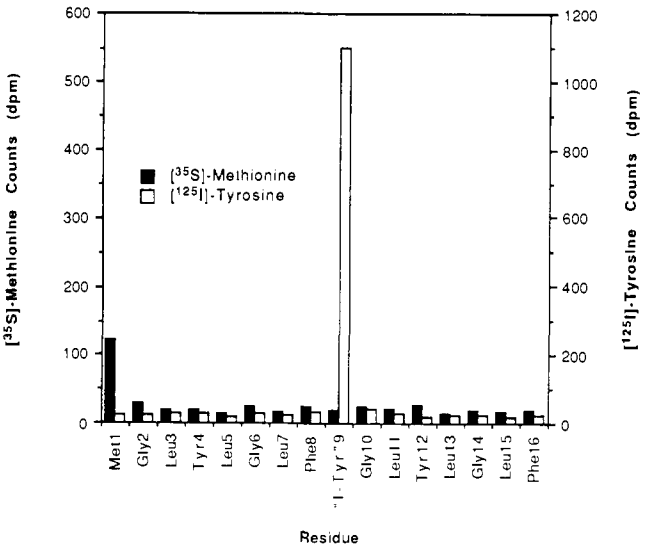

Figure 1. Amino acid sequence determination of the 16-residue polypeptide product from in vitro translation with rabbit reticulocyte lysate. Position 1 corresponds to the amino terminus (methionine), and position 9 corresponds to the suppression site (suppressed by ^{125}I-Tyr-tRNA$^{Gly}_{CUA}$-dCA) of the polypeptide. All values are reported in dpm and have been corrected for incomplete PTH-derivatization and hydrolysis, in addition to cycle losses that occur during sequencing. Values are not corrected for background.

followed by deprotection[9b] and reverse-phase HPLC purification to give the fully deprotected acylated dinucleotide in 54% overall yield. The preparation of Tyr-tRNA$^{Gly}_{CUA}$-dCA was completed by T4 RNA ligase-mediated coupling of 20 molar equiv of the acylated dinucleotide with tRNA$^{Gly}_{CUA}$-C$_{OH}$.[2,5d] Radiolabeling of Tyr-tRNA$^{Gly}_{CUA}$-dCA with carrier-free Na[^{125}I] followed by chromatographic purification gave ^{125}I-Tyr-tRNA$^{Gly}_{CUA}$-dCA.[12] Introduction of the radiolabel was conducted subsequent to T4 RNA ligation to minimize the number of steps that required the handling of radioactive material; however, other misacylated tRNAs have been prepared directly from the non-natural amino acid itself.[9]

The translation experiment[13] was conducted with this synthetic acylated tRNA and an appropriately designed mRNA containing a UAG termination codon at position 9, transcribed from a synthetic gene. Two polypeptides can be translated from this mRNA, either an 8-mer or a 16-mer (refer to Figure 1 abscissa), depending upon whether or not suppression occurs. Nonradiolabeled polypeptide standards of the 8- and 16-mer, synthesized by standard solid phase methods,[14] were added as carriers following termination of the translation reaction. Isolation was facilitated by the hydrophobic nature of both products and was accomplished quantitatively by extraction of the rabbit reticulocyte lysate with $CH_3CN/CHCl_3$ (1:1). After isolation, the extracts were fractionated by reverse-phase HPLC and radioisotope levels detected by scintillation counting. *The results of this experiment clearly show that the non-natural amino acid iodotyrosine*[12] *has been efficiently incorporated exclusively at the designated position.* Total suppression was calculated from the relative levels of [^{35}S]-methionine contained in the 8- and 16-mer polypeptide products (586 and 248 dpm, respectively) to give a value of 30% suppression efficiency. Furthermore, read-through is insignificant at this level of suppression, although small amounts of the 16-mer (3-4%) are produced by read-through in the absence of added ^{125}I-Tyr-tRNA$^{Gly}_{CUA}$-dCA (controls, Table I).

