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Reduction of Benzophenone by SmI_2: The Role of Proton Donors in Determining Product Distribution

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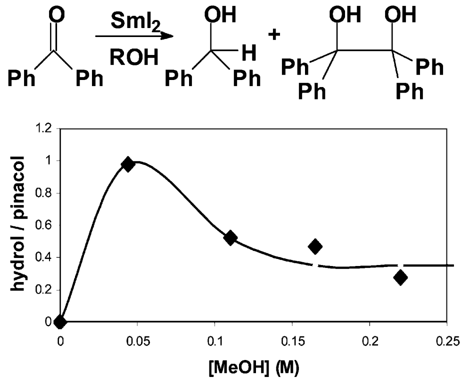
ABSTRACT



Reduction of benzophenone by SmI_2 yields benzopinacol. Addition of proton donors results in an initial increase in the amount of the benzhydrol formed. However, the ratio benzhydrol/benzopinacol reaches a maximum, decreases, and then levels off as the proton donor concentration is further increased. The position of the maximum and its height depend on the proton donor concentration and its kinetic acidity. The momentary concentration of the intermediate radicals governs the product distribution.

Reduction of carbonyl compounds is one of the focal points in the chemistry of SmI_2. It may yield two products, the corresponding alcohol and a coupling product−pinacol (for reviews, see refs 1−3).

Besides numerous synthetic applications, several mechanistic aspects of this reaction have also been investigated. These include the effects of additives such as poly(ethylene glycol) ethers on the diastereoselectivity of the coupling reaction,[4] the effect of solvents on the latter,[5] and the rate acceleration by amines,[6] diols,[7] and β-complexation.[8,9] Daasbjerg and Skrydstrup determined the rate constant for the electron-transfer step between SmI_2 and acetophenone to be 7 M^{-1} s^{-1} and concluded that this was an innersphere process.[10] The same conclusion was reached by Flowers and co-workers who also observed that LiCl or LiBr enhance the coupling process.[11] Recently, Hilmerson and Flowers reported that reduction and coupling of carbonyl compounds can be mediated by microwave heating.[12] Pertinent to the

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[1] Molander, G. A. *Org. React.* **1994**, *46*, 211−367 and references therein.
[2] Molander, G. A. *Chem. Rev.* **1996**, *96*, 307−338.
[3] Kagan, H. B. *Tetrahedron* **2003**, *59*, 10351−10372 and references therein.
[4] Pedersen, H. L.; Christensen, T. B.; Enemaerke, R. J.; Daasbjerg, K.; Skrydstrup, T. *Eur. J. Org. Chem.* **1999**, 565−572.
[5] Chopade, P. R.; Davis, T. A.; Prasad, E.; Flowers, R. A. *Org. Lett.* **2004**, *6*, 2685−2688.
[6] Dahlen, A.; Hilmersson, G. *Tetrahedron Lett.* **2002**, *43*, 7197−7200.
[7] Dahlen, A.; Hilmersson, G. *Tetrahedron Lett.* **2001**, *42*, 5565−5569.
[8] Prasad, E.; Flowers, R. A. *J. Am. Chem. Soc.* **2002**, *124*, 6357−6361.
[9] Prasad, E.; Flowers, R. A. *J. Am. Chem. Soc.* **2002**, *124*, 6895−6899.
[10] Enemaerke, R. J.; Daasbjerg, K.; Skrydstrup, T. *Chem. Commun.* **1999**, 343−344.
[11] Miller, R. S.; Sealy, J. M.; Shabangi, M.; Kuhlman, M. L.; Fuchs, J. R.; Flowers, R. A. *J. Am. Chem. Soc.* **2000**, *122*, 7718−7722.
[12] Dahlen, A.; Prasad, E. Flowers, R. A.; Hilmerson, G. *Chem. Eur. J.* **2005**, *11*, 3279−3284.

