Utilization of 1,1-Dimethyl-4,6-di-*tert*-butylspiro[2,5]octa-3,6-dien-5-one as a 'Hypersensitive' Probe for Single Electron Transfer to Carbonyl Compounds

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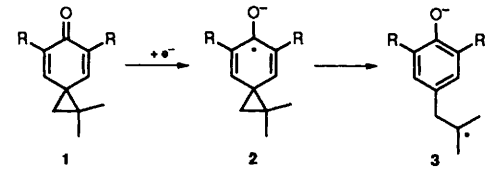
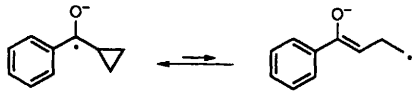
The use of 1,1-dimethyl-4,6-di-*tert*-butylspiro[2,5]octa-3,6-dien-5-one **1** as a 'hypersensitive' probe for single electron transfer in the reaction of several nucleophiles (RMgX, RLi and R_2CuLi) with carbonyl compounds is demonstrated.

We have found that the radical anion generated from 1,1-dimethyl-4,6-di-*tert*-butylspiro[2,5]octa-3,6-dien-5-one **1** undergoes facile ring opening to the tertiary distonic radical anion at a rate constant estimated to be $\geq 10^7\ s^{-1}$ (Scheme 1).[1] In this paper, we illustrate the use of this compound as a 'hypersensitive' probe for single electron transfer to carbonyl compounds from several nucleophiles.

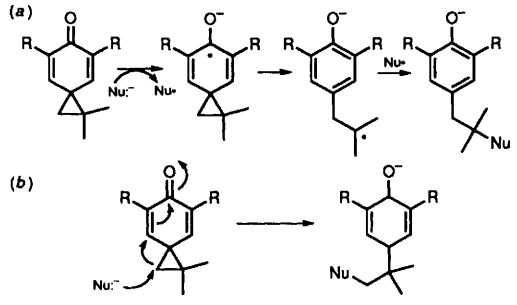
Aryl cyclopropyl ketones have frequently been utilized as probes for SET in the reaction of a variety of nucleophiles and reducing agents with carbonyl compounds with little apparent success because rearrangement of the corresponding radical anion (Scheme 1) is extremely slow ($k \approx 1\ s^{-1}$) and reversible, with an equilibrium constant favouring the ring-closed form ($K \approx 10^{-8}$, Scheme 2).[2–4] (A simple kinetic analysis reveals that this substrate would actually fail to detect a *bona fide* SET process).[6] Moreover, even in studies where 'ring-opening' is observed, the products appear to be derived from direct nucleophilic displacement.



Scheme 1



Scheme 2



Scheme 3 (*a*) SET: attack at most-hindered carbon; (*b*) polar: attack at least-hindered carbon

Table 1 Products from the reaction of 1,1-dimethyl-4,6-di-*tert*-butylspiro[2,5]octa-3,6-dien-5-one with organometallic reagents[a]

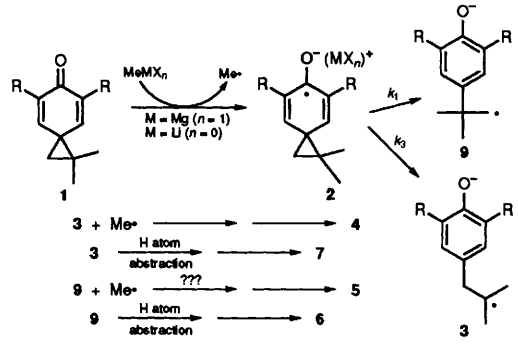
		Products and yields (%)				
Reagent	*t*/h	4	5	6	7	8
MeMgBr	2	35	14	1	3	47
MeLi	20	50				49
Me_2CuLi	1.5		100			

[a] In THF, 0 °C → room temp.

