Pinacol Cross Coupling Reactions of Ethyl 2-Alkyl-2-Formylpropionates. Stereoselective Synthesis of 2,2,4-Trialkyl-3-Hydroxy-γ-Butyrolactones.

Min Kang, Jeonghan Park, and Steven F. Pedersen*
Department of Chemistry, University of California, Berkeley, CA 94706
E-mail; pedersen@cchem.berkeley.edu

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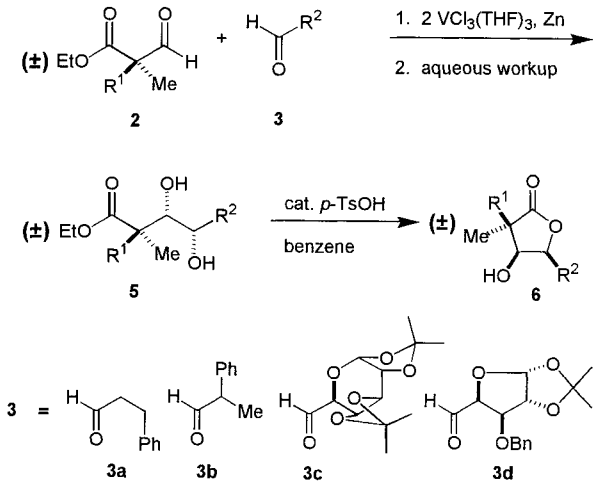
Abstract: Intermolecular pinacol coupling of ethyl 2-alkyl-2-formylpropionates (**2**) (i.e. EtOC(O)CR^{1}MeCHO) with non-chelating aldehydes provides high yields of threo diols. The reaction is promoted by vanadium(II) ions which are conveniently generated in situ from $VCl_3(THF)_3$ and zinc dust. High diastereofacial selectivity is observed when starting with chiral **2**, or chiral non-chelating aldehydes.

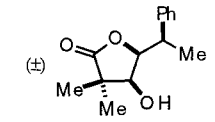
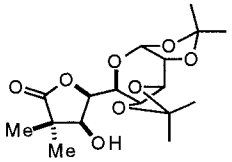
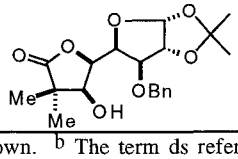
We have previously observed that the pinacol cross-coupling reaction between disubstituted α-diphenylphosphinoyl acetaldehydes (i.e. $Ph_2P(O)CR^1R^2CHO$) (**1**) and a variety of non-chelating aldehydes proceeds in high yields.[1] Furthermore, unusually high diastereofacial selectivity is found, even in cases where an incoming non-chelating aldehyde must choose between encountering an ethyl versus methyl group (14:1 approach from the methyl side).[1] The success of this system led us to examine another class of α,α-dialkyl aldehydes, this time possessing an ester function as the chelating unit (i.e. **2**). Pinacol cross-coupling of such substrates where R^1 is not methyl, would lead to aldol type products bearing a chiral quaternary center alpha to the ester, a class of compounds not easily arrived at in high selectivity's from aldol reactions.[2,3]

The ester aldehydes (**2**) were prepared by formylation of the corresponding ester enolates (LDA, THF, -78 °C) using ethyl formate.



Scheme 1

Table 1

ester aldehydes		non-chelating aldehydes	γ-butyrolactones (**6**)[12]			
no.	R^1	no.	no.	product[a]	ds ratio[b]	yield (%)[c]
2a	Me	**3a**	**6a**	-[d]	-[e]	79
2b	Et	**3a**	**6b**	-[d]	5:1	73[f]
2c	Bn	**3a**	**6c**	-[d]	11:1	78
2d	*i*-Pr	**3a**	**6d**	-[d]	20:1	58[g]
2a	Me	**3b**	**6e**		6:1	68[f]
2a	Me	**3c**	**6f**		18:1	90
2a	Me	**3d**	**6g**		11:1	72

[a] Only the major diastereomer is shown. [b] The term ds refers to the diastereofacial selectivity for these reactions. Except for **6a** (see footnote e), only threo diols were obtained. The ds was determined by ^{1}H NMR, ^{13}C NMR, and (or) GC-mass spectrometry of the crude product mixture before purification. [c] Isolated yield of the major diastereomer. [d] For stereochemistry of the major diastereomer, see **6** in Scheme 1 where R^2 = CH_2CH_2Ph. [e] The ratio of threo:erythro was 22:1 (determined by GC-mass spectrometry). [f] A minor diastereomer was also isolated (see ref. 12). [g] 20% of starting material was recovered.

