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Asymmetric pinacol coupling of aromatic aldehydes with $TiCl_2$/enantiopure amine or hydrazine reagents

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Abstract

Asymmetric pinacol coupling of aromatic aldehydes under homogeneous conditions with $TiCl_2$ in the presence of enantiopure amines or hydrazines afforded 1,2-diols in moderate to excellent yields with good *dl*-diastereoselectivities and enantioselectivities in the range of 6–65% *ee*. A non-linear temperature effect ('principle of isoinversion') has been examined.

One of the most straight forward and efficient methods for the synthesis of vicinal diols is the pinacol coupling reaction of carbonyl compounds.[1] Since the pioneering contributions in this field by Mukaiyama et al.[2] and McMurry et al.,[3] low valent titanium compounds are most prominent for this C–C bond coupling. One general method involves the reduction of titanium-(IV) compounds, for instance with Zn, $LiAlH_4$, etc., usually under heterogeneous conditions.[3,4] Recently, the *dl*-diastereoselectivity of the pinacol coupling reaction has been controlled efficiently by low valent titanium species under homogeneous conditions.[5] Another protocol is based on titanium(II) chloride, easily prepared from titanium(IV) chloride and hexamethyldisilane,[6] in the presence of zinc[7a] or titanium(II) bromide/copper.[7b]

Very recently, Matsubara et al.[8] developed an enantioselective version of the pinacol coupling with titanium(II) chloride and enantiopure tertiary amines or vicinal diamines as additives. In the case of hydrobenzoin enantiomeric excesses of 0–41% were reached.

We now wish to report our independent results[9] on the asymmetric pinacol coupling reaction of aromatic aldehydes with titanium(II) chloride in the presence of enantiopure secondary amines or hydrazines.

As is described in Scheme 1, aromatic aldehydes **1** were treated with a brown black to blue tetrahydrofuran solution generated from titanium(II) chloride and two equivalents of the enantiopure secondary amines and hydrazines **3**–**9**, respectively. In the case of benzaldehyde, the

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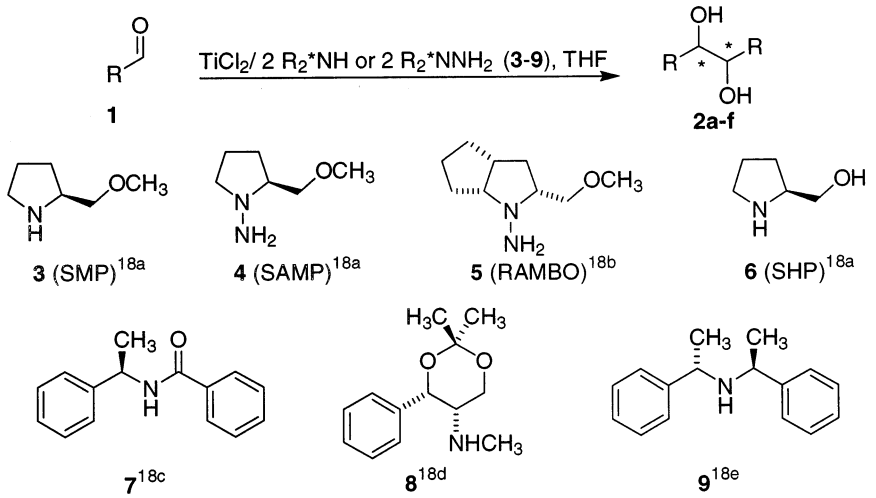
resulting 1,2-diol **2a** was obtained in moderate to excellent yields (33–100%) with good diastereoselectivities (*dl*:*meso* = 71:29–94:6) and enantiomeric excesses in the range 6–65% (Table 1).



Scheme 1. Diastereo- and enantioselective pinacol coupling of aromatic aldehydes by $TiCl_2$/enantiopure amine or hydrazine reagents[18]

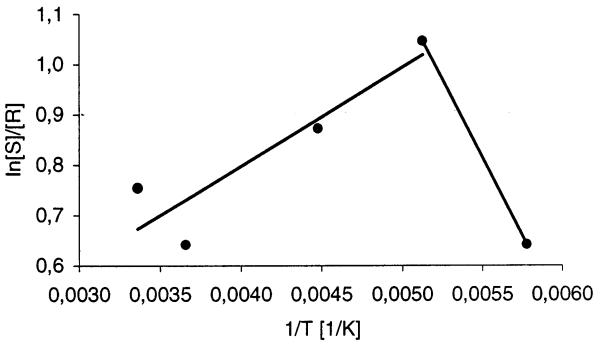
Table 1
Enantioselective pinacol coupling of benzaldehyde by $TiCl_2$/2*R_2NH or 2*R_2NNH_2, THF

Chiral amine	*T* (°C)	*t* (h)	Yield (%)	*dl*:*meso*	*ee* (%)[a] (*S*,*S*)
3	rt	8	42	83:17	36
3	0	8	35	79:21	31
3	−50	8	35	79:21	42
3	−78	23	31	81:19	65
3	−78	8	31	81:19	48
3	−78	48	100	56:44	37
3	−100	8	25	72:28	31
4	rt	7	60	65:35	30
4	−78	8	100	78:22	29
5	rt	8	40	70:30	31
5	−78	8	100	74:26	29
6	rt	7	33	94:6	6
7	rt	7	100	71:29	24
8	rt	7	60	75:25	21
9	rt	7	90	89:11	23

[a] Determined by HPLC on chiral stationary phases.