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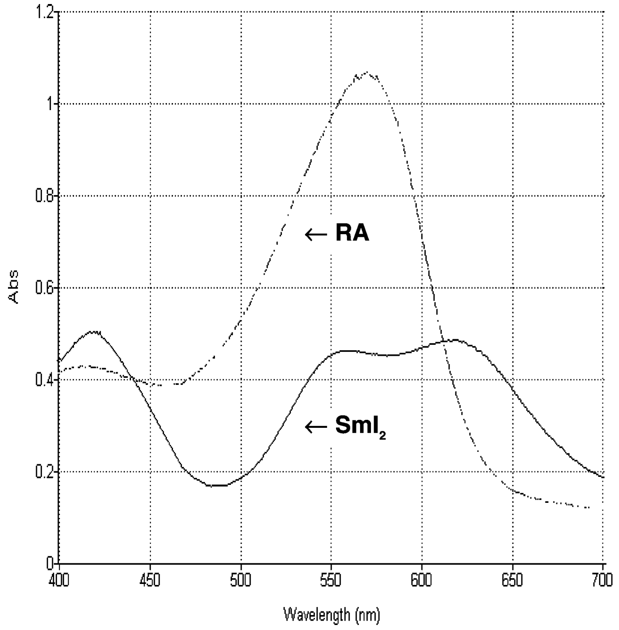
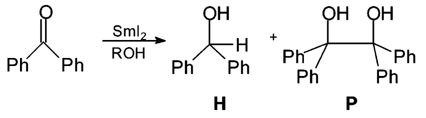


Figure 1. Spectra of SmI_2 and of the radical anion of benzophenone (RA).

present study is another observation by Flowers and coworkers that the reduction of acetophenone is enhanced by proton donors according to their acidity.[13]

In the present work, we will use benzophenone as a model and focus on the unusual effect alcohols have on the product distribution (benzhydrol vs benzopinacol) in its reduction of by SmI_2 (eq 1).



(1)

When equivalent amounts of benzophenone and SmI_2 are mixed in a stopped-flow spectrophotometer, the typical absorption of the SmI_2 vanishes in the dead time and the absorption of the radical anion of benzophenone is immediately obtained (Figure 1).

For a complete formation of benzhydrol, 2 equiv of SmI_2 is required. In the following experiments, we have used the concentrations of 0.0167 M for benzophenone and 0.0334 M for SmI_2 in THF. The reactions were performed in the presence of 0.0334 M MeOH and quenched by an I_2/THF solution. Product analysis was done, in most cases, by both NMR and HPLC. Based on the difference between the two, we estimate the experimental error to be in the range of 5%. It turns out that while the percent of pinacol[14] remains constant at all times, that of the hydrol increases at the expense of the benzophenone until it reaches its final value in 10 min. Since the radical anion is obtained upon mixing, and the pinacol fraction does not change with time, it is clear that product distribution is determined at the beginning of the reaction. The intermediate which is the precursor of the hydrol regenerates the starting material—benzophenone—when it reacts with I_2 of the quench solution. The most likely structure of this intermediate is the dibenzylic carbanion. Under the reaction conditions it cannot generate pinacol, whereas protonation of it will furnish the hydrol. When this intermediate is reacted with the quench I_2 solution, it reverts to the starting material—benzophenone (eq 2).

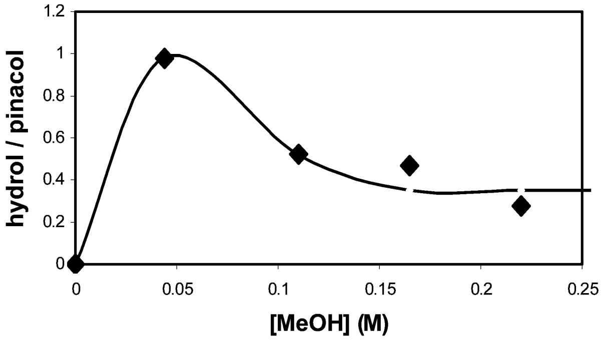
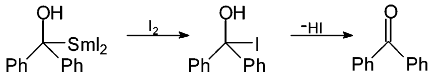


Figure 2. H/P ratio in the reaction of benzophenone (0.022 M) and SmI_2 (0.044 M) as a function of MeOH.



(2)

The existence of a C−Sm bond has been demonstrated previously.[15] However, the fact that it undergoes a slow protonation may seem somewhat surprising; nevertheless, we have previously shown that samarium exchanges ligands surprisingly slowly.[16] As a result of the above observation, all of the product distribution data below was collected 10 min after the beginning of the reaction.

In the absence of a proton source, hydrol is not obtained, and the coupling yielding pinacol is the only reaction. One would therefore expect that the hydrol/pinacol (H/P) ratio would increase with rising concentration of the proton donor. Surprisingly, using MeOH as a proton donor, we found that the ratio indeed increases at the beginning *but then reaches a maximum after which it drops and then nearly levels off* (Figure 2).

The effect of the proton donor on the product distribution can be explained by assuming the mechanism shown in Scheme 1.