The cross coupling reactions were performed by simply combining **2** and a non-chelating aldehyde (**3**) together with $[V_2Cl_3(THF)_6]_2[Zn_2Cl_6]$ (**4**) (generated in situ from $VCl_3(THF)_3$ and zinc dust) in CH_2Cl_2 (Scheme 1).[4] The fact that both substrates can be added at the same time is both convenient and consistent with what has been observed in coupling reactions involving **1**. The crude diols (**5**) prepared from these reactions were always contaminated with some of the corresponding γ-butyrolactone (**6**). Therefore, for convenience of analysis we have converted all diols into **6** by treatment with a catalytic amount of *p*-toluenesulfonic acid in benzene (Scheme 1). In order to ascertain the stereoselectivity associated with diol formation, we began our studies by reacting **2a**, where the geminal substituents are equivalent, with 3-phenylpropanal. An excellent yield of **6a**, containing the expected threo diol core was obtained (Table 1).[5,6]

Having established that these reactions produce predominately threo diols, we turned our attention to the question of diastereofacial selectivity using chiral aldehydes **2b-d**. As can be seen in Table 1, selectivity's are high, though not as high as that observed in the analogous reactions of **1**.[1] However, from a synthetic standpoint, even a selectivity of 5:1 when comparing the two faces of an aldehyde discriminated only by a methyl versus an ethyl group is still important.[7] The sense of selectivity is predictable from a chelation-control model where the non-chelating aldehyde (**3**) binds to vanadium and reacts with the least hindered face of the chelating aldehyde (**2**).[1,6,8]

Finally, we investigated the diastereofacial selectivity of α-chiral, non-chelating[9] aldehydes (**3b-d**) in the pinacol cross-coupling reaction with **2a**. All three cases exhibited high diastereofacial selectivity (Table 1). Moreover, only single diastereomers were obtained after one chromatographic separation. In these examples (**6e-g**), the major isomers are that predicted from a Felkin-Ahn model.[10]

In conclusion, we have developed an efficient and stereoselective synthesis of 2,2,4-trialkyl-3-hydroxy γ-butyrolactones derived from pinacol coupling of ethyl 2-alkyl-2-formylpropionates with non-chelating aldehydes. Since the non-racemic synthesis of ester aldehydes (**2b-c**) has already been reported,[11] an enantioselective synthesis of the class of γ-butyrolactones described within is clearly possible.

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References and Notes

(1) Park, J.; Pedersen, S. F. *J. Org. Chem.* **1990**, *55*, 5924.

(2) Yamago, S.; Machii, D.; Nakamura, E. *J. Org. Chem.* **1991**, *56*, 2098 and references therein.

(3) Starting with **2a**, pinacol cross coupling reactions provide an attractive alternative to well documented aldol reactions between enolates of isobutyric acid derviatives and α-alkoxy aldehydes: (a) Arrastia, I.; Lecea, B.; Cossio, F. P. *Tet. Lett.* **1996**, *37*, 245. (b) Takebuchi, K.; Hamada, Y.; Shioiri, T. *Tet. Lett.* **1994**, *35*, 5239.

(4) *General procedure for the pinacol cross-coupling reaction of* **2** *and* **3**. Under an atmosphere of N_2, a mixture of 1.64 g (4.4 mmol) of $VCl_3(THF)_3$, 0.17 g (2.64 g atoms) of zinc dust, and 10 mL of dry CH_2Cl_2 was stirred vigorously for 10-30 min, giving a green solution. A solution of **3** (2 mmol) in 5 mL of CH_2Cl_2 was added followed by a solution of **2** (2 mmol) in CH_2Cl_2 (5 mL). After stirring for 2 d, the reaction mixture was opened to the air and poured into 10% aqueous sodium tartrate (30 mL). The two phases were stirred vigorously for 6-15 h, giving a violet aqueous layer and a clear CH_2Cl_2 layer. The aqueous phase was separated and extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were dried with $MgSO_4$, and evaporated to give a foam. The foam was dissolved in 20 mL of benzene; 5 mg of para-toluenesulfonic acid (PTSA) was added and the reaction was stirred for 1-2 h. The mixture was concentrated and the residue was purified by chromatography on silica gel using an eluent of ethyl acetate in hexane to give **6**.

