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Enantioselective hydride abstraction in organic substrates: future applications for chiral carbenium ions

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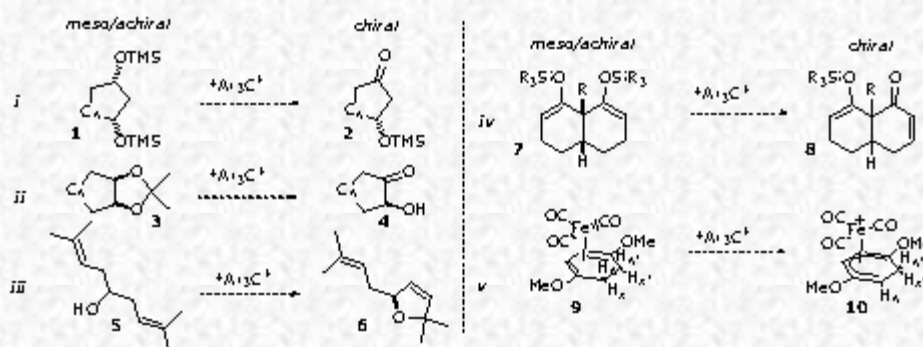
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Abstract

Oxidation reactions are at the core of asymmetric chemistry. It is therefore surprising, in view of the potential applications, not to find any instances of the notion of using a "chiral cation" to distinguish between a pair of *prochiral* hydrides during hydride transfer [H-T]. *To the best of our knowledge, there are none.* Yet, the converse concept of using a "chiral anion" to distinguish between a pair of *prochiral* protons during a deprotonation has led to significant advancements in the field of asymmetric synthesis.^[1] This letter describes the first example of an enantioselective [H-T].

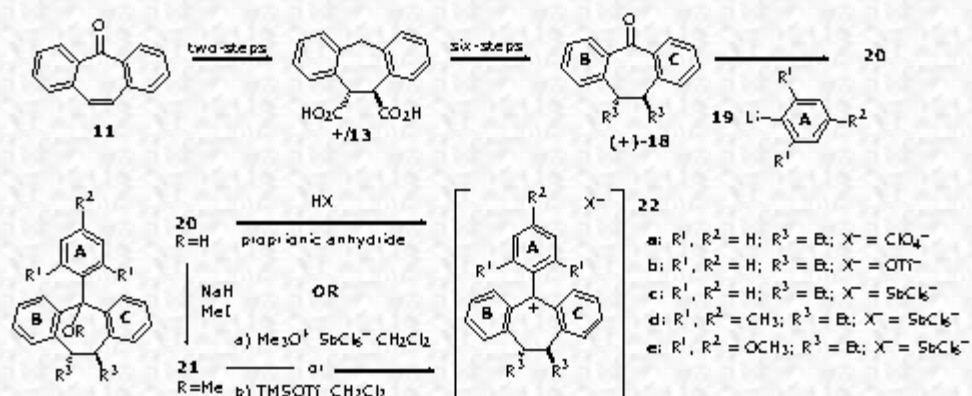
Hydride transfer [H-T] from an organic substrate to a cation is a fundamental oxidation mechanism in organic chemistry.^[2] The reaction can occur by either an ionic mechanism, a series of single electron transfers, or some combination thereof. The exact pathway tends to depend on the steric and electronic attributes of the hydride donor. The majority [H-T]-reactions reported in the chemical literature have utilised a Ph_3C^+ species. Trityl salts of OTf^- , BF_4^- , and PF_6^- dehydrogenate various types of *i*) ethers and *ii*) ketals to carbonyl compounds,^[3] *iii*) promote the formation of lower energy cations,^[4] *iv*) convert enol ethers to enones,^[5] and *v*) are often used in conjunction with organometallic substrates to increase the *hapticity* number, *h*, of metal atoms such as Fe,^[6] Cr,^[7] and Mo^[8] in their corresponding metal complex. In principle, all of these processes could provide chiral material by subjecting a particular *meso* or *achiral* substrate to oxidation with chiral surrogate of Ph_3C^+ (*figure 1*). It is our intent to develop a process using a stoichiometric amount of a chiral trityl surrogate in conjunction with the reactions shown below, and then to further refine the process into a catalytic cycle.

