Evolution of Functional Cyclohexadiene-Based Synthetic Reagents: The Importance of Becoming Aromatic

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ABSTRACT

Suites of new precursors designed around a cyclohexadiene core and intended to mediate "clean" radical chain syntheses have been prepared and tested. 1-Functionalized cyclohexa-2,5-dienes were found to readily donate H-atoms, and the resulting cyclohexadienyl radicals rapidly extruded their functional group as a free radical, because this β-scission restored aromaticity to the ring. This concept was employed to generate designer radicals from esters of the corresponding alcohols with 1-methyl- or 1-phenylcyclohexa-2,5-diene-1-carboxylic acids. In a similar way, pre-adapted carbamoyl radicals were obtained from cyclohexadienyl-amides and proved advantageous for syntheses of α- and β-lactams. Oxime ether substituted carbamoyl radicals cyclized successfully in convenient syntheses of dihydroindolin-2-ones with N-functionality at the 3-position. Similarly, silicon-centered radicals were obtained from 1-silylated cyclohexadienes, and these reagents proved to be very efficient, environmentally benign organotin hydride substitutes. Radical reactions including reductions, cyclizations, intermolecular additions, and hydrosilylations were carried out in high yields with this reagent. Other heteroatom-centered radicals, especially N-centered radicals, were obtained from appropriate cyclohexadienes enabling chain hydroaminations to be conducted. Several of the cyclohexadiene precursors proved to be useful for electron paramagnetic resonance (EPR) spectroscopic purposes, and this enabled rate constants for fragmentations of the cyclohexadienyl radicals to be obtained. Kinetic data for H-atom abstraction from cyclohexadienes, the second propagation step of the chain processes, was derived from customized radical clocks and from EPR measurements. In this way, conceptual tools were developed for improving future synthetic methodology based around these reagents.

Introduction

When an aromatic sextet coalesces during traversal of a reaction coordinate, the resultant gain of resonance stabilization energy (ca. 33 kcal mol^{-1} for benzene), usually guarantees exothermicity of the chemical reaction. Molecules with this potentiality built in as a design feature are styled "pro-aromatic".[1] Numerous chemical processes take advantage of this tactic. For example, in oxidations of alicyclic rings, gain of resonance stabilization leads to formation of aromatic or hetero-aromatic compounds. Similarly, regeneration of aromaticity drives electrophilic, homolytic, and nucleophilic substitution reactions of benzenoid and hetero-aromatic compounds. Furthermore, full or partial aromatic sextet formation in transition states can reduce their activation energies, hence providing kinetic drivers for pericyclic reactions such as the Diels−Alder and 1,3-dipolar cycloadditions, as well as 3,3-sigmatropic rearrangements of the Cope and Claisen types.

Organotin hydrides, working in conjunction with organohalides and -selenides and other functional groups, promote a huge range of radical chain reactions.[2] They enable many types of free radicals to be generated, and in a second propagation step, they selectively donate H-atoms. A major share in the luxuriant flowering of radical-based organic syntheses in the past decades, including natural product preparations and cascade (domino) target-oriented syntheses, can be ascribed to these reagents. However, their usefulness is somewhat impaired because of neurotoxicity problems, and new suites of reagents are needed to supersede them in cleaner radical methodology.[1,3] Hydrogen donation by organostannanes is facilitated by their weak Sn−H bonds [$\Delta H°$(R−H) = 78 kcal mol^{-1}].[4] This fragility is not shared by most organic compounds, which have comparatively strong C−H bonds making hydrogen abstraction very unselective and consequently triggering chain branching and multiple radical generation. However, bisallylic H-atoms are strongly activated [$\Delta H°$(R−H) = 76 kcal mol^{-1}][5] and are regioselectively donated to approaching radicals. Suitably functionalized cyclohexa-1,4-dienes (CHDs) contain these weakly bound H-atoms, in combination with the inbuilt potential for restoration of aromaticity by subsequent expulsion of a neutral radical. Our concept was to incorporate both these features into tractable new reagents, hence mimicking organotin compounds but without releasing toxic byproducts. The carbocyclic ring structures also offer flexibility superior to that of organometallics because substituents of differing stereoelectronic