(5) The threo-diol core and remaining relative stereochemistry of **6c,e,f** was confirmed by X-ray structural analysis. For compounds **6a, g**, the $J_{3,4}$ in the ^1H NMR spectra are consistent with calculated coupling constants (Jaime, C.; Segura, C.; Dinares, I.; Font, J. *J. Org. Chem.* **1993**, *58*, 154). In all other cases the stereochemistry is inferred based on the established stereochemisties of **6c,e,f**.

(6) (a) Freudenberger, J. H.; Konradi, A. W.; Pedersen, S. F. *J. Am. Chem. Soc.* **1989**, *111*, 8014. (b) Konradi, A. W.; Pedersen, S. F. *J. Org. Chem.* **1990**, *55*, 4506. (c) Konradi, A. W.; Pedersen, S. F. *ibid.* **1992**, *57*, 28. (d) Kraynack, E.; Pedersen, S. F. *ibid.* **1993**, *58*, 6114. (e) Konradi, A. W.; Kemp, S. J.; Pedersen, S. F. *J. Am. Chem. Soc.* **1994**, *116*, 1316.

(7) To our knowledge, diastereofacial selective additions of this magnitude to a prochiral carbonyl bearing three non-hydrogen α-substituents, two of which are methyl and ethyl, is without precedent except for the chemistry described in ref. 1. For examples of chelation-controlled addition reactions to α-hydroxy (or alkoxy) carbonyls bearing two different non-hydrogen substituents, see: (a) Reetz, M. T.; Steinbach, R.; Westermann, J.; Urz, R.; Wenderoth, B.; Peter, R. *Angew. Chem. Int. Ed. Engl.* **1982**, *21*, 135. (b) Cram, D. J.; Kopecky, K. R. *J. Am. Chem. Soc.* **1959**, *81*, 2748. (c) Cram, D. J.; Allinger, J. *ibid.* **1954**, *76*, 4516. (d) Cram, D. J.; Elhafez, F. A. A. *ibid.* **1952**, *74*, 5828. For an additional example related to this area see: Reetz, M. T. *Nach. Chem. Tech. Lab.* **1981**, *29*, 165.

(8) For reviews of chelation-controlled addition reactions see: (a) Reetz, M. T. *Accts. Chem. Res.* **1993**, *26*, 462. (b) Reetz, M. T. *Organotitanium Reagents in Organic Synthesis*; Springer Verlag: Berlin, 1986. (c) Reetz, M. T. *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 556.

(9) It is known that **3c** can function as a chelating aldehyde (using the pyranose oxygen) in reactions with methyl magnesium bromide (ref. 8c). However, we have found that this aldehyde does not function in this manner when forced to compete with the strongly chelating substrates **1** and **2**.

(10) For pertinent references and a discussion, see, Lodge, E. P.; Heathcock, C. H. *J. Am. Chem. Soc.* **1987**, *109*, 3353.

(11) Renaud, P.; Hurzeler, M.; Seebach, D. *Helv. Chim. Acta* **1987**, *70*, 292.

(12) Analytical data for lactones **6a-g**:

6a. An analytical sample was prepared by recrystallization from dichloromethane/hexane to give a white solid: mp 126-127 °C; ^1H NMR (400 MHz, $CDCl_3$, D_2O) δ 7.32-7.29 (m, 2H), 7.20-7.23 (m, 3H), 4.47 (ddd, J = 8.8, 5.2, 3.6, 1H), 3.90 (d, J = 3.6, 1H), 2.91 (m, 1H), 2.75 (m, 1H), 2.22 (m, 1H), 2.00 (m, 1H), 1.25 (s, 3H), 1.23 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.5 (C), 141.0 (C), 128.5 (CH), 128.3 (CH), 126.1 (CH), 80.5 (CH), 76.6 (CH), 45.8 (C), 31.7 (CH_2), 30.1 (CH_2), 22.7 (CH_3), 17.7 (CH_3); Anal. Calcd for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74; Found: C, 71.95; H, 7.76; TLC (30% ethyl acetate in hexane) R_f 0.20.