Table I. Suppression Efficiency and Controls

	decays per minute[a] (dpm)			
	8-mer		16-mer	
experiment[b]	[^{35}S]-Met	[^{125}I]-Tyr	[^{35}S]-Met	[^{125}I]-Tyr
^{125}I-Tyr-tRNA$^{Gly}_{CUA}$-dCA	586	–	248	2120
control 1[c]	836	–	26	–
control 2[c]	863	–	37	–
control 3[c]	815	–	23	–

[a] Counts per min have been converted into decays per min (dpm) and are corrected for background. Dashes (—) indicate no dpm above background levels. [b] In vitro rabbit reticulocyte lysate translation experiments were carried out as described in ref 13. Crude polypeptides were injected onto a Vydac C-4 column equilibrated in 0.1% TFA in H_2O/CH_3CN (1:1). Gradient elution with 0.1% TFA in CH_3CN (50-100% CH_3CN in 30 min) resolved the 8- and 16-mer peaks eluting at 60-80% CH_3CN. [c] Controls were conducted in the absence of added ^{125}I-Tyr-tRNA$^{Gly}_{CUA}$-dCA but were supplemented as follows: Control (1) buffer alone, control (2) 0.5 μg of nonacylated tRNA, and control (3) 0.5 μg of nonacylated tRNA plus 100 μCi carrier-free [^{125}I]-tyrosine.

Finally, in order to rigorously demonstrate the site-specificity of this process, the HPLC-purified 16-mer was sequenced by standard gas-phase analysis. Phenylthiohydantoin (PTH) derivatives were identified by reverse-phase HPLC followed by detection of both [^{35}S]-methionine and [^{125}I]-tyrosine through scintillation counting of the individual fractions (Figure 1). Only position 9, the expected site of suppression, contained ^{125}I above background levels, unequivocally establishing that [^{125}I]-tyrosine is incorporated exclusively at that position. These studies are currently being expanded to include the incorporation of a variety of other amino acids, the introduction of several different residues into the same protein, and an in vivo translation system.

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(11) Hudson, D. *J. Org. Chem.* **1988**, *53*, 617-624.
(12) The reaction was carried out under conditions to minimize nucleotide substitution (Scherberg, N. H.; Seo, H.; Hynes, R. *J. Biol. Chem.* **1978**, *253*, 1773-1779).
(13) A typical reaction (10 μL) contained commercially available rabbit reticulocyte lysate (8 μL), L-[^{35}S]-methionine (1 μL, 100 μCi), mRNA (0.5 μg in 0.5 μL of H_2O), ^{125}I-Tyr-tRNA$^{Gly}_{CUA}$-dCA (5 μg), and H_2O (0.5 μL). The mixture was incubated for 1 h at 30 °C followed by addition of 1.0 M sodium hydroxide/hydrogen peroxide (0.5 mL) and warming to 37 °C for 10 min.
(14) Dryland, A.; Sheppard, R. C. *J. Chem. Soc., Perkin Trans. 1* **1986**, 125-137.

Intermolecular Pinacol Cross Coupling of Electronically Similar Aldehydes. An Efficient and Stereoselective Synthesis of 1,2-Diols Employing a Practical Vanadium(II) Reagent

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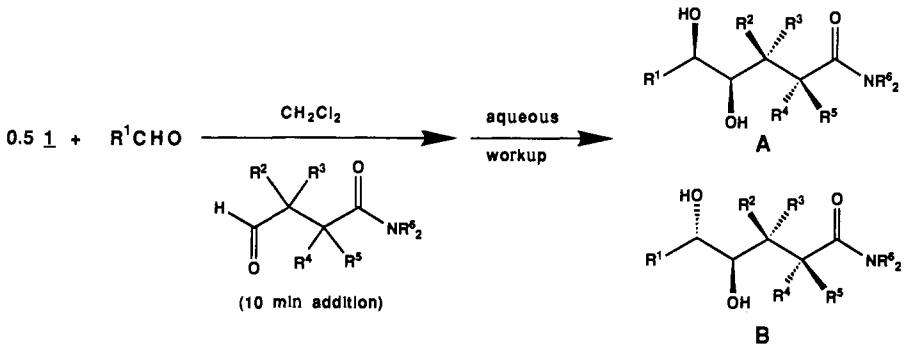
The 1,2-diol unit is one of the most ubiquitous functional groups in nature, and consequently a wealth of methods leading to its synthesis have been developed. Foremost in this arsenal are the catalytic osmylation of olefins,[1] ring opening of epoxides,[2] and reduction or alkylation of α-hydroxy/alkoxy carbonyls.[3] Common