Figure 1



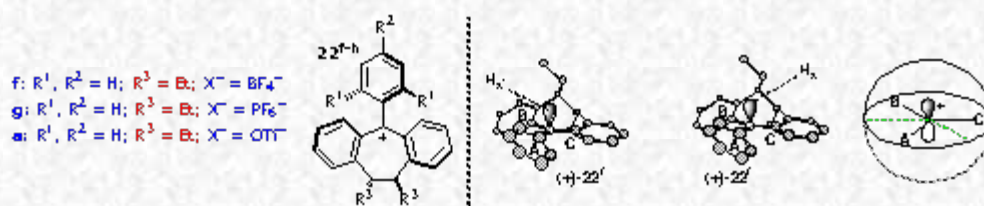
We began our investigation with the only known example of a nonracemic surrogate of trityl cation, **22**. Chen using Snatzke's ketone **18**,^[9] had reported the preparation several chiral trityl species, by implementing Dauben's procedure (HX / propionic anhydride)^[10] in conjunction with the alcohols, **20**, or by combining the Me₃O⁺SbCl₆⁻ salt and the methyl ethers **21**. Chen subsequently described the effectiveness of **22**^{a-e} in Lewis acid catalysed Mukiyama-type reactions.^[11] From the malleable synthesis of **22**, we perceived that a range of chiral cations would be accessible by this scheme. Furthermore, their capacity for hydride abstraction^[12] as well as the enantioselectivity of the abstraction could be tuned to some degree by the choice of the substituents on the phenyl-A ring, which is added to **18** as the corresponding anion **19**. Although Chen presented no data in regards to the conformation of these systems, after extensive modeling of **22** with Macromodel[®] using MM2 parameters we concluded that the S₂-symmetry in seven membered ring of **22** effectively establishes the chirality with regards to the pitch of the "blades" of the phenyl propeller **22**.

Scheme 1



However, our intentions for **22**, particularly in relation to **9**, significantly limited the counter-ions available to us. The explosive nature of perchlorates, especially metal perchlorates, excluded these. The low hydride affinity of [SbCl₆⁻] species precluded them from further consideration.^[13] Thus, we focused our attentions on [OTf⁻] **22**^b and the [BF₄⁻] and [PF₆⁻] species **22**^{f-g}, which we hoped to prepare by slightly modifying Dauben's and Chen's procedures.

Figure 2

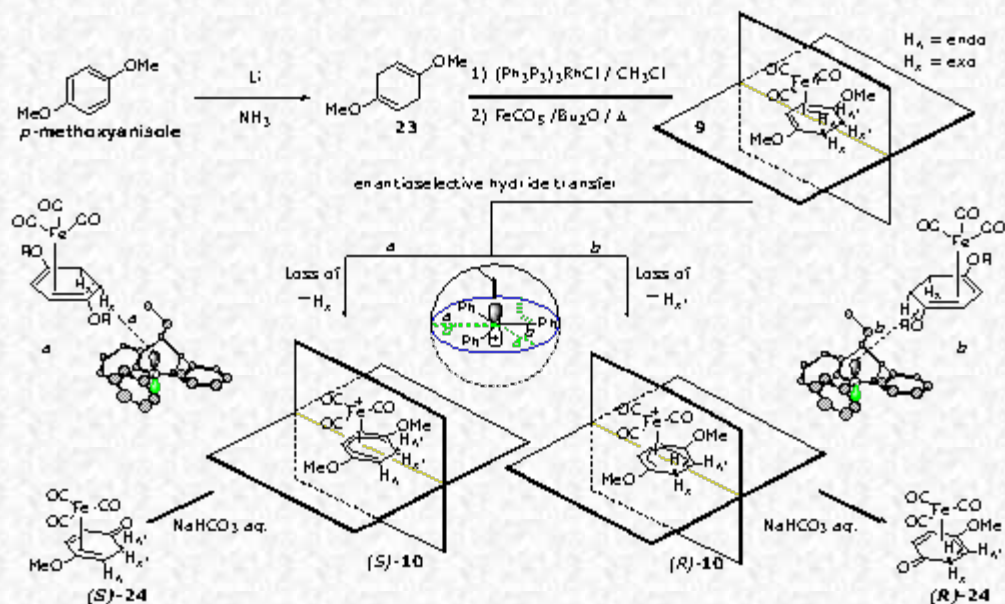


We reasoned after careful modeling, that the top and bottom hemispheres of the cation should be identical. Hence, only the transition states associated with one side of the chiral cation need to be considered. Hydride abstraction results in conversion of the sp²-cation to a sp³-product. Reasoning along Bürgi-Dünitz principles,^[14] the most probable approach vectors are 71°, [180°-109°] above the ABC plane. If the mechanism of the oxidation were ionic rather than electron transfer in origin, the hydride should approach the cation from one of three probable vectors; opposite either the [sp²-A], [sp²-B] or [sp²-C] bonds in order to minimize steric interactions.^[15] Addition opposite the [sp²-A] bond, however, is discouraged by an intervening R³ residue. Those remaining, opposite the [sp²-B] and [sp²-C] bonds (*cf.* the dotted lines of the sphere in Figure 2) have distinct energies and would lead to enantiomers. One vector is along the edge of the phenyl A ring, the other along its surface, and [H-T] should favor the approach along the flat surface of the A-ring rather than opposite the [sp²-C] bond. Furthermore, the amount of

induction should depend upon the difference in steric interactions associated with these two approaches in regards to the substrate.

