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[12] The stereochemistry of **13** was determined by correlation with (*Z*)-**18**, whose synthesis will be reported elsewhere.

[13] X-ray structure data: Nonius KappaCCD diffractometer, ϕ and ω scans, $Mo_{K\alpha}$ radiation ($\lambda = 0.71073$ Å), graphite monochromator, $T = 150$ K, structure solution with maXus,[14] refinement against F^2 (SHELXL-97[15]) with anisotropic thermal parameters for all non-hydrogen atoms, hydrogen positions were calculated with riding isotropic thermal parameters. Data collection for **14**: crystal dimensions $0.20 \times 0.20 \times 0.20$ mm^3, monoclinic, space group $P2_1/c$, $a = 8.7890(3)$, $b = 20.7820(3)$, $c = 9.9300(8)$ Å, $\alpha = 90.0000(19)$, $\beta = 107.7280(16)$, $\gamma = 90.0000(19)^\circ$, $V = 1727.61(15)$ Å^3, $Z = 4$, $\rho_{calcd} = 1.124$ g cm^{-3}, $\mu = 0.070$ cm^{-1}, $F(000) = 648$, $\theta_{max} = 27.48^\circ$, h, k, l ranges: 0 11, 0 26, −12 12, 3958 data collected, 3958 unique data ($R_{int} = 0.025$), 3378 data with $I > 2\sigma(I)$, 196 parameters refined, GOF(F^2) = 1.058, final R indices ($R_1 = S||F_o| - |F_c||/S|F_o|$, $wR_2 = [Sw(^2_o - F^2_c)^2/Sw(F^2_o)^2]^{1/2}$): $R_1 = 0.0425$, $wR_2 = 0.1083$, max./min. residual electron density 0.266(0.038)/−0.180(0.038) e A^{-3}. Data collection for **18**: crystal dimensions $0.20 \times 0.20 \times 0.20$ mm^3, monoclinic, space group $P2_1/c$, $a = 8.4850(4)$, $b = 15.6940(5)$, $c = 13.9450(7)$ Å, $\alpha = 90.000(3)$, $\beta = 106.2550(18)$, $\gamma = 90.000(3)^\circ$, $V = 1782.73(14)$ Å^3, $Z = 4$, $\rho_{calcd} = 1.186$ g cm^{-3}, $\mu = 0.078$ cm^{-1}, $F(000) = 696$, $\theta_{max} = 30.03^\circ$, $-11 \le h \le 9$, $-22 \le k \le 14$, $-12 \le l \le 19$, 10513 data collected, 5193 unique data ($R_{int} = 0.036$), 4160 data with $I > 2\sigma(I)$, 212 parameters refined, GOF($F2$) = 1.038, final R_{ind}: $R_1 = 0.0475$, $wR_2 = 0.1320$, max./min. residual electron density 0.431(0.046)/−0.396(0.046) e A^{-3}. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC-135213 and 135214. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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Diastereoselective Pinacol Coupling Reactions of α-Ketoamides Mediated by SmI_2: Synthesis of Enantiomerically Pure *R* and *S* Quaternary Tartaric Acids**

Sam Min Kim, Il Suk Byun, and Yong Hae Kim*

Multidentate, chiral, C_2-symmetric ligands are well-known for their ability to impart asymmetry to transition and main group elements.[1] C_2-Symmetric diols are among the most frequently applied examples of such molecules, especially in the area of asymmetric catalysis.[2] Most diol ligands have been derived from C_2-symmetric molecules which occur naturally in optically pure form (such as tartaric acid).[2] However, the number of chiral precursors available from natural products is seriously limited.