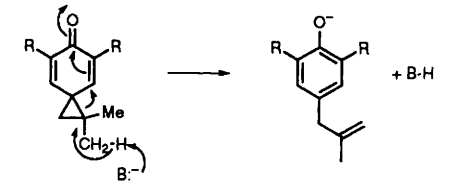
This latter problem was noted by House in his pioneering studies of the mechanism of reaction of dialkyllithium cuprates with carbonyl compounds.[5] Specifically, the observed regiochemistry (*i.e.* direct nucleophilic attack at the least-hindered carbon) provides definitive evidence that ring opening must be occurring *via* a polar pathway.[6]

Based upon these principles, **1** emerges as a potentially powerful SET probe. The estimated reduction potential of this compound (−2.5 V *vs.* 0.1 mol dm^{-3} Ag^+/Ag)[4] is similar to that of an aromatic ketone (*e.g.* PhCOPh, −2.2 V; PhCOR, R = alkyl, −2.5 V).[2,3] However, unlike aryl cyclopropyl ketones, the rate of ring opening of **2** is several orders of magnitude faster than that of arylcyclopropylketyl anions. Furthermore, the geminal dimethyl groups on the cyclopropane ring may allow differentiation between the SET and polar pathways (Scheme 3).

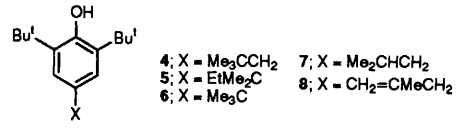
There is a large body of evidence which suggests that aromatic ketones react with Grignard reagents (RMgX) *via* SET.[7–12] While there appears to be some disagreement as to whether electron transfer is actually outer or inner sphere,[12]

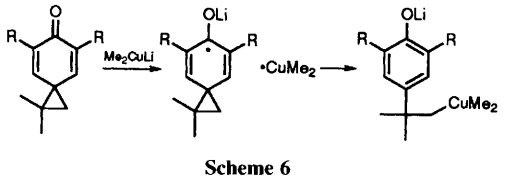


Scheme 4



Scheme 5





Scheme 6

there is general consensus regarding the intermediacy of ketyl anions in this reaction.

The reaction RMgX with phenyl cyclopropyl ketone yields solely the 1,2-addition product with the cyclopropane ring intact,[13] consistent with the proposal that this substrate would fail to detect a *bona fide* SET pathway.[3] In contrast, reaction of MeMgBr with **1** yields solely ring-opened products (Table 1). Three of the observed products, **4**, **6** and **7**, formed in a combined yield of 39%, unequivocally diagnose ketyl anion intermediacy and a single electron transfer process (Scheme 4).[14] cannot be excluded. Conceivably **5** might also arise (at least partially) from single electron transfer,† however, this product might also arise from a direct nucleophilic addition. Similarly, while alkene **8** might arise from a disproportionation reaction between **3** and Me•, a simple E_2 reaction (Scheme 5) (Treatment of **1** with NaH in DMF yields alkene **8** in quantitative yield).

In analogy to Grignard reagents, a considerable body of experimental evidence suggests alkyllithium reagents react with aromatic carbonyl compounds by SET.[7,9b,c,10,15–17] Reaction of MeLi with phenyl cyclopropyl ketone yields exclusively the 1,2-addition product.[18] In contrast, reaction of **1** with MeLi (Table 1) yields the expected SET product **4** in 50% yield, presumably *via* a mechanism similar to that proposed for the Grignard reaction (Scheme 4).

The importance of electron transfer in the reactions of dialkyllithium cuprates with aromatic and α,β-unsaturated carbonyl compounds is generally recognized.[6,8,19] House has suggested that substrates whose reduction potentials lie in the range of −1.4 to −2.35 V (*vs.* SCE), react with dimethyllithium cuprate *via* SET.[5] Based upon the estimated reduction potential of **1** (−2.5 V *vs.* 0.1 mol dm^{-3} $Ag^+/Ag \approx -2.2$ V *vs.* SCE),[1] reaction of this substrate with Me_2CuLi should proceed *via* SET.

Surprisingly, the only product arising from the reaction of **1** with Me_2CuLi is **5**, formed in quantitative yield (Table 1). Two mechanisms may account for this product: (*a*) Direct nucleophilic displacement, or (*b*) a copper assisted cyclopropylcarbinyl → homoallyl rearrangement of a radical anion intermediate similar to that proposed by Bertz and Cook (Scheme 6).[6] In either case, however, this was the only instance where the results obtained using **1** were ambiguous on the issue of SET.

In summary, the results presented in this paper demonstrate that **1** is a highly effective, hypersensitive probe for single electron transfer in the reaction of several nucleophilic species with carbonyl compounds. The cyclopropylcarbinyl → homoallyl rearrangement of the corresponding radical anion is sufficiently rapid that ring opening can occur on a time scale competitive with other competing processes (*i.e.* ketyl anion/radical combination). The geminal dimethyl groups on the cyclopropane ring allow clear differentiation between ring-opened products formed as the result of SET *vs* direct nucleophilic attack on the cyclopropane ring based upon the observed regiochemistry of the reaction. Furthermore, in addition to detecting ketyl anion intermediates, the rearranged radical anions efficiently trap the radical intermediate derived from the nucleophile in high yield.

