alpha]_D^{22}$ +86 (*c* 0.92, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (t, *J* = 7 Hz, 3H), 0.99 (t, *J* = 7 Hz, 3H), 1.21 (s, 9H), 1.20–1.62 (m, 10H), 1.89–1.98 (m, 1H), 4.25 (br s, 1H), 5.68 (d, *J* = 11 Hz, 1H), 5.76 (ddt, *J* = 11, 5, 2 Hz, 1H), 6.01 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.3 (−), 14.1 (−), 22.6 (+), 24.5 (+), 26.4 (+), 27.1 (−), 31.9 (+), 34.8 (+), 39.0 (+), 39.4 (−), 69.3 (−), 94.2 (−), 125.3 (−), 128.2 (−), 177.3 (+).
21. Maruoka, K.; Ooi, T.; Nagahara, S.; Yamamoto, H. *Tetrahedron* **1991**, *47*, 6983–6998.