(1) (a) Wai, J. S. M.; Marko, I.; Svendsen, J. S.; Finn, M. G.; Jacobsen, E. N.; Sharpless, K. B. *J. Am. Chem. Soc.* **1989**, *111*, 1123. (b) Schroder, M. *Chem. Rev.* **1980**, *80*, 187.
(2) (a) Behrens, C. H.; Sharpless, K. B. *J. Org. Chem.* **1985**, *50*, 5696. (b) Behrens, C. H.; Ko, S. Y.; Sharpless, K. B.; Walker, F. J. *Ibid.* **1985**, *50*, 5687. (c) Caron, M.; Sharpless, K. B. *Ibid.* **1985**, *50*, 1557. (d) Gorzynski Smith, J. *Synthesis* **1984**, 629. (e) Behrens, C. H.; Sharpless, K. B. *Aldrich. Acta* **1983**, *16*, 67.

0002-7863/89/1511-8014$01.50/0

Table I. Pinacol Cross Coupling[a]

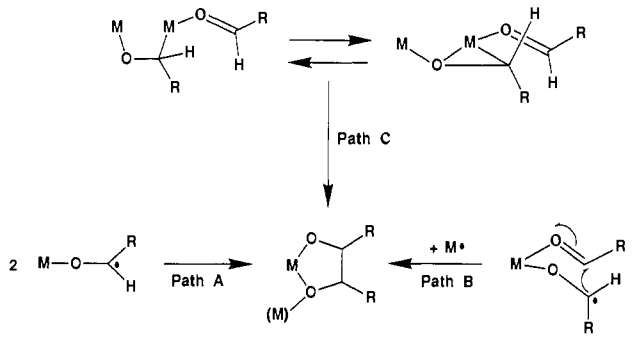


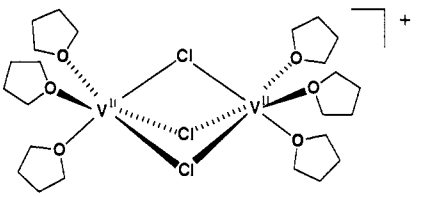
entry	R^1	R^2	R^3	R^4	R^5	R^6	ds(A:B)	yield (%)
1	$PhCH_2CH_2$	H	H	H	H	Bn	4:1	67[b]
2	*i*-Pr	H	H	H	H	Bn	8:1	73[b]
3	*t*-Bu	H	H	H	H	Bn	>100:1	42[c]
4	$PhCH_2CH_2$	H	H	H	H	*i*-Pr	7:1	56
5	*n*-Pr	H	Me	H	H	Me	5:1[d]	61 (63)[e]
6	*i*-Pr	H	Me	H	H	Bn	14:1	81
7	*i*-Bu	H	H	H	Me	Bn	4:1[d]	80 (84)[e]
8	$PhCH_2CH_2$	Me	Me	H	H	Me	>50:1	81[e]
9	$PhCH_2CH_2$	H	H	Me	Me	Bn	2:1	57

[a] See Supplementary Material for a general experimental procedure. [b] Twenty minute addition of CA aldehyde. [c] Six hour addition of CA aldehyde. [d] A third minor diastereomer was also detected; see paper and Supplementary Material for further details. [e] Yield from **1** generated in situ.

to all of these approaches is the preexistence of the central carbon–carbon bond of the diol function. Methods that lead directly to a 1,2-diol via formation of this bond are less common and include the reaction of an α-alkoxy anion[4] with a carbonyl and the reductive coupling of two carbonyls (i.e., pinacol coupling).[5] The latter is conceptually one of the simplest methods for the synthesis of 1,2-diols, yet a general and efficient method for *intermolecular*[6] pinacol cross coupling has proven elusive. Only in cases where one of the carbonyls is electronically activated (e.g., benzophenone[7]) or when an excess of one carbonyl is employed[8] have cross coupling reactions given rise to good yields of the desired unsymmetrical diols. Herein we describe a practical method for the stereoselective coupling of two different, yet electronically similar aldehydes employing the well-characterized vanadium(II) complex, $[V_2Cl_3(THF)_6]_2[Zn_2Cl_6]$ (**1**).[9]