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Footnote

† Generated electrochemically (DMSO, $Bu^n_4N^+$ counter-ion), radical-anion **2** undergoes ring opening to both the tertiary and primary distonic radical ions ($k_3/k_1 = 9$, Scheme 4, ref. 4). It is unclear as to how ion-pairing to Mg^{2+} might affect the rate and selectivity of the ring opening process, and thus whether some or all of **5** arises from SET.

References

1 J. M. Tanko, L. E. Brammer, Jr., M. Hervas' and K. Campos. Unpublished results at Virginia Polytechnic Institute and State University.
2 J. M. Tanko and R. E. Drumright *J. Am. Chem. Soc.*, 1990, **112**, 5362.
3 J. M. Tanko and R. E. Drumright, *J. Am. Chem. Soc.*, 1992, **114**, 1844.
4 D. D. Tanner, J. J. Chen, C. Luelo and P. M. Peters, *J. Am. Chem. Soc.*, 1992, **114**, 713.
5 H. O. House, A. V. Prabhu, J. M. Wilkins and L. F. Lee, *J. Org. Chem.*, 1976, **41**, 3067.
6 For a review of the mechanisms of reaction between dialkyllithium cuprates and activated cyclopropanes, see S. H. Bertz, G. Dabbagh, J. M. Cook and V. Honkan, *J. Org. Chem.*, 1984, **49**, 1739.
7 For a review, see T. Holm, *Acta Chem. Scand, Ser. B*, 1983, **37**, 567.
8 D. Liotta, M. Saindane and L. Waykole, *J. Am. Chem. Soc.*, 1983, **105**, 2922.
9 (*a*) H. Yamataka, U. Kawafuji, K. Nagareda, N. Miyano and T. Hanafusa, *J. Org. Chem.*, 1989, **54**, 4706; (*b*) H. Yamataka, T. Matsuyama and T. Hanafusa, *J. Am. Chem. Soc.*, 1989, **111**, 2912; (*c*) H. Yamataka, N. Miyano and T. Hanafusa, *J. Org. Chem.*, 1991, **56**, 2573; (*d*) H. Yamataka, K. Yamaguchi, T. Takatsuka and T. Hanafusa, *Bull. Chem. Soc. Jpn.*, 1992, **65**, 1157.
10 D. Nasipuri and A. Saha, *Indian J. Chem., Sect. B*, 1990, **29**, 474.
11 J. Frey, D. A. Nugiel and Z. Rappoport, *J. Org. Chem.*, 1991, **56**, 466.
12 T. Holm, *J. Am. Chem. Soc.*, 1993, **115**, 916.
13 E. Breuer, E. Segall, Y. Stein and S. Sarel, *J. Org. Chem.*, 1972, **37**, 2242; P. Traas, H. Boeleus and H. Takken, *Recl. Trav. Chim Pays-Bas*, 1976, **95**, 57; W. Schliemann, A. Buege and L. Reppel, *Pharmazie*, 1980, **35**, 140.
14 Through a detailed kinetic analysis, Walling has argued that high yields of addition products are possible in the reaction of Grignard reagents with carbonyl compounds without assuming significant cage-processes. See C. Walling, *J. Am. Chem. Soc.*, 1988, **110**, 6846.
15 L. Eberson, *Electron Transfer Reactions in Organic Chemistry*, Springer-Verlag, New York, 1987, pp. 132–136.
16 H. O. House and P. D. Weeks, *J. Am. Chem. Soc.*, 1975, **97**, 2785.
17 K. Rein, Z.-H. Chen, P. T. Peruman, L. Echegoyen and R. E. Gawley, *Tetrahedron Lett.*, 1991, **32**, 1941.
18 P. Blumbergs, M. LaMontagne and J. Stevens, *J. Org. Chem.*, 1972, **37**, 1248; S. Hall, C. Sha and F. Jordan, *J. Org. Chem.*, 1976, **41**, 1494.
19 For a review, see H. O. House, *Acc. Chem. Res.*, 1976, **9**, 59.