This is a general mechanism from which various reaction steps were omitted for the sake of simplicity. According to this scheme, we start at the radical anion (RA) formed quantitatively at the dead time. In the absence of a proton donor, two radical anions paired to samarium will couple to produce pinacol (k_1). As the concentration of the MeOH is

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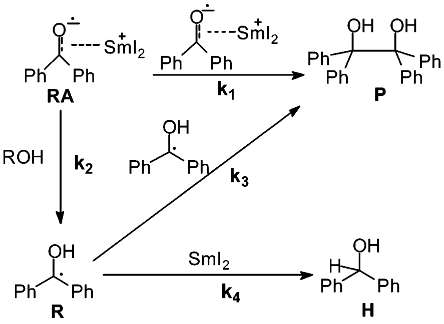
(13) Chopade, P. R.; Prasad, E.; Flowers, R. A. *J. Am. Chem. Soc.* **2004**, *126*, 44−45.

(14) The percent yield for pinacol is based on the number of benzophenone molecules used for its production, namely, mol % pinacol × 2.

Scheme 1. Reaction Mechanism



increased, protonation (k_2) to form the radical (R) will be enhanced and the importance of k_1 will diminish. Since R is a precursor of the hydrol (H), the H/P ratio will begin to increase. At a high enough concentration of alcohol, the initially formed radical anion will be fully and rapidly converted to the radical via k_2. Product distribution will be determined by the relative rates of the pinacol producing coupling (k_3) and further reduction by the SmI_2 (k_4). Since the proton donor concentration does not enter the rate equations for these two processes, the product ratio dependence on the proton donor concentration (Figure 2) must evolve from the previous step—the protonation of the radical anion (k_2). The molecularities of these reactions (k_3 and k_4) are such that the formation of pinacol is second order in the radical, whereas that of the hydrol is only first order in this radical. Thus, slow protonation of the radical anion will produce a momentary low concentration of the radical. This will reduce the probability of a bimolecular reaction of the radical (pinacol formation via k_3) and, therefore, increase the fraction of the formed hydrol. As the protonation rate grows faster due to an increase in the MeOH concentration, the momentary concentration of the radical (R) increases, raising the probability for the bimolecular coupling to yield pinacol. Hence, the H/P ratio will decrease. In the extreme case where protonation is instantaneous, product distribution will be independent of the proton donor concentration and a plateau will be achieved. The plateau level will be determined by the ratio of the coupling (via k_3) and the reduction (via k_4) rates.

Based on the above mechanism, one can predict a twofold consequence of increasing the protonation rate (k_2) by using a more acidic alcohol: (a) the maximum in the H/P vs [ROH] plot will be achieved at a lower H/P value, and (b) the plateau will be achieved earlier.[17] To examine these predictions we have conducted experiments with two alcohols, trifluoroethanol (TFE) as the more acidic alcohol and 2-propanol as an alcohol of a weaker acidity (Table 1 and Figure 3).

Table 1. Product Distribution in the Reaction of Benzophenone (0.022 M) and SmI_2 (0.044 M) as a Function of [ROH]

	[ROH] (M)	hydrol (%)	pinacol[14] (%)	ketone (%)	H/P
MeOH	0	0	100	0	0.00
	0.044	47	48	5	0.98
	0.110	33	63	4	0.52
	0.165	31	66	3	0.47
	0.220	21	76	3	0.28
	0.275	19	77	4	0.25
i-PrOH	0	0	100	0	0.00
	0.029	67	31	2	2.23
	0.055	57	42	1	1.38
	0.114	55	45	0	1.22
	0.165	50	50	0	1.00
	0.220	50	50	0	1.00
TFE	0	0	100	0	0
	0.028	27	73	0	0.37
	0.055	21	79	0	0.27
	0.083	17	83	0	0.20
	0.138	16	84	0	0.19
	0.275	18	82	0	0.22

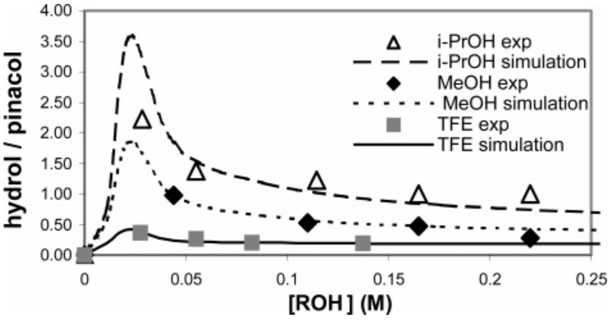


Figure 3. H/P ratio in the reaction of benzophenone (0.022 M) and SmI_2 (0.044 M) as a function of alcohol concentration.

