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Influence of a dimetal ion binding ferrocene ligand on the samarium diiodide promoted pinacol coupling reaction

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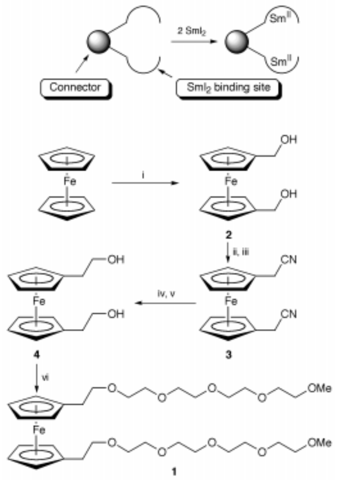
Substantial yield increases have been noted in the use of a di-SmI_2 binding ligand for the pinacol coupling of alkyl aldehydes compared to 1 : 1 complexes of SmI_2 and tetraglyme. High diastereoselectivities of *ca*. 10 : 1 are also observed for α-substituted alkyl aldehydes in favour of the (±)-isomers.

Samarium diiodide is an important one-electron reducing agent which has been employed in a multitude of organic synthetic transformations.[1] When pertinent, these reactions are generally associated with high levels of stereochemical control. One exception is the intermolecular pinacol coupling reaction of carbonyl compounds[2] to access vicinal diol systems. With aryl ketones or aldehydes, these reactions have been reported to be high yielding,[3,4] but are also characterised by low diastereoselectivities (± : *meso, ca.* 1.3 : 1), the exception being when certain metal complexes of aryl aldehydes are used.[5] Only a few examples of alkyl aldehydes have been studied so far where similar ± : *meso* ratios were noted.[3] In our efforts to improve the diastereoselectivities of the SmI_2 promoted pinacol coupling of aryl and alkyl aldehydes, we have recently reported on the beneficial effects the addition of tetraglyme derivatives to the one electron reducing agent may have prior to the coupling step.[6]

We have been interested in synthesising ligands which can bind two divalent samarium ions with the purpose of investigating their influence on the diastereoselectivities and yields in the SmI_2-induced pinacol coupling (Scheme 1). Here we show that the use of one such example may significantly increase yields of the vicinal diols obtained from branched alkyl aldehydes, while still retaining the high ±-selectivity.

As a dimetal ion complexing agent, we prepared the bis-tetraglyme derivative **1** possessing a metallocene unit as the connector (Scheme 1). This ligand was chosen primarily because of the affinity of tetraglyme for divalent samarium ions,[6,7] while rotational freedom of the cyclopentadienyl rings around the iron core[8] allows radical or anionic intermediates of the pinacol coupling to easily find suitable conformations between the two lanthanide metal centers. The ability of ferrocene to absorb in the visible light region also simplifies the isolation of this ligand type upon chromatographic separation of the products.



Scheme 1 *Reagents and conditions:* i, 2.1 equiv. BuLi, 2.1 equiv. TMEDA, then $(CH_2O)_n$, 54%; ii, PCl_3, THF–Pyr; iii, KCN, H_2O–THF, 52% (2 steps); iv, NaOH, EtOH, 89%; v, $LiAlH_4$, THF, 77%; vi, 3.0 equiv. NaH, DMF, then 3.5 equiv. $MeO(CH_2CH_2O)_4Ts$, 86%.

The synthesis of the ferrocene ligand **1** is depicted in Scheme 1, adapting procedures previously developed by Frejd[9] and Moritani.[10] Formation of bis(hydroxymethyl)ferrocene **2** was easily achieved by direct lithiation of ferrocene with 2 equiv. of BuLi followed by addition of paraformaldehyde. The dichloride obtained by treating **2** with PCl_3 was immediately converted to the dicyanide **3**. Basic hydrolysis and reduction then gave the crystalline diol **4** (mp 43–44 °C). Introduction of the complete side chains was achieved by alkylation of **4** with the tosylate of tetraethylene glycol monomethyl ether affording **1** as an orange–brown coloured oil in 86% yield.

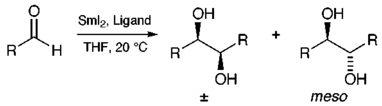
Addition of a 0.1 M THF solution of SmI_2 to 0.5 equiv. of ligand **1** at 20 °C leads to darkening of the solution with eventual precipitation of a black solid. An immediate reaction was noted upon subjecting this mixture to benzaldehyde affording a *ca*. 5 : 1 diastereoselectivity in favour of the *meso*-isomer (Table 1, entry 1). Augmenting the ligand to divalent samarium ratio to 1 : 1 had no effect on either the *meso* : ± selectivity nor the yields (entry 2). Whereas no notable improvement in the diastereoselectivity of the diol product is noted with ligand **1** compared with a similar reaction using 1 equiv. of tetraglyme (entry 3), these results do suggest that **1** binds two metal ions.†

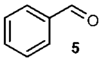
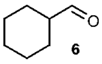
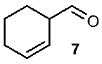
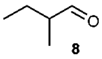
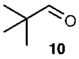
Noteworthy are the effects observed in the pinacol coupling of alkyl aldehydes. The tetraglyme–SmI_2 complex converts cyclohexanecarbaldehyde to a 10 : 1 mixture of ± : *meso* isomers albeit in low yield (29%) after 24 h at 20 °C (entry 4). Under similar conditions with **1**–2SmI_2, this yield was remarkably increased to 81% (entry 5) while still maintaining the high diastereoselectivity, making this method competitive with other metal reducing systems.[2] On the other hand, premixing SmI_2 to 1 equiv. of ligand **1** prior to the addition of cyclohexanecarbaldehyde maintains the high diastereoselectivity but lowers the yield of the reaction to 38% (entry 6), a result which resembles that of the tetraglyme–SmI_2 complex. The same trend was noted with tetrahydrobenzaldehyde, where a 24% increase in the pinacol coupling yield was noted with a ± : *meso* selectivity of 11 : 1 (entries 7 and 8) when ligand **1** was employed instead of tetraglyme.