6b. An analytical sample was prepared by recrystallization from dichloromethane/hexane to give a white solid: mp 107-108 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 7.31-7.26 (m, 2H), 7.22-7.20 (m, 3H), 4.43 (ddd, J = 8.6, 5.1, 3.4, 1H), 3.95 (dd, J = 5.6, 3.4, 1H), 2.86 (m, 1H), 2.74 (m, 1H), 2.43 (d, J = 5.6, 1H, O*H*), 2.20 (m, 1H), 1.99 (m, 1H), 1.82 (m, 1H), 1.64 (m, 1H), 1.17 (s, 3H), 0.97 (t, J = 7.5, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 181.1 (C), 141.0 (C), 128.5 (CH), 128.4 (CH), 126.2 (CH), 80.4 (CH), 75.7 (CH), 48.9 (C), 31.7 (CH_2), 30.2 (CH_2), 23.4 (CH_2), 18.6 (CH_3), 8.1 (CH_3); Anal. Calcd for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12; Found: C, 72.92; H, 8.27; TLC (30% ethyl acetate in hexane) R_f 0.40. A minor diastereomer (8%) was also isolated by chromatography as a white foam: ^1H NMR (500 MHz, $CDCl_3$) δ 7.31-7.28 (m, 2H), 7.22-7.19 (m, 3H), 4.45 (m, 1H), 3.97 (m, 1H), 2.88 (m, 1H), 2.73 (m, 1H), 2.18 (m, 1H), 1.99 (m, 1H), 1.94 (d, J = 5.2, 1H, O*H*), 1.59

(m, 1H), 1.49 (m, 1H), 1.20 (s, 3H), 0.95 (t, J = 7.5, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 180.7 (C), 141.0 (C), 128.5 (CH), 128.4 (CH), 126.1 (CH), 80.5 (CH), 75.2 (CH), 49.6 (C), 31.8 (CH_2), 30.3 (CH_2), 28.3 (CH_2), 23.4 (CH_2), 14.5 (CH_3), 8.5 (CH_3); TLC (30% ethyl acetate in hexane) R_f 0.35.

6c. An analytical sample was prepared by recrystallization from dichloromethane/hexane to give a white solid: mp 147-148 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35-7.29 (m, 6H), 7.27-7.22 (m, 4H), 4.45 (ddd, J = 8.4, 5.3, 3.1, 1H), 3.86 (m, 1H), 3.38 (d, J = 13.9, 1H), 2.91 (m, 1H), 2.82 (d, J = 13.9, 2H), 2.80 (m, 1H), 2.45 (m, 1H), 2.27 (m, 1H), 2.02 (m, 1H), 1.08 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.5 (C), 140.8 (C), 136.8 (C), 130.4 (CH), 128.6 (CH), 128.4 (CH), 128.3 (CH), 126.6 (CH), 126.3 (CH), 80.4 (CH), 75.4 (CH), 50.0 (C), 35.8 (CH_2), 31.7 (CH_2), 30.2 (CH_2), 19.3 (CH_3); Anal. Calcd for $C_{20}H_{22}O_3$: C, 77.39; H, 7.14; Found: C, 77.22; H, 7.17; TLC (30% ethyl acetate in hexane) R_f 0.44.

6d. An analytical sample was prepared by recrystallization from dichloromethane/hexane to give a white solid: mp 102-104 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 7.31-7.28 (m, 2H), 7.21-7.23 (m, 3H), 4.41 (ddd, J = 8.2, 5.0, 3.1, 1H), 3.95 (d, J = 3.2, 1H), 2.85 (m, 1H), 2.73 (m, 1H), 2.56 (bs, 1H, O*H*), 2.20 (m, 2H), 1.98 (m, 1H), 1.19 (d, J = 6.8, 3H), 1.10 (s, 3H), 0.99 (d, J = 6.8, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 180.4 (C), 141.0 (C), 128.5 (CH), 128.3 (CH), 126.1 (CH), 79.7 (CH), 77.3 (CH), 50.9 (C), 31.6 (CH_2), 30.2 (CH_2), 28.1 (CH), 18.5 (CH_3), 16.6 (CH_3), 14.6 (CH_3); Anal. Calcd for $C_{16}H_{22}O_3$: C, 73.25; H, 8.45; Found: C, 73.00; H, 8.48; TLC (30% ethyl acetate in hexane) R_f 0.53.