Scheme I. Three Mechanisms for Pinacol Coupling





Dimer Core of **1**

The mechanism generally written for pinacol coupling promoted by low-valent metals[10] involves the dimerization of two ketyl radicals (Scheme I, path A). Given the lack of selectivity observed with intermolecular radical reactions, when operative this mechanism precludes the efficient coupling of two carbonyls with similar reduction potentials. An alternative pathway involving ketyl radical attack on a coordinated aldehyde has also been proposed (path B).[11] We chose to examine the known dimeric

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(4) (a) Cohen, T.; Lin, M. T. *J. Am. Chem. Soc.* **1984**, *106*, 1130. (b) Cohen, T.; Matz, J. R. *Ibid.* **1980**, *102*, 6900. (c) Still, W. C.; Mitra, A. *Ibid.* **1978**, *100*, 1927. (d) Still, W. C. *Ibid.* **1978**, *100*, 1481. (e) Seebach, D.; Meyer, N. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 438. For alkoxy allylic anion approaches, see: (f) Takai, K.; Nitta, K.; Utimoto, K. *Tetrahedron Lett.* **1988**, *29*, 5263 and references therein. For enolate ion approaches, see: (g) Heathcock, C. H. *Asymmetric Synthesis*; Morrison, J. P., Ed.; Academic Press: Orlando, FL, 1984; Vol. 3, pp 111–212.

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(6) Intramolecular pinacol coupling has found widespread use, for examples, see: (a) McMurry, J. E.; Rico, J. G.; Shih, Y. *Tetrahedron Lett.* **1989**, *30*, 1173. (b) McMurry, J. E.; Rico, J. G. *Ibid.* **1989**, *30*, 1169. (c) Kato, N.; Kataoka, H.; Ohbuchi, S.; Tanaka, S.; Takeshita, H. *J. Chem. Soc., Chem. Commun.* **1988**, 354. (d) Molander, G. A.; Kenny, C *J. Org. Chem.* **1988**, *53*, 2134. (e) Nakayama, J.; Yamaoka, S.; Hoshino, M. *Tetrahedron Lett.* **1987**, *28*, 1799. (f) Ghiringhelli, D. *Ibid.* **1983**, *24*, 287. (g) Corey, E. J.; Danheiser, R. L.; Chandrasekaran, S. *J. Org. Chem.* **1976**, *41*, 260.

(7) (a) Hou, Z.; Takamine, K.; Aoki, O.; Shiraishi, H.; Fujiwara, Y.; Taniguchi, H. *J. Org. Chem.* **1988**, *53*, 6077. (b) McMurry, J. E.; Fleming, M. P.; Kees, K. L.; Krepski, L. R. *Ibid.* **1978**, *43*, 3255. (c) McMurry, J. E.; Krepski, L. R. *Ibid.* **1976**, *41*, 3929.

(8) Reference 6g and (a) Clerici, A.; Porta, O.; Zago, P. *Tetrahedron* **1986**, *42*, 561. (b) Clerici, A.; Porta, O. *Tetrahedron* **1983**, *39*, 1239. (c) Clerici, A.; Porta, O. *J. Org. Chem.* **1983**, *48*, 1690. (d) Clerici, A.; Porta, O. *Ibid.* **1982**, *47*, 2852.

(9) (a) Cotton, F. A.; Duraj, S. A.; Roth, W. J. *Inorg. Chem.* **1985**, *24*, 913. (b) Bouma, R. J.; Teuben, J. H.; Beukema, W. R.; Bansemer, R. L.; Huffman, J. C.; Caulton, K. G. *Ibid.* **1984**, *23*, 2715. (c) Cotton, F. A.; Duraj, S. A.; Extine, M. W.; Lewis, G. E.; Roth, W. J.; Schmulback, C. D.; Schwotzer, W. *J. Chem. Soc., Chem. Commun.* **1983**, 1377.