The pinacol coupling was first described a long time ago,[3] but this reaction is still a versatile tool for chemists. The intermolecular coupling of various aldehydes or ketones to the corresponding pinacols has been extensively studied.[4] However, pinacols in an enantiopure form have not really been obtained using this type of coupling.[5] Although the asymmetric dihydroxylation of olefins mediated by osmium tetroxide has become one of the most useful methods for the preparation of C_2-symmetric diols,[6] asymmetric dihydroxylations of tetrasubstituted olefins are extremely rare[7a] and give low enantioselectivity.[7]

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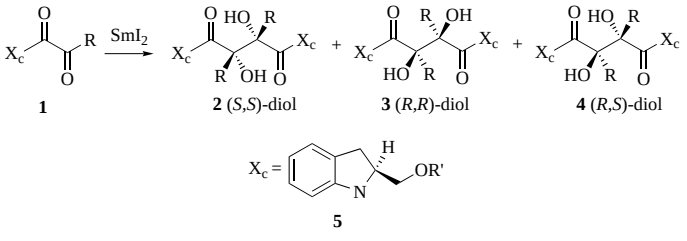
SmI_2 has been utilized successfully as a one-electron donating agent for diverse organic reactions[8] including intermolecular[9] or intramolecular[10] pinacol coupling reactions of aldehydes. However, the intermolecular coupling of ketones has afforded low diastereoselectivities.[11]

Chiral 2,3-dialkyltartaric acids could be utilized for designing chiral catalysts or auxiliaries for use in various asymmetric reactions[2] and as chiral intermediates in the synthesis of natural products. However, to our knowledge, the synthesis of enantiopure 2,3-disubstituted tartaric acid (a quaternary pinacol) has never been reported, although a chiral 2,3-dimethyltartaric acid was obtained by chiral resolution.[12] A chiral tertiary pinacol can be obtained by using pinacol coupling of ketones by photolysis in a chiral solvent[11a] or by using a chiral auxiliary,[11b, c] however, the diastereoselectivities are low.

We report here the coupling of the chiral α-ketoamides **1** in the presence of SmI_2, HMPA, and *t*BuOH in THF to give pinacol **2** with extremely high diastereoselectivity (>98% *de* in some cases; Scheme 1). This is the first example of such high stereoselectivity for disubstituted tartaric acid derivatives in intermolecular pinacol coupling reactions of α-ketoamides.



1a: R= R'= Me
1b: R= Et, R'=Me
1c: R= Ph, R'= Me
1d: R= Me, R'= TBPS
1e: R= Et, R'= TBPS
1f: R= *n*Pr, R'= TBPS
1g: R= *n*Hex, R'= TBPS
1h: R= Ph, R'= TBPS
5a: R' = Me
5b: R' = TBPS

Scheme 1. Pinacol coupling reactions of **1a**–**h** in the presence of SmI_2, HMPA, and *t*BuOH. TBPS = *tert*-butyldiphenylsilyl, HMPA = hexamethyl phosphoramide.

The results obtained are summarized in Table 1. The coupling of pyruvamide **1a** using SmI_2 in the absence of HMPA and *t*BuOH gave low stereoselectivity (**2**:**3**:**4** = 71:≈0:29, entry 1). However, the coupling of **1a** in the presence of SmI_2, HMPA, and *t*BuOH occurred with high diastereoselectivity (**2**:**3**:**4** = 95:≈0:5, entry 5). Moreover, the coupling of **1e** and **1f** resulted in extremely high diastereofacial selectivity (**2**:**3**:**4** = >99:≈0:1, entries 13 and 14). HMPA is known to increase the reaction rate and stereoselectivity of SmI_2-mediated rections and *t*BuOH is often used as a proton source for these reactions.[13] The pinacol coupling reaction can form three stereoisomers (*S*,*S*), (*R*,*R*), and (*S*,*R* or *R*,*S*; *meso* form). The *meso* form was easily confirmed by ^{13}C NMR spectroscopy;[14] however, formation of (*R*,*R*)-pinacol could not be detected.

When the *tert*-butyldiphenylsilyl (TBPS) substituent was introduced to give the chiral auxiliary **5b**, the pinacol coupling reactions of **1d**–**g** had a longer reaction time (5 h) and gave

Table 1. Pinacol coupling of **1a**–**h**.[a]