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John Walton was born in St. Albans, England, in 1941. He graduated from Sheffield University in 1963 and studied for his Ph.D. under the supervision of Lord John Tedder at Sheffield and Dundee Universities. He joined the science faculty of St. Andrews University in 1970 as an assistant lecturer rising to full Professor in 1997. His research has focused on synthetic, mechanistic, and EPR spectroscopic aspects of free radical chemistry. He was awarded a D.Sc. degree by Sheffield University in 1979 and the Royal Society of Chemistry silver medal for Organic Reaction Mechanisms in 1994 and was elected Fellow of the Royal Society of Edinburgh in 1995. His current research interests include organic synthetic methods, cascade reactions, and EPR spectroscopy.

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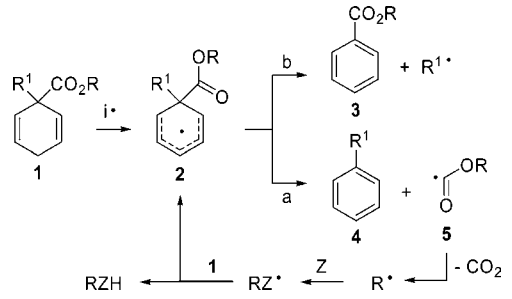
Scheme 1. Radical Generation from Cyclohexa-2,5-diene-1-carboxylates



character may be introduced, thus enabling the rate of release of the desired radical and also the rate of hydrogen donation to be varied.

Validation of the Concept with Esters and Acids of 1,4-Cyclohexadiene—Generation of C-Centered Radicals

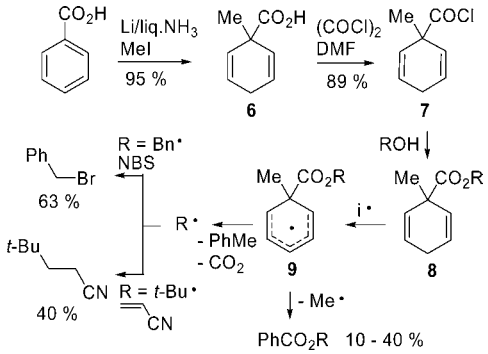
Exploratory research was carried out with cyclohexa-2,5-diene-1-carboxylates, **1**. Selective abstraction of a bis-allylic H-atom by an initiator radical (i•) was expected to generate cyclohexadienyl radical **2**, which could undergo re-aromatization by β-scission (Scheme 1). Route a β-scission causes extrusion of alkoxycarbonyl radical **5** together with aromatic compound **4** as a benign byproduct. Radical **5** will lose CO_2, particularly for *secondary* and *tertiary* alkyl groups, to release the desired radical, R•. The latter may be transformed to new radical RZ• either by reaction with added partner Z or by a cyclization step. H-atom abstraction from more **1** results in production of the target product RZH together with more radical **2.** The overall process then constitutes a chain reaction.

A substituent R^1 was needed to block unwanted H-abstraction from ring C(1) and was chosen to minimize β-scission by the competing route b, which would yield an aromatic ester **3** together with undesired radical R^{1}•. Clearly, a substituent strongly bound to the ring was needed that would not be released as a stabilized radical. The simplest such group was R^1 = Me, which had the added bonus of furnishing toluene (**4**, R^1 = Me) as a volatile and easily removed byproduct.

