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Samarium Diiodide-Catalyzed Diastereoselective Pinacol Couplings

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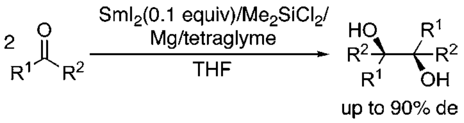
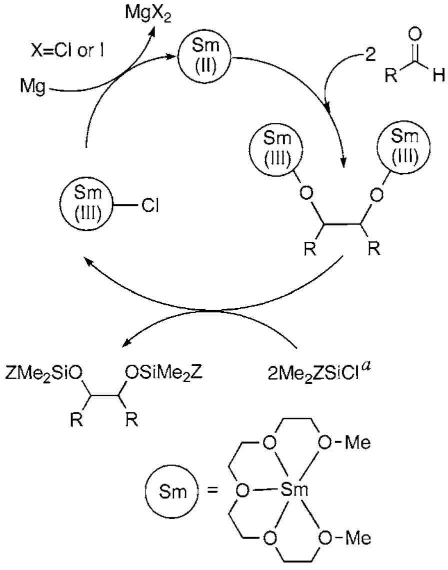
ABSTRACT



A complex of samarium diiodide (SmI_2) with tetraglyme catalyzes the intermolecular pinacol coupling of aromatic or aliphatic aldehydes at loadings of 10 mol % in the presence of Me_2SiCl_2 and Mg. Diastereoselectivity of up to 95/5 (±/meso) has been achieved for aliphatic aldehydes and up to 19/81 (±/meso) for aromatic aldehydes. De values of up to 99% have been achieved in intramolecular pinacol coupling reactions using the SmI_2/tetraglyme/Mg/Me_2SiCl_2 catalytic system.

SmI_2 is a unique one-electron reducing agent, and since Kagan reported the first reliable preparation in 1977, it has become widely used in synthetic chemistry.[1−3] However, its use in large-scale reactions is precluded by the need to use stoichiometric quantities of this relatively expensive reagent. The development of a straightforward system in which a catalytic quantity of SmI_2 is regenerated by a cheap reducing agent would make SmI_2 chemistry accessible for larger scale chemistry. Previous examples of catalytic Sm(II) systems have used electrochemical reduction,[4] and zinc[5] or mischmetall as the reductant.[6] We chose to investigate the pinacol coupling reaction, which works well for aromatic aldehydes when stoichiometric SmI_2 is used but is rather slower for ketones and aliphatic aldehydes.[7] A useful catalytic system for the pinacol coupling reaction should deliver high diastereoselectivity as well as good yields. Endo has reported a catalytic pinacol coupling using SmI_2 with Mg as the reducing agent, but although good yields were obtained, no distereoselectivity was obtained for intermolecular reactions.[8] More recently, there has been a report of the use of $SmBr_2$-catalyzed pinacol coupling with mischmetall as the coreductant.[9] The addition of chelating ligands to the stoichiometric SmI_2-promoted pinacol coupling is known to influence the diastereoselectivity of the reaction:[10,11] a ±/meso ratio of 15/85 was achieved in the coupling of benzaldehyde in the presence of 1 equiv of tetraglyme per SmI_2.

Scheme 1. SmI_2-Catalyzed Pinacol Coupling Reaction



[a] Me_2ZSiCl is Me_2SiCl_2 or Me_3SiCl.