(10) (a) McMurry, J. E. *Acc. Chem. Res.* **1983**, *16*, 405. (b) Mundy, B. P.; Srinivasa, R.; Kim, Y.; Dolph, T.; Warnet, R. J. *J. Org. Chem.* **1982**, *47*, 1657. (c) Dams, R.; Malinowski, M.; Westdrop, I.; Geise, H. Y. *Ibid.* **1982**, *47*, 248.

vanadium(II) reagent, **1**, with the intent that any ketyl generated upon reaction with one vanadium(II) center might be rapidly reduced by the second vanadium(II) leading to an organometallic intermediate.[12] Controlled coupling by insertion of a second carbonyl might then be possible (see Scheme I, path C). Reagent **1** is readily prepared from $VCl_3(THF)_3$[13] and zinc dust (95%, >100 g).[9] More importantly, this reagent may also be generated and used in situ.[14]

We began our studies with a general survey of pinacol coupling reactions.[15] Reagent **1** couples aryl aldehydes in high yield (>90%) and with *high diastereoselectivity* (i.e., 12:1-100:1; *d,l*:meso). However, non-aryl aldehydes such as isobutyraldehyde do not couple at an appreciable rate (13% after 12 h). Aryl as well as dialkyl ketones give little or no coupling products under the same conditions. An important observation made during these initial studies was that 2-methoxybenzaldehyde couples much more rapidly (<2 h; >90%) than 4-methoxybenzaldehyde (>24 h; >90%). This dramatic difference in the rate of coupling is best ascribed to the ability of 2-methoxybenzaldehyde to form a chelate with a vanadium(II) center.[16]

The above experiments suggested that the rate of coupling for non-aryl aldehydes might be accelerated if they contained an appropriately placed chelating group. This was found to be true for several functionalized aldehydes, in particular, compounds capable of forming stable six- and seven-membered chelate rings with a vanadium center (such aldehydes will be referred to as chelation-accelerated aldehydes or CA aldehydes).[17]

It was apparent that intermolecular cross coupling might be possible if a CA aldehyde was slowly added to a solution of **1** and 1 equiv of a less reactive aldehyde assuming that either pathway B or C (Scheme I) were operative. We began our investigations with a variety of 3-formylpropanamides.[18] As indicated in Table I such reactions do provide 1,2-diols in good-to-excellent yields. The major diastereomer in all of the cross coupling reactions is a threo diol and the threo:erythro ratio increases as α-branching in either aldehyde increases (entries 2, 3, 6, and 8). The origin of the threo selectivity can be rationalized by invoking either a ketyl radical or organometallic intermediate. In both cases, the less reactive aldehyde would bind to the metal and prefer to orient its substituent away from the chelate ring formed from the CA aldehyde.

When a 3-formyl-*N,N*-dialkylbutanamide is employed, only two major products are obtained after workup: a threo and an erythro diol (entries 5 and 6). The relative configuration between the 3-methyl and 4-hydroxy groups is "anti" in both diastereomers. In one case (entry 5), a third diastereomer has been detected in trace quantities and shown to be the "syn" threo diol (anti:syn = 35:1). Beginning with a 3-formyl-2-methylpropanamide the minor threo isomer becomes more prominent (major:minor = 12:1; entry 7). Attempts to improve the diastereoselectivity of these reactions by going to lower temperature (-30 °C) have proven unsuccesful due to a preponderance of CA aldehyde homo coupling. A detailed explanation for the observed face selectivity in the above set of CA aldehydes will ultimately depend on the intermediate(s) involved. However, from the standpoint of predicting the stereochemical outcome of these reactions, one can conclude that the less reactive aldehyde reacts with the least hindered face of a vanadium bound CA aldehyde. Studies aimed at elucidating the reactive intermediates involved in these reactions are underway.

Being that **1** is one of the few, *well-characterized*, and homogeneous low-valent metal halides available in large quantities, we anticipate many further applications of this reagent within the general realm of cross coupling reactions. Furthermore, this vanadium(II) reagent is clearly a mild reducing agent, a feature which will provide the opportunity for coupling highly functionalized substrates.

Acknowledgment. S.F.P. is grateful to the National Institutes of Health (GM38735), the National Science Foundation for a Presidential Young Investigator Award (Grant No. CHE-8552735), and Eli Lilly and Company for financial support. J.H.F. thanks the Miller Institute of U.C. Berkeley for a Postdoctoral Fellowship.

