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Synthesis of Unnatural Amino Acids via Suzuki Cross-Coupling of Enantiopure Vinyloxazolidine Derivatives

Mark Sabat and Carl R. Johnson*

Department of Chemistry, Wayne State University, Detroit, Michigan 48202-3489

crj@chem.wayne.edu

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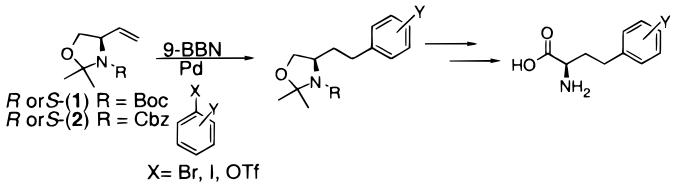
ABSTRACT



(*R* and *S*)-α-Amino alcohols and α-amino acids, including 4-methoxyhomophenylalanine, with a variety of unnatural side chains have been synthesized via palladium-catalyzed cross-coupling Suzuki reactions. The key building blocks 1 and 2, synthesized from the common achiral precursor 2-butene-1,4-diol, were made enantiopure utilizing a *Pseudomonas cepacia* lipase-catalyzed kinetic resolution. The optimal conditions for the Suzuki cross-coupling and the subsequent oxidations of the resultant α-amino alcohols are described.

Nonproteinogenic α-amino acids have been widely used as synthetic building blocks and display interesting biological properties.[1] Analogues of homophenylalanines,[2] such as 4-methoxyhomophenylalanine (**40**),[2e,3] have received particular attention as constituents of potential pharmaceuticals. A methodology to the synthesis of α-amino acids and α-amino alcohols, of both *R* and *S* epimers and containing a variety of unnatural side chains was desired. Recently Taylor and co-workers published the synthesis of unnatural α-amino acids utilizing palladium-catalyzed Suzuki cross-coupling.[4] Similar work has been the focus of this laboratory; however, the protocol disclosed in this Letter offers significant advantages in terms of coupling efficiency and diversity: specifically, the synthesis and use of (*R*)- and (*S*)-**1** and -**2**, the development of cross-coupling methodology compatible with aryl triflates and nitrogen heterocycles, and facile oxidation protocols.

Compounds **1**[5] and **2**[6] have previously been prepared and exploited as versatile intermediates. The Suzuki cross-coupling reaction of these compounds would constitute an efficient synthesis of unnatural α-amino acids through direct introduction of functional groups to the amino acid moiety. Our synthesis of (*R*)- and (*S*)-**1** and (*R*)- and (*S*)-**2** is illustrated in Scheme 1. Commercial grade *cis*-butene-1,4-diol (**3**) was converted to bis-imidate **4**.[7] Treatment of this material with $PdCl_2(CH_3CN)_2$ afforded the unexpected oxazoline **5** presumably via a π-allyl mechanism.[8] Hydrolysis

(1) (a) Sardina, F. J.; Rapoport, H. *Chem. Rev.* **1996**, *96*, 1825. (b) Duthaler, R. O. *Tetrahedron* **1994**, *50*, 1539. (c) Williams, R. M. *Synthesis of Optically Active* α*-Amino Acids*; Baldwin, J. E., Ed.; Pergamon Press: Oxford, 1989. (d) Barrett, G. C. *Chemistry and Biochemistry of the Amino Acids*; Chapman and Hall: London, 1985.

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(4) Campbell A. D.; Raynham T. M.; Taylor R. J. K. *Tetrahedron Lett.* **1999**, *40*, 5263.

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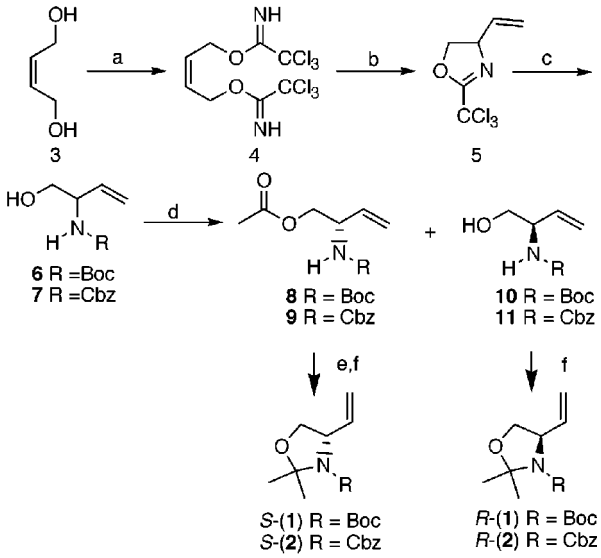
Scheme 1[a]