6e. An analytical sample was prepared by recrystallization from dichloromethane/hexane to give a white solid: mp 109-111 °C; ^1H NMR (300 MHz, $CDCl_3$, 35 °C) δ 7.38-7.24 (m, 5H), 4.54 (dd, J = 10.5, 3.2, 1H), 3.63 (m, 1H), 3.26 (dq, J = 10.5, 6.8, 1H), 1.61 (bs, 1H, O*H*), 1.47 (d, J = 6.8, 3H), 1.22 (s, 3H), 1.21 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 181.0 (C), 142.0 (C), 129.0 (CH), 127.5 (CH), 127.1 (CH), 85.1 (CH), 75.9 (CH), 45.8 (C), 38.9 (CH), 22.5 (CH_3), 20.2 (CH_3), 17.7 (CH_3); Anal. Calcd for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74; Found: C, 71.39; H, 7.72; TLC (30% ethyl acetate in hexane) R_f 0.43. A minor diastereomer (11%) was also isolated by chromatography as a white solid: mp 217-219 °C; ^1H NMR (300 MHz, $CDCl_3$, 35 °C) δ 7.35-7.20 (m, 5H), 4.48 (dd, J = 10.3, 3.3, 1H), 4.11 (dd, J = 4.8, 3.3, 1H), 3.28 (dq, J = 10.3, 7.0, 1H), 1.78 (d, J = 4.8, 1H, O*H*), 1.35 (d, J = 7.0, 3H), 1.28 (s, 3H), 1.26 (s, 3H); TLC (30% ethyl acetate in hexane) R_f 0.26.

6f. An analytical sample was prepared by recrystallization from diisopropyl ether/hexane: $[\alpha]_D$ = -119.8° (c 0.0253, CH_2Cl_2); mp 133-135 °C; ^1H NMR (300 MHz, $CDCl_3$, 35 °C) δ 5.52 (d, J = 5.0, 1H), 4.66 (dd, J = 8.0, 2.4, 1H), 4.62 (dd, J = 9.6, 3.4, 1H), 4.43 (dd, J = 8.0, 1.6, 1H), 4.35 (dd, J = 5.0, 2.4, 1H), 4.13 (m, 1H), 4.04 (dd, J = 9.6, 1.6, 1H), 2.57 (d, J = 2.3, 1H), 1.53 (s, 3H), 1.47 (s, 3H), 1.37 (s, 3H), 1.33 (s, 3H), 1.28 (s, 3H), 1.26 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.3 (C), 109.4 (C), 109.2 (C), 96.4 (CH), 76.1 (CH), 75.5 (CH), 70.7 (CH), 70.4 (CH), 70.3 (CH), 65.1 (CH), 44.3 (C), 25.8 (CH_3), 25.5 (CH_3), 24.7 (CH_3), 23.9 (CH_3), 22.9 (CH_3), 17.5 (CH_3); Anal. Calcd for $C_{17}H_{26}O_8$: C, 56.97; H, 7.31; Found: C, 56.80; H, 7.26; TLC (30% ethyl acetate in hexane) R_f 0.26.

6g. An analytical sample was prepared by recrystallization from dichloromethane/hexane to give a cotton-like solid: $[\alpha]_D$ = -73.7° (c 0.0143, CH_2Cl_2); mp 155-157 °C; ^1H NMR (300 MHz, $CDCl_3$, 35 °C) δ 7.38-7.28 (m, 5H), 5.91 (d, J = 3.6, 1H), 4.77 (dd, J = 9.2, 3.5, 1H), 4.66 (m, 3H), 4.44 (dd, J = 9.2, 3.0, 1H), 4.16 (d, J = 3.0, 1H), 4.13 (m, 1H), 2.59 (d, J = 2.9, 1H, O*H*), 1.48 (s, 3H), 1.32 (s, 3H), 1.29 (s, 3H), 1.26 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.4 (C), 137.1 (C), 128.6 (CH), 128.4 (CH), 128.0 (CH), 127.9 (CH), 127.6 (CH), 112.4 (C), 105.0 (CH), 82.5 (CH), 81.6 (CH), 77.3 (CH), 75.8 (CH), 75.6 (CH), 72.7 (CH_2), 44.6 (C), 26.8 (CH_3), 26.2 (CH_3), 22.9 (CH_3), 17.5 (CH_3); Anal. Calcd for $C_{20}H_{26}O_7$: C, 63.48; H, 6.92; Found: C, 63.45; H, 6.97; TLC (50% ethyl acetate in hexane) R_f 0.23.