Entry	Substrate	SmI_2 [equiv]	HMPA [equiv]	*t*BuOH [equiv]	Time [h]	Yield [%]	**2**:**3**:**4**[b]
1	**1a**	1.5	0	0	0.1	64	71:≈0:29
2	**1a**	2.0	2	4	0.1	51	94:≈0:6
3	**1a**	2.0	4	4	0.1	42	95:≈0:5
4	**1a**	2.0	4	4	1	61	95:≈0:5
5	**1a**	2.0	4	4	2	57	95:≈0:5
6	**1a**	2.0	4	4	5	58	94:≈0:6
7	**1b**	2.0	2	4	0.1	61	95:≈0:5
8	**1b**	2.0	4	4	0.1	39	98:≈0:2
9	**1c**	2.0	4	4	5	–[c]	–
10	**1d**	2.5	4	4	5	69	96:≈0:4[d]
11	**1e**	2.5	0	0	5	87	95:≈0:5
12	**1e**	3.0	4	4	5	87	95:≈0:5[e]
13	**1e**	2.5	4	4	5	79	>99:≈0:1
14	**1f**	2.5	4	4	5	67	>99:≈0:1
15	**1g**	2.5	4	4	5	83	97:≈0:3
16	**1h**	2.5	4	4	5	–[c]	–

[a] Reactions carried out at −78 °C in THF. [b] Determined by HPLC analysis. [c] The reduction of the α-carbonyl group to the secondary alcohol was the major reaction. [d] After recrystallization the ratio of **2**:**4** = >99:1. [e] Toluene was used as the solvent.

extremely high diastereoselectivities (**2**:**3**:**4** up to >99:≈0:1, entries 10–15 in Table 1), probably due to the steric effect of the bulky TBPS moiety. The coupled product **2a** was readily hydrolyzed with 3 M HCl in dioxane at 25 °C for 4 h to give (*S*,*S*)-2,3-dimethyltartaric acid (**6a**) (85% yield) together with recovered chiral auxiliary,(*S*)-2-methoxymethylindolinone, (90%) with no loss of chirality. (*S*,*S*)-2,3-Diethyltartaric acid was obtained by hydrolysis of **2b** and shows an opposite sign of specific rotation ($[\alpha]_D^{16} = -6.37$ ($c = 0.926$, H_2O)) to that of (*S*,*S*)-2,3-dimethyltartaric acid ($[\alpha]_D^{16} = +13.1$ ($c = 0.598$, H_2O), $[\alpha]_D^{20} = +13.4$ ($c = 4.0$, H_2O)[12]). As the specific rotation and the absolute configuration of (*S*,*S*)-2,3-diethyltartaric acid have not been reported previously, its absolute configuration was determined by comparison of the CD spectra of *O*,*O*-dianisoyl-2,3-diethyltartaric anhydride with that of the previously known *O*,*O*-dianisoyl-2,3-dimethyltartaric anhydride.[15] The absolute configuration of **2d** was also determined by X-ray analysis (Figure 1).[16]

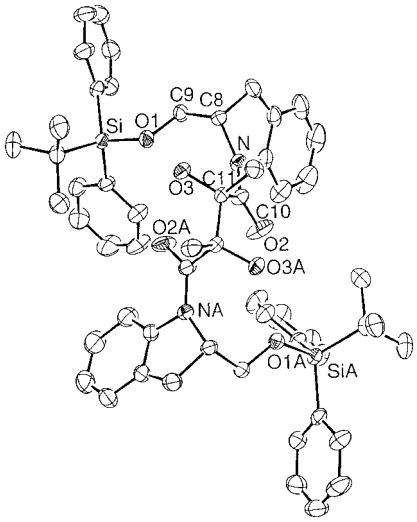


Figure 1. X-ray structure of **2d**.

Although the detailed mechanism is not yet clear, the reaction appears to be initiated by formation of a ketyl radical **A** with a one-electron transfer to SmI_2 followed by coupling of the two ketyl radicals (Figure 2). The coupling takes place at the sterically less hindered *si* face and gives the high diastereoselectivities.