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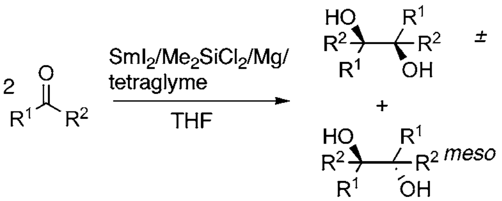
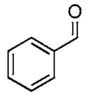
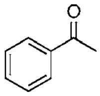
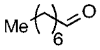
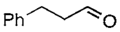
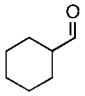
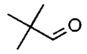
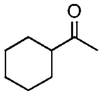
(1) Molander, G. A. *Chem. Rev.* **1992**, *92*, 29−68.
(2) Molander, G. A.; Harris, C. R. *Chem. Rev.* **1996**, *96*, 307−338.
(3) Molander, G. A. *Acc. Chem. Res.* **1998**, *31*, 603−609.
(4) Léonard, E.; Duñach, E.; Périchon, J. *J. Chem. Soc., Chem. Commun* **1989**, 276−277.
(5) Corey, E. J.; Zheng, G. Z. *Tetrahedron Lett.* **1997**, *38*, 2045−2048.
(6) Hélion, F.; Namy, J.-L. *J. Org. Chem.* **1999**, *64*, 2944−2946.
(7) Namy, J. L.; Souppe, J.; Kagan, H. B. *Tetrahedron Lett.* **1983**, *24*, 765.

10.1021/ol050256f CCC: $30.25

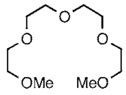
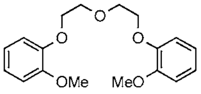
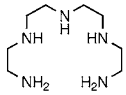
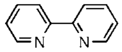
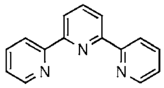
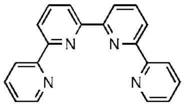
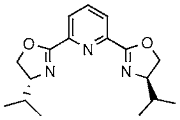
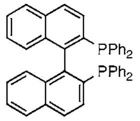
Table 1. Pinacol Coupling of Aldehydes and Ketones Catalyzed by SmI$_2$/Tetraglyme



entry	substrate	mol% SmI$_2$	time/h	isolated yield (%)[a]	±/meso[a]
1		10	4	83	20/80
2		10	4	62	19/81
3		20	15	97	68/32
4		10	15	76	65/35
5		10	15	63	81/19
6		10	20	76	95/5
7		20	20	74	94/6

[a] After purification by flash chromatography. [b] Ratio determined by GC and confirmed by GCMS.

Table 2. Effect of Added Ligand on SmI$_2$-Catalyzed Pinacol Coupling of Benzaldehyde[a]

entry	L	conversion/%	±/meso	byproduct/%
1	none	80	50/50	
2			15/85	
3		>99	43/57	<1
4[b]		>90	35/65	<1
5[b]		>90	47/53	15
6		>90	34/66	15
7		>90	38/62	15
8[b]		>99	28/72	<1
9		>99	35/65	<1

[a] Conditions: 10 mol % SmI$_2$/L/PhCHO (2 equiv)/Me$_3$SiCl (2 equiv)/Mg (16 equiv)/THF, rt [b] Performed with 2 equiv of L

We began our investigations using a catalytic system as shown in Scheme 1, which is closely related to Endo's system but with the addition of potentially chelating ligands in order to induce some diastereoselectivity. In the catalytic reaction, it is necessary for the chelating agent to be sufficiently flexible to bind both to the very large Sm^{2+} ion (eight-coordinate radius 141 pm) and to the smaller Sm^{3+} ion (eight-coordinate radius 122 pm). Tetraglyme fulfills the requirement of binding to lanthanide (Ln) ions in the +2 and +3 oxidation states: [EuI$_2$(tetraglyme)(THF)][12] and several complexes with Ln^{3+} have been characterized by X-ray diffraction.[13] Tetraglyme has the added advantage of low cost and ready availability.

The catalytic pinacol coupling requires the concentration of Sm(II) to be higher than that of the carbonyl substrate; otherwise, side reactions such as benzoin condensation or Tischenko reaction can occur, and so the rate of addition of carbonyl compound was carefully optimized to preserve the deep blue color of Sm(II) throughout the reaction. The precise nature of the Sm(II) species is not clear due to the presence of both chloride and iodide in the reaction mixture; indeed chloride may be beneficial to the reaction.[14] Despite our best efforts, when we used Me$_3$SiCl as the reagent to cleave the pinacol−Sm(III) bond, we were unable to reduce the SmI$_2$ loading below 50 mol %. However, after investigation of a range of chlorosilanes, we found that use of Me$_2$SiCl$_2$ allowed us to reduce the SmI$_2$ loading to as little as 10 mol %. We found that the order of addition of reagents was important: Me$_2$SiCl$_2$ must be added to SmI$_2$ *before* the tetraglyme; otherwise, the diastereoselectivity achieved is negligible. The use of more than 1 equiv of tetraglyme per mol of SmI$_2$ had no significant effect on the outcome of the reaction. As expected, the reaction was slower for aliphatic compared with aromatic substrates. In the absence of SmI$_2$, very little coupling occurred (<10%). Our optimized results for a range of aliphatic and aromatic carbonyl substrates are summarized in Table 1.