The diastereomeric excesses (*dl*/*meso*) were determined by ^1H NMR analysis, the enantiomeric excesses by HPLC using chiral stationary phases. In the cases of the hydrazines SAMP **4** and RAMBO **5** as chiral additives the yield of hydrobenzoin **2a** was higher at −78°C than at room temperature. This may be explained by the competing formation of the corresponding hydrazones as a side reaction at room temperature.

The pinacol coupling reaction of benzaldehyde **1a** in the presence of two equivalents of the enantiopure secondary amine (*S*)-2-methoxymethyl-pyrrolidine **3** (SMP) in THF generates the *dl*-1,2-diol **2a** at 78°C with an enantiomeric excess of 65% and at 100°C with an *ee* value of 31%. In the case of a decreasing enantioselectivity in combination with a decreasing reaction temperature the principle of isoinversion introduced by Scharf et al.[10] can be applied. The Eyring plot $\ln [S]/[R]$ against $1/T$ of this system showed two linear regions intersecting at an inversion point T_{inv} (Fig. 1).[11,19] The activation parameters $\Delta\Delta H^{\#}$ and $\Delta\Delta S^{\#}$ are accessible from the Eyring plot. From these parameters the isoinversion temperature was calculated to be $T_{inv} = 194$ K. For this temperature the best enantioselectivity is expected.



(1) Eyring-plot:[19] $k = k_0 e^{-\Delta G^{\#}/RT} = k_0 e^{-\Delta H^{\#}/RT + \Delta S^{\#}/R}$

(2) $\ln \frac{k_1}{k_2} = \ln \frac{[S]}{[R]} = -\frac{\Delta\Delta H^{\#}}{R} \frac{1}{T} + \frac{\Delta\Delta S^{\#}}{R}$

$T_{inv} = \frac{\partial(\delta\Delta\Delta H^{\#})}{\partial(\delta\Delta\Delta S^{\#})} = 194$ K

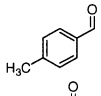
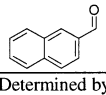
(3) $\delta\Delta\Delta H^{\#} = \Delta\Delta H_2^{\#} - \Delta\Delta H_1^{\#}$,

$\delta\Delta\Delta S^{\#} = \Delta\Delta S_2^{\#} - \Delta\Delta S_1^{\#}$

Figure 1. Eyring plot and calculation of the inversion temperature T_{inv}

In addition we varied the aldehydes **1** under the optimum pinacol coupling conditions with SMP as the auxiliary ligand at −78°C and established that the yields are in the range of 15–100% reaching enantioselectivities of 26–65% *ee*. The absolute configurations of the *dl*-1,2-diols given

Table 2
Enantioselective pinacol coupling of aromatic aldehydes by $TiCl_2$/2SMP, THF[12]

aromatic aldehydes **1**	1,2-diols **2**	yield [%]	t [h]	*dl*:*meso*	*ee* [%][a] (*S*,*S*)
	**2a**	31	23	81:19	65
	**2b**	59	8	73:27	47
	**2c**	100	23	88:12	28
	**2d**	33	23	76:24	41 (*R*,*R*)[b]
	**2e**	15	23	96:4	44
	**2f**	15	8	95:5	26

[a] Determined by HPLC on chiral stationary phases.
[b] Enantiomeric configuration due to CIP-rules.

were determined by comparison of the specific rotations with compounds of known configuration (Table 2).

Additionally, we tried the asymmetric pinacol coupling reaction with three heteroaromatic aldehydes, namely 2-pyridinecarbaldehyde, 1*H*-2-pyrrolecarbaldehyde and 2-furaldehyde. With the two nitrogen-containing aldehydes no reaction was observed and no starting material was recovered. With 2-furaldehyde a good *dl*:*meso* selectivity of 91:9 and a remarkable enantiomeric excess of 45% of the (*R*,*R*)-diol was obtained, however only in low yield.

In conclusion, the new variant of the asymmetric pinacol coupling of aromatic aldehydes with $TiCl_2$ in the presence of two equivalents of SMP leads to 1,2-diols in moderate to excellent yields, good *dl*-diastereoselectivities and enantiomeric excesses of up to 65%.