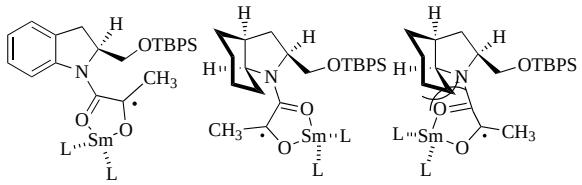
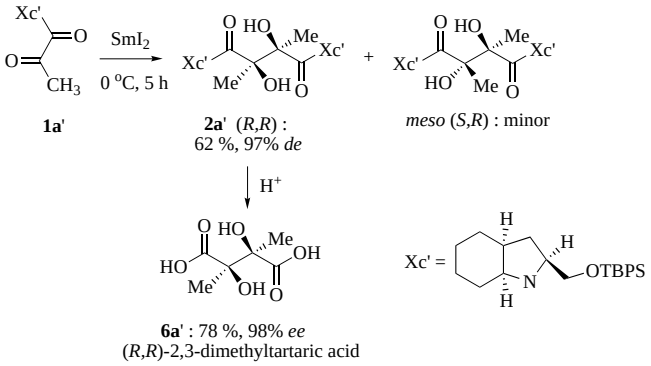


Figure 2. Possible intermediates of the asymmetric pinacol coupling reactions.

In chemical transformations, the synthesis of the individual enantiomers is generally achieved by using chiral sources. However, sometimes natural sources of one of the enantiomers may be limited. Thus, it is desirable and important to obtain both enantiomers by stereocontrolled reactions of prochiral compounds that utilize the same chiral source.[17] We have found that (2*S*,3a*S*,7a*S*)-*N*-pyruvoyl-2-(*tert*-butyldiphenylsilyloxy)octahydroindoline (**1a′**) (99.8% *ee*),[18] affords the opposite configuration of **2a′** (*R*,*R* diol:97% *de*). The ratio of *R*,*R*:*S*,*S*:*meso* is 98.5:≈0:1.5. The ratio was determined by chiral HPLC analysis with a Daicel OD column. The absolute configuration of **2a′** was determined by comparison of the measured optical rotation of (*S*,*S*)-2,3-dimethyltartaric acid (**6a′**) ($[\alpha]_D^{20} = -13.2$ ($c = 4.0$, H_2O)), obtained by hydrolysis of **2a′**, with the literature value.[12]



Scheme 2. Pinacol coupling reaction of compound **1a′** and subsequent hydrolysis to form **6a′**.

The different configurations of the adducts produced can be rationalized by the different intermediates formed from **1a** and **1a′** with SmI_2. Instead of **A**, the intermediate **A′** is favorable in the case of **1a′**; more so than **A″** due to the steric repulsion between the chair formation of the cyclohexane ring and the amide carbonyl moiety (Figure 2).

In conclusion, we have demonstrated diastereo- and enantioselective pinacol coupling reactions of chiral α-ketoamides mediated by SmI_2 with extremely high diastereoselectivities (>99% *de* in some cases). Enantiopure (*S*,*S*)- or (*R*,*R*)-2,3-dialkyltartaric acid derivatives can now be synthesized for the first time depending on the structure of α-ketoamides. When a similar chiral auxiliary, (*S*)-*N*-pyruvoyl-2-(*tert*-butyldiphenylsilyloxy)proline was used, low diastereoselectivities were obtained.[19]

Experimental Section

A solution of SmI_2 (0.1M in THF, 6.70 mL) was added dropwise to a solution of (*S*)-*N*-pyruvoyl-2-(methoxymethyl)indoline (78.1 mg, 0.335 mmol), HMPA (1.34 mmol), and *t*BuOH (1.34 mmol) in THF (4 mL) at −78 °C. After stirring at −78 °C for the appropriate time, the mixture was quenched with 1N HCl solution, extracted with CH_2Cl_2, dried over $MgSO_4$, and then concentrated. The crude product was purified by chromatography to give a solution suitable for HPLC analysis of the mixture of pinacol stereoisomers. The diastereomeric ratio of (*S*,*S*) and (*S*,*R*) was determined by HPLC analysis using a chiral column (Daicel OD, 90% *de*). (*S*,*S*)-Diastereomer **2a** (64% yield): $[\alpha]_D^{18} = +3.08$ ($c = 0.778$ in CH_2Cl_2); ^1H NMR (200 MHz, $CDCl_3$, 25 °C): $\delta = 1.53$ (s, 6H), 2.96 (d, 2H), 3.1–3.3 (m, 4H), 3.32 (s, 6H), 3.62 (m, 2H), 5.35 (m, 2H), 6.09 (s, 2H), 7.00–7.20 (m, 6H), 7.88 (d, 2H); ^{13}C NMR ($CDCl_3$): $\delta = 20.12$, 32.43, 59.14, 59.58, 73.67, 80.45, 119.64, 124.96, 125.21, 126.92, 131.53, 142.83, 177.95; IR (NaCl): $\tilde{\nu} = 3350$ (br), 1620.9, 1590.1, 1478.3, 1265.0, 1121.3 cm^{-1}; MS (70 eV), *m*/*z* (%): 468.2221 ([M^+], 84), 306 (48.3), 278 (95.8), 260 (9.4), 235 (24.7), 190 (20.5), 164 (55.1), 163 (13.8), 132 (26.6), 118 (100), 97 (11.6).