The conversion of **9** to **10**, (*figure 1, v*) was of great interest to us. The usefulness of iron tricarbonyl as a diastereomeric control element for stereospecific preparation of quaternary carbons from species similar to **10** is well known.^[16] Generally [H-T] in substrates similar to **9** occurs opposite the metal atom. Thus, the enantiotopic *exo* H_x atoms had to be distinguishable to the chiral cation **22**. To test our assumptions above, **9** was constructed by Stephenson's procedure: subjecting *p*-methoxyanisole to reduction by lithium ammonia, the resulting non-conjugate diene **23** to isomerization with a catalytic quantity of (Ph₃P)₃RhCl and finally complexation of the diene with Fe(CO)₅ to form **9**.^{16a-e}

Scheme 3



Our preliminary results are presented in table 1. The result of [H-T] from **9** to **22f** and **22g** are describe *entries 1-2*. In *entry 3*, the use of **22a** generated in situ by the addition of TMSOTf to the corresponding ether **21** in the presence of the h₄ diene complex **9** is reported. In all of these reactions once starting material was consumed, the h⁵ intermediate was subjected to NaHCO₃ to produce ketone **24** in situ. This material was then purified by column chromatography and analyses by chiral stationary phase HPLC, using a chiracel® OF column.^[17]

Table 1

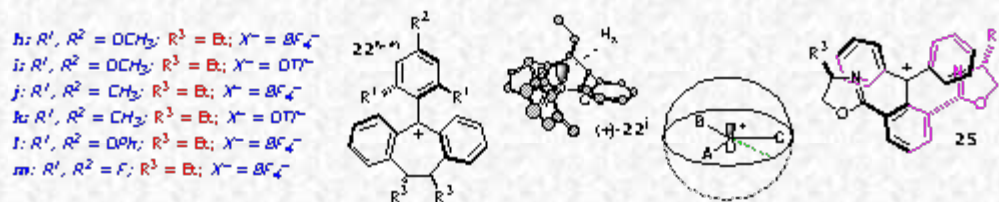
Enantioselectivities resulting from **9**→**10**→**24**, when chiral cations of type **22** are used

Entry	substrate	cation	Conditions	Product	ee	Yield %
1	9	22f	9 , 1M in CH ₂ Cl ₂ + 22f , 25 C 3hrs, then	(+)- 24	12%	52

			NaHCO ₃			
2	9	22g	9, 1M in CH ₂ Cl ₂ + 22g, 25 C 3hrs, then NaHCO ₃	(+)-24	14%	56
3	9	22b	9, 1M in CH ₂ Cl ₂ + 21 + TMSOTf, 25 C 3hrs, then NaHCO ₃	(+)-24	15%	71

The percentage of enantioselectivity obtained in this process is quite modest. However, to the best of our knowledge it represented the first example of such in regards to a [H-T] oxidative process. Three possible scenarios might explain the low *ee*'s. 1) The conversion of **9** to **10** occurs by way of a SET pathway and therefore is less susceptible to steric interactions. 2) [H-T] occurs at perpendicular to the ABC plane rather than at 71° as assumed from Bürgi-Düinitz principles. 3) The steric interactions are not sufficient to distinguish between the enantiotopic [sp²—C] and [sp²—B] vectors. Please note that depiction of **10** with the H_x and H_{x'} in a coplanar relationship is merely a time-averaged approximation of two interconverting conformers. However, the first two possibilities seemed somewhat improbable. Although [H-T] often involve SET pathways in organometallic substrates, the tricarbonyl ligands of the iron complex all but guaranteed an ionic mechanism at room temperature. The redox potential for **9** with CO ligands is significantly greater than (0.2V vs. SCE), the oxidation potential for the conversion of Ph₃C[•] to Ph₃C⁺.^[18] If [H-T] occurred at 90° with regards to the ABC plane then the enantioselectivity ought to be essentially 0% *ee*. The noticeable *enantiomeric excess*, albeit low, clearly indicates 0.25 Kcals difference in steric interactions between the two approach [sp²—C] and [sp²—B] vectors. Thus, we concluded to increase the enantioselectivity the difference needed to be magnified and that this could be accomplished by adding larger R₁ substituents thereby shutting down the [sp²—C] mode of addition. Thus, further investigations are preceding with cations **22ⁱ⁻ⁿ** as well as with derivatives of **25**.

Figure 3



In conclusion, we believe that the results obtained thus far clearly warrant additional study in regards to the application of chiral carbeniums to processes such as *i-v* in figure 1. It is hoped that this letter has revealed a new fertile area for continued asymmetric research and that in due course higher enantioselectivities will be achieved as will the invention of a catalytic cycle, possibly through the use of electrochemistry.

Acknowledgments

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12. The angle of pitch greatly effects hydride affinity, see reference 1f.
13. The [SbCl₆?] species, unlike [BF₄?], [PF₆?], and [OTf?] systems, is rarely used as a reagent for hydride abstraction. In the few examples reported reaction leads to a highly stabilized cation such as tropylium. To the best of our knowledge there are no examples of a [Ph₃C⁺ SbCl₆?] species used in combination with an organometallic substrate. The reason for the distinction between this species and the others may reside with the apparent "softness" of this type cation as well as the labile nature of its [Cl?] ligands, which can result in a media dependent equilibrium [Ph₃C⁺ SbCl₆? goes to Ph₃CCl + SbCl₅].
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