Supplementary Material Available: NMR, IR, and mass spectral data and C, H, and N analysis information and stereochemical assignments for diols and a detailed experimental procedure for the synthesis of 1,2-diols via pinacol cross coupling (9 pages). Ordering information is given on any current masthead page.

(11) See ref 6d and Clerici, A.; Porta, O.; Riva, M. *Tetrahedron Lett.* **1981**, *22*, 1043.

(12) For examples of early transition-metal aldehyde or ketone complexes (metallaoxiranes), see: (a) Waymouth, R. M.; Grubbs, R. H. *Organometallics* **1988**, *7*, 1631. (b) Bryan, J. C.; Mayer, J. M. *J. Am. Chem. Soc.* **1987**, *109*, 7213. (c) Erker, G.; Czisch, P.; Schlund, R.; Angermund, K.; Kruger, C. *Angew. Chem.* **1986**, *98*, 356. (d) Erker, G.; Dorf, U.; Czisch, P.; Petersen, J. L. *Organometallics* **1986**, *5*, 668. (e) Waymouth, R. M.; Clauser, K. R.; Grubbs, R. H. *J. Am. Chem. Soc.* **1986**, *108*, 6385. (f) Martin, B. D.; Matchett, S. A.; Norton, J. R.; Anderson, O. P. *Ibid.* **1985**, *107*, 7952. (g) Kropp, K.; Skibbe, V.; Erker, G. *Ibid.* **1983**, *105*, 3353. (h) Erker, G.; Kropp, K.; Kruger, C.; Chiang, A.-P. *Chem. Ber.* **1982**, *115*, 2447. (i) Erker, G.; Rosenfeldt, F. *J. Organomet. Chem.* **1982**, *224*, 29. (j) Wood, C. D.; Schrock, R. R. *J. Am. Chem. Soc.* **1979**, *101*, 5421.

(13) Manzer, L. E. *Inorg. Synth.* **1982**, *21*, 135.

(14) In situ generation of **1** entails dissolving $VCl_3(THF)_3$ in dichloromethane (ca. 0.5 M) and adding 0.6 equiv of zinc dust (20% excess). The reagent is ready for use when the solution color changes from red to green (ca. 15 min). No filtration is necessary.

(15) To our knowledge this reagent has not been previously used in organic synthesis.

(16) Aldehydes and ketones capable of forming chelates with early metals often exhibit accelerated rates of alkylation: (a) Reetz, M. T.; Maus, S. *Tetrahedron* **1987**, *43*, 101. (b) Reetz, M. T. *Top. Curr. Chem.* **1982**, *106*, 1. Chelation also appears to be necessary in the deoxygenation of α-oxygenated esters by SmI_2/HMPA. (c) Kusuda, K.; Inanaga, J.; Yamaguchi, M. *Tetrahedron Lett.* **1989**, *30*, 2945.

(17) Functionalized aldehydes capable of forming a five-membered chelate ring with a vanadium center in some cases also exhibit accelerated coupling. However, in these cases the inductive effect of the α-heteroatom undoubtedly contributes to increased reactivity, and the separation of these factors in these cross coupling reactions has not yet been investigated.

(18) These were one of our better class of substrates in the homocoupling experiments. However, other types of CA aldehydes are effective in this general reaction. Details will be reported in the future.

Magnesium Amide Bases and Amido-Grignards. 1. Ortho Magnesiation

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Hauser bases (R_2NMgBr) and magnesium diamides [$(R_2N)_2Mg$] are known,[1,2] but their uses in organic synthesis have barely been explored.[3,4] With this communication we introduce the first of our work with these bases and demonstrate their exceptional utility and bright future.

Ortho lithiation of substituted aromatics has been developed elegantly into one of the major tools of organic synthesis.[5] It

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(2) (a) Ashby, E. C.; Lin, J. J.; Goel, A. B. *J. Org. Chem.* **1978**, *43*, 1564. (b) Ashby, E. C.; Goel, A. B. *J. Inorg. Chem.* **1978**, *17*, 1862. (c) Ashby, E. C.; Willard, G. F. *J. Org. Chem.* **1978**, *43*, 4750.

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(4) (a) Sanchez, R.; Scott, W. *Tetrahedron Lett.* **1988**, *29*, 139. (b) Rathman, T. L. Chemspec USA '88 Symposium, Boston, MA, Sept, 1988.

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