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[14] Due to hindered rotation, the (*S*,*R*)-diastereomer is unsymmetrical and gives twin peaks of equal height. (*S*,*R*)-diastereomer of **3a**: ^{13}C NMR ($CDCl_3$) δ = 23.9, 25.6, 32.3, 58.9, 59.0, 59.4, 59.9, 73.8, 74.2, 79.5, 81.7, 119.9, 124.9, 125.0, 125.1, 125.2, 126.7, 131.5, 131.8, 142.8, 151.3, 175.2, 175.3.

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[16] Empirical formula $C_{56}H_{64}N_2O_6Si_2$: M_r = 917.27, C_2 (no. 5), a = 18.828(5), b = 10.4438(16), c = 13.293(4) Å, β = 100.26(2)°, V = 2572.0(10) Å^3, Z = 2, ρ_{calcd} = 1.184 g cm^{-3}, $\lambda Mo_{K\alpha}$ = 0.71073 Å, μ = 0.120 mm^{-1}, $F(000)$ = 284, T = 293(2) K, $R1$ = 0.0458, $wR2$ = 0.1309, absolute structure parameter = 0.07(16). Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-137 887. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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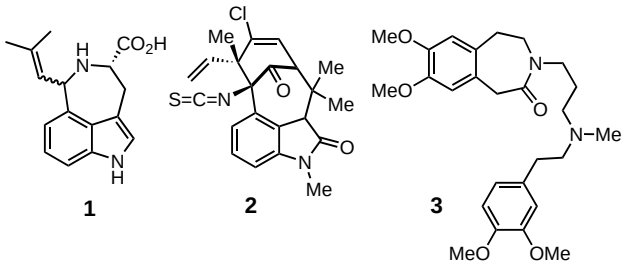
An Expedient Construction of Seven-Membered Rings Adjoining Aromatic Systems**

Talbi Kaoudi, Béatrice Quiclet-Sire, Stéphanie Seguin, and Samir Z. Zard*

Dedicated to Professor Pierre Potier on the occasion of his 65th birthday

In contrast to the closure of five- and six-membered rings, the direct formation of a seven-membered ring by radical addition to an olefin is a relatively uncommon transformation.[1, 2] Examples of the even more difficult corresponding cyclization onto an aromatic ring are very rare.[3] Yet, seven-membered rings adjoining aromatic systems can be found in a variety of biologically active compounds, for example, clavicipitic acid (**1**), a metabolite related to lysergic acid,[4] the more complex, recently isolated welwitindolinones (e.g. *N*-methylwelwitindolinone C isothiocyanate (**2**)),[5] and the benzazepine family of drugs[6] such as Zatebradine (**3**), an antianginal and one of a new group of specific bradycardic agents.[6c,d]



Construction of such seven-membered rings has relied almost exclusively on ionic chemistry.[7] Methods based on radicals have been very rarely applied, mainly because the desired cyclization is too slow to compete with other pathways open to the radical intermediate. Premature reduction, for example, is what is usually observed when organotin hydride based procedures are applied.[1, 2, 8] Indeed, the very few examples involving stannanes are generally low yielding and concern invariably pyrrole- or imidazole-type heteroaromatic structures activated by electron-withdrawing groups.[3a–d] Compounds with seven-membered (and even larger) rings fused to an aromatic nucleus have been obtained in modest yield by photolysis of suitable chloroamides.[3e–j] The mechanism here is not clear; formation of exciplexes and electron

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