In the SmI_2 induced dimerisation of isobutyraldehyde, the reaction is less clean affording a modest yield of the diol (entry 9, 44%) with a diastereoselectivity of 1.9 : 1. Whereas, this yield is even lower with tetraglyme (entry 10), the use of the **1**–2SmI_2 complex retains the 44% yield while increasing the selectivity to 10 : 1 (entry 11).

The Tischenko-type side reactions are problematic with linear aldehydes such as *n*-octanal, but again an increase in the yield of the coupled product is observed when using ligand **1** (entries 12 and 13). Interestingly, in this case the diastereo-

Table 1 Effect of a dimetal ion binding ligand on the SmI_2 promoted pinacol coupling.[a]

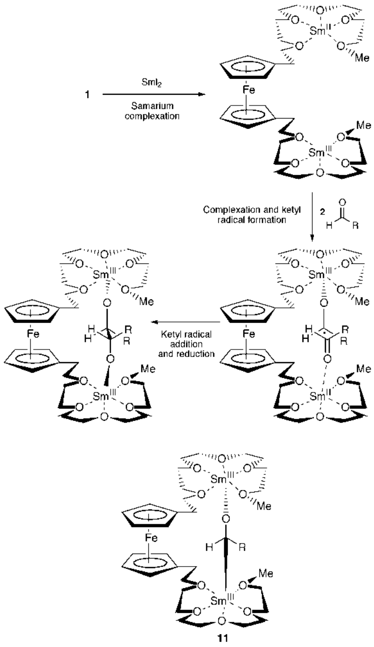


Entry	Aldehyde	Ligand (equiv.)[b]	Yield (%)[c]	Diastereosel (±: *meso*)
1	 **5**	1 (0.5)	89	1:5.0
2	**5**	1 (1.0)	92	1:5.5
3	**5**	Tetraglyme (1.0)	83	1:5.9[d]
4	 **6**	Tetraglyme (1.0)	29	10:1
5	**6**	1 (0.5)	81	10:1
6	**6**	1 (1.0)	38	13:1
7	 **7**	Tetraglyme (1.0)	53	14:1[e]
8	**7**	1 (0.5)	77	11:1[e]
9	 **8**	None	44	1.9:1
10	**8**	Tetraglyme (1.0)	24	10:1
11	**8**	1 (0.5)	44	10:1
12	$CH_3(CH_2)_6CHO$ **9**	Tetraglyme (1.0)	45	3.0:1
13	**9**	1 (0.5)	68	2.2:1
14	 **10**	None	79	8.5:1
15	**10**	Tetraglyme (1.0)	0	—
16	**10**	1 (0.5)	0	—

[a] Conditions: complexed or uncomplexed SmI_2 (0.1 M, 1.5 equiv.), aldehyde (1 equiv.), THF, 20 °C. [b] Based on the number of equivalents of SmI_2 added. [c] Based on isolated, chromatographically pure material. [d] Taken from ref. 6. [e] Determined after catalytic hydrogenation (Pd/C, H_2) of the diastereomeric mixture of diols.

selectivity is low suggesting that substitution at the α-position of the alkyl aldehyde is necessary for obtaining the high ±: *meso* ratio when using the polyethyleneglycol complexing agents. Increasing the steric bulkiness, as exemplified with pivalaldehyde, surprisingly led to no pinacol coupling with either tetraglyme or **1** (entries 15 and 16). Nevertheless, without these ligands SmI_2 promoted this dimerisation with an 8.5:1 selectivity (entry 14). The steric bulkiness of the aldehyde was sufficient to induce a high diastereoselectivity. These results again support the notion that uncomplexed SmI_2 is not available in solution when the one electron reducing agent is added to 0.5 equiv. of ligand **1**.

The combined findings suggest the formation of a complex between two samarium(II) metal ions and **1** as illustrated in Scheme 2. Coordination of the two aldehyde units to each of the two oxophilic metallic centers may then take place. The slow reactivity of alkyl aldehydes also suggests that there is only a low concentration of a ketyl radical species in solution. The close proximity of the carbon radical center to the other aldehyde, which possesses a low-lying LUMO due to its coordination to SmI_2, could lead to a radical addition step with concomitant reduction of the resulting alkoxyl radical by SmI_2.[6] A two electron reduction of the aldehyde to dianion **11**, which eventually couples to a second aldehyde, is a possible alternative mechanism because ligand **1** improves significantly the yields of these pinacol coupling reactions compared to that of tetraglyme, and although little effect is seen on the diastereoselectivities, these preliminary observations tend to support the radical addition mechanism where the entropy contribution is less important owing to the pseudo-intramolecular nature of this reaction.



Scheme 2

In conclusion, we have shown that dimetal binding ligands can have a substantial effect on the SmI_2 induced pinacol coupling of alkyl aldehydes compared to that of tetraglyme. Efforts are underway to increase the utility of such ligands. The introduction of either planar chirality in the connector or asymmetric carbon centers in the tetraglyme units may also lead to the development of an asymmetric version of the pinacol coupling reaction with alkyl aldehydes.

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Notes and references

† Preliminary investigations of this complex by cyclic voltametry imply that the metallocene center does not influence the oxidation potential of SmI_2 (ref. 6 and 11).

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