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12. Typical procedure for asymmetric pinacol coupling: To a solution of $TiCl_2$ (2.0 mmol) in THF (10 ml) was added the amine (4.0 mmol) at 0°C. The mixture was stirred for 15 min at room temperature. In the case of amine **3** the solution of the coupling reagent $TiCl_2$/2SMP in THF was homogeneous and dark blue. The solution was cooled to the desired temperature, the aldehyde (1.0 mmol) was added and the resulting mixture was stirred. The mixture was poured into 1 M HCl_{aq} and extracted with ether. Purification by silica gel column chromatography gave the corresponding 1,2-diols.
(S,S)-*1,2-Diphenyl-1,2-ethanediol* (S,S)-**2a** mp 99°C; $[\alpha]_D^{25} = -7.90$ ($c = 0.12$, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 3.21 (2H, s, O*H*), 4.63 (2H, s, C*H*, *dl*), 4.84 (2H, s, C*H*, *meso*), 7.03–7.25 (m, 10H, arom. *H*). Enantiomeric

excess by HPLC: (*S*,*S*)-Whelk-01 (hexane:2-propanol 95:5, flow rate = 1.0 mL/min): $t_r(S,S) = 9.4$ min, $t_r(R,R) = 11.4$ min. All other data were identical with those given in lit.[13]

(S,S)-*1,2-Di(4-chlorophenyl)-1,2-ethanediol* (S,S)-**2b** mp 142°C; $[\alpha]_D^{25} = +9.73$ ($c = 0.18$, $CHCl_3$); ^1H NMR (400 MHz, CD_3OD) δ 4.64 (2H, s, O*H*), 4.73 (2H, s, C*H*, *meso*), 4.86 (2H, s, C*H*, *dl*), 6.95–7.35 (8H, m, arom. *H*). Enantiomeric excess by HPLC: (*S*,*S*)-Whelk-01 (hexane:2-propanol 95:5, flow rate = 1.0 mL/min): $t_r(S,S) = 9.1$ min, $t_r(R,R) = 10.8$ min. All other data were identical with those given in lit.[13,14]

(S,S)-*1,2-Di(4-methylphenyl)-1,2-ethanediol* (S,S)-**2c** mp 156°C; $[\alpha]_D^{25} = -1.55$ ($c = 0.52$, EtOH); ^1H NMR (400 MHz, CD_3OD) δ 2.16 (6H, s, CH_3), 3.24 (2H, s, C*H*, *meso*), 4.48 (2H, s, C*H*, *dl*), 6.87 (8H, m, arom. *H*). Enantiomeric excess by HPLC: (*S*,*S*)-Whelk-01 (hexane:2-propanol 95:5, flow rate = 1.0 mL/min): $t_r(S,S) = 10.9$ min, $t_r(R,R) = 14.2$ min. All other data were identical with those given in lit.[13,15]

(R,R)-*1,2-Di(2-thienyl)-1,2-ethanediol* (R,R)-**2d** mp 69°C; $[\alpha]_D^{25} = +3.70$ ($c = 0.41$, EtOH); ^1H NMR (400 MHz, $CDCl_3$) δ 4.00 (2H, s, O*H*), 4.84 (2H, s, C*H*, *dl*), 5.00 (2H, s, C*H*, *meso*), 6.64–7.11 (6H, m, arom. *H*). Enantiomeric excess by HPLC: Chiralcel OD2 (hexane:2-propanol 95:5, flow rate = 1.0 mL/min): $t_r(S,S) = 26.4$ min, $t_r(R,R) = 30.3$ min. All other data were identical with those given in lit.[16]

(S,S)-*1,2-Di(2-bromophenyl)-1,2-ethanediol* (S,S)-**2e** mp 97°C; $[\alpha]_D^{25} = +2.74$ ($c = 0.73$, EtOH); ^1H NMR (400 MHz, CD_3OD) δ 4.72 (2H, s, O*H*), 5.19 (2H, s, C*H*, *dl*), 5.41 (2H, s, C*H*, *meso*), 6.85–7.66 (8H, m, arom. *H*). Enantiomeric excess by HPLC: (*S*,*S*)-Whelk-01 (hexane:2-propanol 90:10, flow rate = 1.0 mL/min): $t_r(S,S) = 5.4$ min, $t_r(R,R) = 6.4$ min. All other data were identical with those given in lit.[17]

(S,S)-*1,2-Di(2-naphthyl)-1,2-ethanediol* (S,S)-**2f** mp 209°C; $[\alpha]_D^{25} = +4.62$ ($c = 0.26$, d^4-THF); ^1H NMR (400 MHz, THF) δ 2.50 (2H, s, O*H*), 4.84 (2H, s, C*H*, *dl*), (2H, s, C*H*, *meso*), 7.16–7.72 (14H, m, arom. *H*). Enantiomeric excess by HPLC: (*S*,*S*)-Whelk-01 (hexane:2-propanol 90:10, flow rate = 1.0 mL/min): $t_r(S,S) = 20.8$ min, $t_r(R,R) = 29.2$ min. All other data were identical with those given in lit.[16]

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