It should be pointed out that at alcohol concentrations lower than 1 equiv, the results are of low relevance. This is because the alcohol is completely consumed before the reaction is completed, and in addition, traces of water may affect the distribution. As a result, data points are not available for the lower concentration range.

Using computer simulation, we can analyze the data in a more quantitative manner. Stopped flow measurements[18] in the absence of a proton donor yield a k_1 value of 5×10^2 M^{-1} s^{-1}. The coupling rate constant k_3 is known for acetonitrile as a solvent.[19] We will use this value (2×10^8 M^{-1} s^{-1}) on the assumption that radical coupling is not much

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(15) (a) Curran, D. P.; Fevig, T. L.; Totleben, M. J. *Synlett* **1990**, 773–774. (b) Curran, D. P.; Totleben, M. J. *J Am. Chem. Soc.* **1992**, *114*, 6050–6058. (c) Molander, G. A.; Kenny, C. *J. Org. Chem.* **1991**, *56*, 1439–1445. (d) Namy, J. L.; Collin, J.; Bied, C.; Kagan, H. B. *Synlett* **1992**, 733–734.

(16) Yacovan, A.; Bilkis, I.; Hoz, S. *J. Am. Chem. Soc.* **1996**, *118*, 261–262. This contradicts somewhat the statement made by Kagan describing organosamarium compounds as highly reactive intermediates.[3] However, the nature of the two systems is entirely different.

(17) One could intuitively conclude that the maximum in the simulation line will move towards lower [ROH] with the increase in the alcohol acidity. However when [ROH] < [RA], stoichiometry controls the H/P value, and for all the alcohols, the maximum value will be achieved at [ROH] = [RA].

affected by the change of solvent from MeCN to THF. Product distribution at the plateau of TFE (where k_1 is probably not operative) together with the k_3 value, yield, by computer simulation a k_4 value of 2×10^7 M^{-1} s^{-1}. Manual variation of k_2 (until reasonable fit to the experimental data was obtained) gave the following rate constants: $k_2^{\mathrm{TFE}} = 10^8$ M^{-1} s^{-1}, $k_2^{\mathrm{MeOH}} = 2.5 \times 10^6$ M^{-1} s^{-1}, and $k_2^{\mathrm{iPrOH}} = 7 \times 10^5$ M^{-1} s^{-1}. Due to the assumptions used in the mechanistic scheme,[20] these can be considered only approximate values. It should be pointed out that we have performed the simulation from different starting points to minimize the probability of the solution being a local minimum.

This simple model also provides an explanation for the long puzzling difference observed between aromatic and aliphatic ketones. While under normal conditions (in the presence of proton donors), aliphatic ketones yield mainly the corresponding alcohols, benzophenones yield also the corresponding pinacols.[1,21] The key to the product partition between hydrol and pinacol lies in the momentary concentration of the radical. The electron-transfer process in aliphatic ketones is relatively slow. Therefore, the momentary concentration of the candidates for bimolecular coupling—the radical anions and the corresponding radicals—is low. As a result, the rate of the bimolecular steps leading to pinacol formation (steps corresponding to k_1 and k_3 in Scheme 1) cannot compete effectively with the step leading to reduction. On the other hand, the radical anion of an aromatic ketone such as benzophenone is formed very rapidly. As a result, the momentary concentration of these intermediates is high, increasing the probability of the bimolecular coupling reaction to give pinacol.

In conclusion, the key to a good yield of coupling products is a high momentary concentration of radical anions and, more importantly, a high concentration of the derived radicals. Slow reduction will produce a low momentary concentration of the radical anions/radicals which will favor the complete reduction of the carbonyl function. Thus, a recipe based on the reducing power of the reagent,[22] its concentration, and the characteristics of the proton donor can be tailored, in principle, for most substrates to channel the reaction to the desired products.

Supporting Information Available: Experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) See the Experimental Section in the Supporting Information.

(19) Shield, S. R.; Harris, J. M. *Anal. Chem.* **1998**, *70*, 2576−2583.

(20) A more refined scheme should also include additional factors and steps such as the complexation of MeOH to samarium at high MeOH concentrations, possible coupling between a radical and a radical anion, disproportionation of two samarium paired radical anions to give a bridged dimer, etc.

(21) Kagan, H. B.; Namy, J. L.; Girard, P. *Tetrahedron* **1981**, *37*, 175−180.

(22) This could be also achieved with SmI_2 itself since adding HMPA increases its reduction potential from −0.89 to −1.79V vs SCE (ref 10 above).