[a] (a) CCl_3CN, KH, 90−93%; (b) $PdCl_2(CH_3CN)_2$, THF, 85%; (c) i. 6 N HCl; ii. Boc_2O (**6**), Cbz_2O (**7**), 55%-65% (two steps); (d) PS-30 lipase, isopropenyl acetate, 38−46% (94%-99% ee); (e) KCN, 93% MeOH; (f) DMP, acetone, $BF_3{\cdot}Et_2O$, quantitative.

of the somewhat volatile **5** proceeded best under acidic conditions. Subsequent protection of the resultant amine salt with either Boc_2O or Cbz_2O[10] under biphasic conditions afforded compounds **6**[11] or **7**, respectively.[12] Kinetic resolutions of these compounds were achieved with *Pseudomonas cepecia* (Amano PS-30) lipase in CH_2Cl_2/isopropenyl acetate. For the *N*-Boc protected **6**, the kinetic resolution was stopped at 50% completion to afford **10** in 46% chemical yield with $[\alpha]^{20}_D$ −28.5 (*c* 1.0, $CHCl_3$) [lit.[5i] $[\alpha]^{25}_D$ −30.5 (*c* 1.2, $CHCl_3$)]. Treatment of **8** with KCN followed by 2,2-dimethoxypropoane (DMP) afforded *S*-(**1**), $[\alpha]^{20}_D$ −17.0 (*c* 1.4, $CHCl_3$) [lit.[5i] $[\alpha]^{20}_D$ −17.1 (*c* 1.2, $CHCl_3$)]. Similar treatment of **10** with DMP resulted in (*R*)-**1**, $[\alpha]^{20}_D$ +17.2 (*c* 1.2, $CHCl_3$). The kinetic resolution of the *N*-Cbz protected **7** proved more difficult and required termination at 40% conversion to obtain **11**, or at 60% conversion to obtain **9** with high enantioenrichment. Compound **11** displayed $[\alpha]^{20}_D$ −32.3 (*c* 1.0, $CHCl_3$) [lit.[12g] $[\alpha]^{25}_D$ −32.1 (*c* 3.1, $CHCl_3$)]. Treatment of **9** with KCN resulted in the epimer of **11** with $[\alpha]^{20}_D$ +31.2 (*c* 1.0, $CHCl_3$). The analogous (*S*)-**2** and (*R*)-**2** were obtained by similar treatment with DMP.

With the key building blocks **1** and **2** in hand, we embarked on the investigation of conditions for hydroboration of **1** and coupling with *p*-bromoanisole (Table 1) en route to 4-methoxyhomophenylalanine (**40**). Hydroboration of **1** in THF at rt proved to be exceedingly slow, and considerable starting material was present even after 24 h. However, when the reaction was run in toluene at 80 °C, the starting material disappeared completely within 15−30 min (entry 6).

Table 1. Hydroboration Using 9-BBN and Suzuki Cross-Coupling Studies of Compound **1** with **12**[13]

entry	hydroboration conditions	Pd cat.	coupling conditions	yield of **12a** (%)
1	THF, rt	*a*	Cs_2CO_3, rt	39
2	THF, rt	*a*	K_2CO_3, DMF, rt	25
3	THF, 67 °C	*a*	K_3PO_4, DMF, rt	29
4	THF, rt	*a*	3.2 N NaOH, 55 °C	66
5	THF, 67 °C	*b*	3.2 N NaOH, 80 °C	72
6	toluene, 80 °C	*b*	3.2 N NaOH, 99 °C	94
7	toluene, 67 °C	*b*	CsF, 88 °C	78
8	toluene, 80 °C	*b*	3 N NaOH, 80 °C	80
9	toluene, 80 °C	*b*	K_3PO_4, DMF, 100 °C	75
10	toluene, 80 °C	*b*	K_2CO_3, DMF, 100°C	56

[a] 5 mol % of $PdCl_2(dppf)_2$. [b] 3 mol % of $Pd(PPh_3)_4$.

With this satisfactory result, a wide variety of cross-coupling conditions were explored (Table 1). Our experiments indicate that a biphasic toluene/3.2 N NaOH system

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(6) Reginato, G.; Mordini, A.; Capperucci, A.; Degl'Innocenti, A.; Manganiello, S. *Tetrahedron* **1998**, *54*, 10217.