Daasbjerg and Skrydstrup have investigated the effect of tetraglyme on pinacol couplings promoted by stoichiometric

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(10) Pedersen, H. L.; Christensen, T. B.; Enemaerke, R. J.; Daasbjerg, K.; Skrydstrup, T. *Eur. J. Org. Chem.* **1999**, 565−572.

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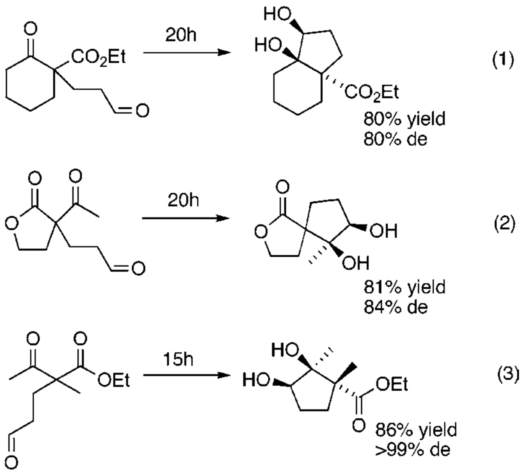
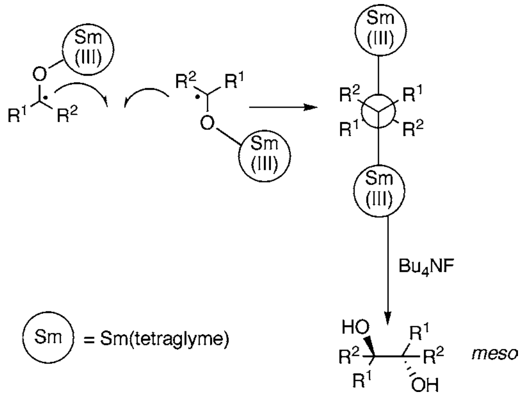
Scheme 2. Intramolecular Pinacol Couplings Catalyzed by SmI_2/Tetraglyme[a]



[a] Conditions: SmI_2/tetraglyme (10 mol %), Mg (16 equiv), Me_2SiCl_2 (2 equiv), THF, rt.

Scheme 3. Proposed Mechanism for the Diastereoselective Pinacol Coupling of Aromatic Carbonyl Substrates



SmI_2, and our catalytic results show some notable differences. For example, we obtained good to excellent yields for the coupling of octanal (entry 3), cyclohexane carboxaldehyde (entry 5), and pivaldehyde (entry 6), whereas the stoichiometric reaction in the presence of tetraglyme gave only 45, 29, and 0% yield of product, respectively.

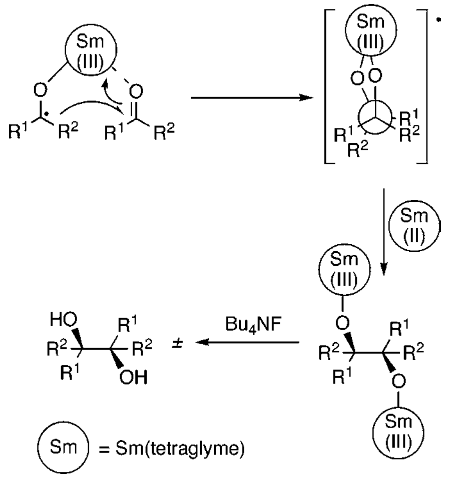
Tetraglyme was our first choice of ligand because of its ready availability and its known ability to bind to Sm(II) and Sm(III). However, we felt that it was important to investigate other potential chelating agents, and some of our results are summarized in Table 2. Addition of any of these ligands to a blue solution of SmI_2 resulted in some color change, indicating that complex formation had occurred. The most obvious point to note is that none of the ligands is as effective as tetraglyme in promoting diastereoselectivity. In many cases, substantial quantities of byproduct (e.g., benzyl alcohol) were formed; this was not observed for tetraglyme.

Having established optimized conditions for the intermolecular pinacol coupling of a range of substrates, we then applied our method to intramolecular couplings of synthetic interest as shown in Scheme 2. Reactions 2 and 3 have been carried out by Molander using stoichiometric SmI_2;[15,16] reaction 2 gave 44% yield with a de of 99%, and reaction 3 gave 77% yield with a de of 99%. The stereochemistry of the product from reaction 2 was established by X-ray diffraction.

The precise mechanism of the pinacol coupling reaction is not known, but the reversal of diastereoselectivity that we observe between aromatic and aliphatic substrates is indicative of different reaction mechanisms in these two cases. The LUMO of an aromatic carbonyl has lower energy than that of an aliphatic carbonyl, and so the one-electron reduction of an aromatic carbonyl to give a Sm(III)-bound ketyl radical is a relatively facile process. The concentration of these radical species will be sufficiently high to allow the dimerization process shown in Scheme 3. The size of the Sm centers is increased by coordination of tetraglyme, and mutual steric repulsion between the Sm centers in the transition state leads to a *meso* product.

The LUMO of an aliphatic carbonyl is higher in energy, and so the formation of the Sm(III)-bound ketyl radical is slower, resulting in very low concentrations of these species in solution and significantly reducing the possibility of the dimerization of Sm(III)-bound ketyl radicals outlined in Scheme 3. Instead, a second molecule of carbonyl substrate binds to the Lewis acidic Sm center of the Sm(III)-bound ketyl radical. The stereochemistry of this complex formation is dictated by steric interactions between the alkyl groups of the ketyl radical and the carbonyl. The ketyl radical then adds to the bound carbonyl, and the resulting Sm(III)-bound radical undergoes a further one-electron reduction by SmI_2 to give a disamarium diolate. If there is a significant size difference between R^1 and R^2, formation of the ± diastere-

Scheme 4. Proposed Mechanism for the Diastereoselective Pinacol Coupling of Aliphatic Carbonyl Compounds



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(14) Fuchs, J. R.; Mitchell, M. L.; Shabangi, M.; Flowers, R. A., II. *Tetrahedron Lett.* **1997**, *38*, 8157–8158.

(15) Molander, G. A.; Kenny, C. *J. Am. Chem. Soc.* **1989**, *111*, 8236–8246.

(16) Molander, G. A.; Kenny, C. *J. Org. Chem.* **1988**, *53*, 2134–2136.

omer will be favored. A similar mechanism has been proposed for the Mg-promoted cross coupling of aliphatic and aromatic carbonyl compounds.[17]

In the case of the intramolecular pinacol coupling, a mechanism similar to that shown in Scheme 4 is likely, but because of molecular constraints, formation of the syn diastereomer is favored.

In conclusion, we have developed a convenient method for diastereoselective inter- and intramolecular pinacol coupling of aliphatic and aromatic carbonyl compounds using a catalytic quantity of SmI_2 (10 mol %) coordinated by tetraglyme.

Acknowledgment. We thank the Leverhulme Centre for Innovative Catalysis for financial support (studentship to C.V.).

Supporting Information Available: Experimental details for the synthesis of dicarbonyl substrates in Scheme 2 and characterization of diol products in Scheme 2; CIF file for the diol product of reaction 2 in Scheme 2. This material is available free of charge via the Internet at http://pubs.acs.org.

OL050256F

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(17) Maekawa, H.; Yamamoto, Y.; Shimada, H.; Yonemura, K.; Nishiguchi, I. *Tetrahedron Lett.* **2004**, *45*, 3869−3872.