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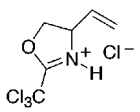
(8) In our hands Overman rearrangement of the bisimidate **4** under reported conditions[7a] resulted in incomplete conversion of starting material. Under more forceful thermal rearrangement conditions, significant losses were incurred due to charring and the formation of **5**·HCl



which sublimed at 180 °C. The structure of this material was verified by treatment of **5** with a dry ether solution of HCl which yielded a crystalline product with identical spectroscopic properties. Overman rearrangement (heating, K_2CO_3 to neutralize acidic species)[9] likewise resulted in only partial conversion of starting material **4**.

(9) Nishikawa, T.; Asai, M.; Ohyabu, N.; Isobe, M. *J. Org. Chem.* **1998**, *63*, 188.

(10) Sennyey, G.; Barcelo, G.; Senet, J. *Tetrahedron Lett.* **1986**, *27*, 5375.

(11) (a) Horikawa, M.; Hashimoto, K.; Shirahama, H. *Tetrahedron Lett.* **1993**, *34*, 331. (b) Kurokawa, N.; Ohfune, Y. *Tetrahedron* **1993**, *49*, 6195. (c) Ohfune, Y.; Kurokawa, N. *Tetrahedron Lett.* **1984**, *25*, 1071. (d) Crisp, G. T.; Gebauer, M. G. *Tetrahedron* **1996**, *52*, 12465. (e) Naito, T.; Ikai, M.; Shirakawa, M.; Fujimoto, K.; Ninomiya, I.; Kiguchi, T. *J. Chem. Soc., Perkin Trans. 1* **1994**, *7*, 773. (f) Ohfune, Y.; Kurokawa, N. *Tetrahedron Lett.* **1984**, *25*, 1587. (g) Matsunaga, H.; Ishizuka, T.; Kunieda, T. *Tetrahedron* **1997**, *53*, 1275. (h) Kiguchi, T.; Ikai, M.; Shirakawa, M.; Fujimoto, K.; Ninomiya, I.; Naito, T. *J. Chem. Soc., Perkin Trans. 1* **1998**, *5*, 893. (i) Naito, T.; Shirakawa, M.; Ikai, M.; Ninomiya, I.; Kiguchi, T. *Recl. Trav. Chim. Pays-Bas* **1996**, *115*, 13. (j) See also refs 5a, 5b, 5c, 5d, 5g, and 5i.

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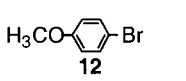
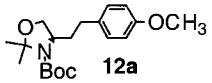
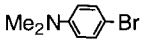
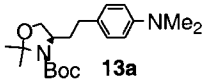
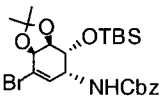
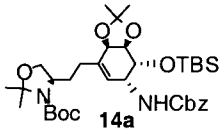
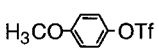
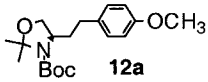
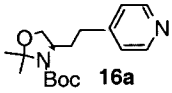
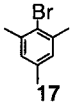
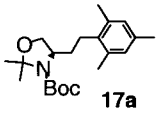
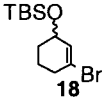
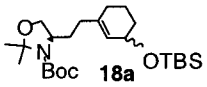
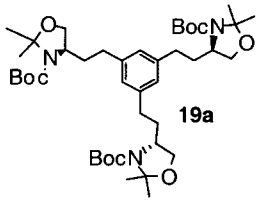
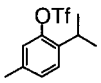
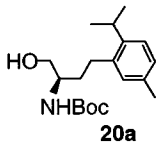
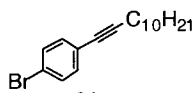
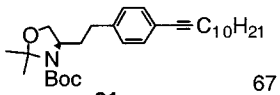
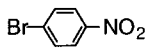
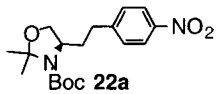
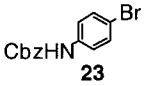
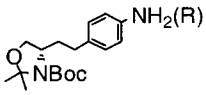
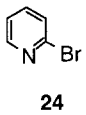
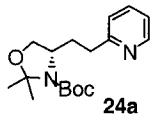
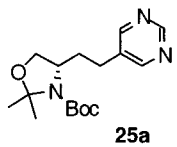
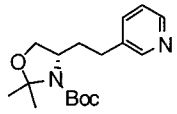
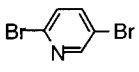
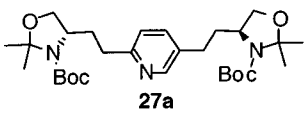
Table 2. Suzuki Coupling of (*R* and *S*)-3-(*tert*-Butoxycarbonyl)-2,2-dimethyl-4-vinyloxazolidine

entry	coupling partner	product	yield (%)
1	 **12**	 **12a**	94
2	 **13**	 **13a**	85
3	 **14**	 **14a**	87
4	 **15**	 **12a**	85
5	 **16**	 **16a**	82
6	 **17**	 **17a**	77
7	 **18**	 **18a**	75
8	 **19**	 **19a**	74
9	 **20**	 **20a**	72[a]
10	 **21**	 **21a**	67
11	 **22**	 **22a**	36
12	 **23**	 **23a** R=H, **23b** R=Cbz	78[b]
13	 **24**	 **24a**	66
14	 **25**	 **25a**	64
15	 **26**	 **26a**	63
16	 **27**	 **27a**	61

[a] PPTS in MeOH. [b] Chromatographically separable 1:1 mixture.

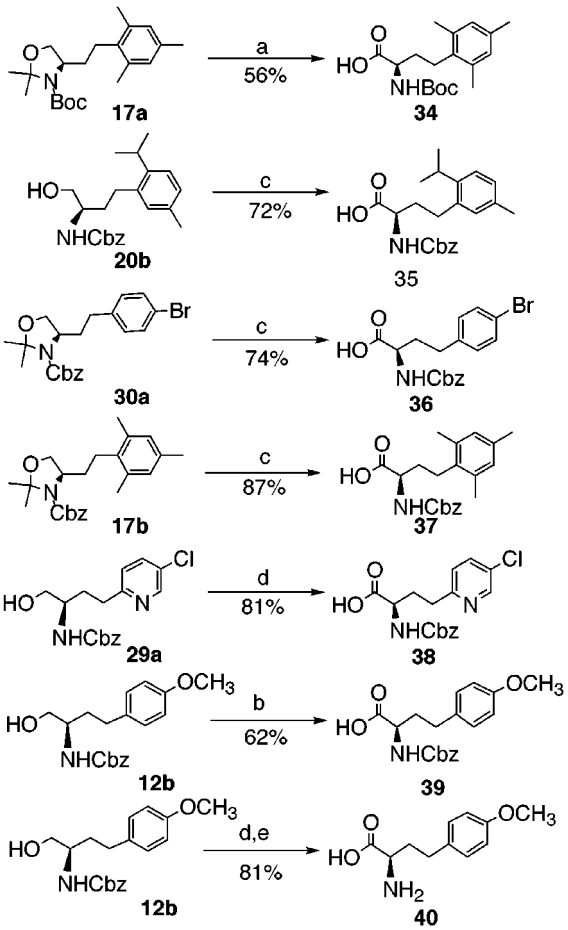
at elevated temperature and with $Pd(PPh_3)_4$ as catalyst resulted in maximum yields. Under these reaction conditions a variety of aryl halides and triflates including nitrogen heterocyles[13c] underwent Suzuki cross-coupling with good to excellent yields (Table 2).

With a variety of protected chiral amino alcohol derivatives in hand, ways to convert these to amino acids were sought. Compounds **12a** and **17a** were chosen as representative examples (Scheme 2). The isopropylidene moiety was first removed using PPTS. Subsequent oxidation with various agents including PDC,[14a] Jones,[14b] O_2/Pt,[14c] TPAP,[14d] and CrO_3/H_5IO_6[14e] gave either no reaction or a complex mixture of products. TEMPO[14h] proved to be a capricious oxidant which afforded no reaction in acetone[14i] but delivered the aldehyde smoothly in toluene/H_2O;[14g] subsequent oxidation by $NaClO_2$ resulted in a modest yield of amino acid. A two-step procedure consisting of Sharpless $RuCl_3$ oxidation[14i] to the aldehyde stage followed with $NaClO_2$ treatment to obtain the amino acid **34** gave the best result.[14f] However, even these conditions resulted in modest yields and were not general. As a more robust system was deemed necessary, the *N*-Cbz-protected analogues (Table 3) were examined. Compounds

(13) (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457. (b) Miyaura, N.; Ishiyama, T.; Sasaki, H.; Ishikawa, M.; Satoh, M.; Suzuki, A. *J. Am. Chem. Soc*. **1989**, *111*, 314. (c) Watanabe, T.; Miyaura, N.; Suzuki, A. *Synlett* **1992**, 207. (d) Ishikura, M.; Kamada, M.; Terashima, M. *Synthesis* **1984**, 936. (e) Wright, S. W.; Hageman, D. L.; McClure, L. D. *J. Org. Chem*. **1994**, *59*, 6095.

(14) (a) Matsunaga, H.; Ishizuka, T.; Kunieda, T. *Tetrahedron* **1997**, *53*, 1275. (b) Dondoni, A.; Marra, A.; Massi, A. *Chem. Commun.* **1998**, 1741. (c) Maurer, P. J.; Takahata, H.; Rapoport, H. *J. Am. Chem. Soc.* **1984**, *106*, 1095. (d) Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994**, 639. (e) Zhao, M.; Li, J.; Song, Z.; Desmond, R.; Tschaen, D. M.; Grabowski, E. J. J.; Reider, P. J. *Tetrahedron Lett.* **1998**, *39*, 5323. (f) Lubell, W. D.; Jamison, T. F.; Rapoport, H. *J. Org. Chem*. **1990**, *55*, 3511. (g) Leanna, M. R.; Sowin, T. J.; Morton, H. E. *Tetrahedron Lett.* **1992**, *33*, 5029. (h) de Nooy, A. E. J.; Besemer, A. C.; van Bekkum, H. *Synthesis* **1996**, 1153. (i) Reddy, K. L.; Sharpless, K. B. *J. Am. Chem. Soc.* **1998**, *120*, 1207.

Scheme 2[a]



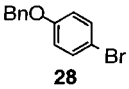
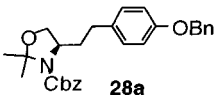
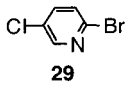
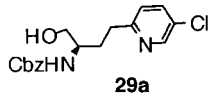
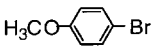
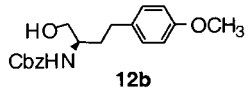
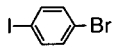
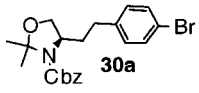
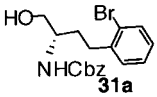
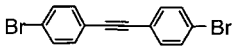
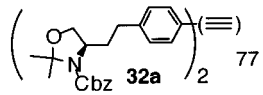
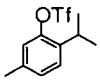
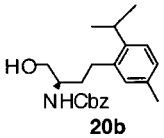
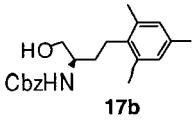
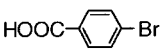
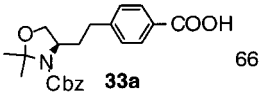
[a] (a) i. PPTS, MeOH, 24 h; ii. $RuCl_3$, H_5IO_6, CCl_4/CH_3CN; (b) i. TEMPO, NaOCl; ii. $NaClO_2$; (c) 1 M Jones reagent; (d) i. Dess−Martin/THF; ii. $NaClO_2$, NaH_2PO_4; (e) H_2, Pd/C.

17b, 20b, and **30a** were oxidized efficiently with 1 N Jones reagent.[14b] These conditions, however, afforded low yields in the cases of analogues protected with *N*-Boc or analogues containing activated aromatic rings such as **29a** and **12a/b**. Only analogues with alkyl-substituted aromatic groups were stable to the 1 N Jones reagent.

Dess−Martin oxidation of compound **29a** to the aldehyde stage followed by $NaClO_2$ treatment afforded the optically pure amino acid **38** in excellent yield. Compound **12b** after identical oxidation was fully deblocked to afford 4-methoxyhomophenylalanine (**40**) in excellent yield: $[\alpha]^{20}_D$ −43.4 (*c* 0.1, 5 M HCl) [lit.[3a] for (*S*)-**40** $[\alpha]^{25}_D$ +42.2 (*c* 0.1, 5 M HCl)].

In summary, a concise method for the preparation of diverse α-amino alcohols and α-amino acids in both enantiomeric series from readily available achiral starting materials has been developed. Included in the analogues is 4-methoxyhomophenylalanine, a compound of current interest. The precursor vinyl amino alcohols and vinyl oxazolidines were obtained via lipase-catalyzed kinetic resolutions. Key in this convergent approach was Pd-mediated Suzuki cross-coupling.

Table 3. Suzuki Coupling of (*R* and *S*)-3-(Benzyloxycarbonyl)-2,2-dimethyl-4-vinyloxazolidine

entry	coupling partner	product	yield (%)
1	 **28**	 **28a**	89
2	 **29**	 **29a**	81[a]
3	 **12**	 **12b**	71[a]
4	 **30**	 **30a**	80
5	 **31**	 **31a**	81[a]
6	 **32**	 **32a**	77
7	 **20**	 **20b**	73[a]
8	 **17**	 **17b**	68[a]
9	 **33**	 **33a**	66

[a] HCl in MeOH, 24 h.

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Supporting Information Available: Experimental procedures and full characterization for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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