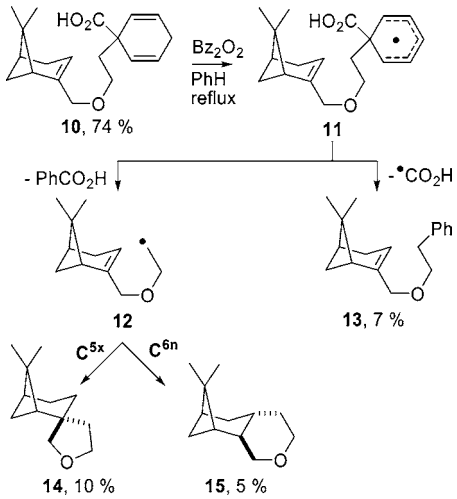
Alkyl 1-methylcyclohexa-2,5-diene-1-carboxylates **8** were prepared in high yields by Birch reduction/alkylation of benzoic acid as shown in Scheme 2.[6] Treatment of **8** with benzoyl or lauroyl peroxide as initiator in the presence of *N*-bromosuccinimide (NBS; 2 equiv) gave moderate yields of alkyl bromides. Alkene alkylations were accomplished by inclusion of an alkene such as acrylonitrile instead of NBS. In each case, however, significant amounts (10−40%) of alkyl benzoates $PhCO_2R$ accompanied the desired products showing that the alternative extrusion of a methyl radical from intermediate **9** competed materially.[7]

A range of 1-alkylcyclohexa-2,5-diene-1-carboxylic acids was also accessible via Birch reduction/alkylation methodology. β-Scission of the intermediate CHD-radicals derived from these precursors could release C-centered radicals and benzoic acid (easily removed by an alkali

Scheme 2. Preparation and Homolytic Reactions of Cyclohexadiene Carboxylates



Scheme 3. Cyclization of a Radical Derived from a CHD-1-carboxylic Acid

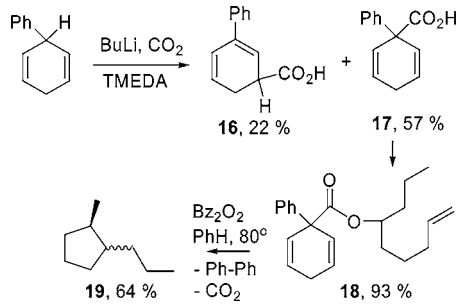


wash) in competition with extrusion of the unstabilized formate radical ($•CO_2H$) and an alkylbenzene. A number of acids were examined to determine the viability of this approach.[8] The process was moderately successful, even with only 1 or 2 equiv of alkene, for simple secondary, tertiary, and benzylic radicals and amounts to a reductive alkylation. Acids with primary alkyl substituents were less tractable. Cyclizations were also examined and an acid containing a cyclohex-2-enyloxyethyl substituent was prepared in good yield and afforded 55% of octahydrobenzofuran via a 5-*exo*-cyclization of the released C-centered radical. This compared well with 60% of the same product obtained by treatment of the corresponding iodide with tributyltin hydride. The C−C bond to the cyclohexadiene ring was comparatively strong for primary substituents, and consequently, competition from the unwanted extrusion of formate together with an alkylbenzene was significant (Scheme 3).

Scheme 3 shows that ring closure of the radical derived from myrtenyl-containing acid **10** took place in both 5-*exo*-(C^{5x}) and 6-*endo*-(C^{6n}) modes to afford cyclic ethers **14** and **15** with substituted-benzene **13** as byproduct.[9] Introduction of branched groups was difficult by the Birch reduction/alkylation method, which either failed or gave low yields of cyclohexadienyl acids.

We reasoned that use of a 1-phenyl substituent in place of a 1-methyl group should overcome the problem of

Scheme 4. Cyclization of a Radical Derived from a 1-Phenyl-CHD-ester



competing β-scission modes because Ph$^{\bullet}$ is a destabilized σ-radical and its expulsion from **2** should be disfavored. The 1-phenyl acid **17** was prepared by treatment of dihydrobiphenyl with BuLi and solid CO_2, but under all conditions, significant amounts of the inseparable isomer **16** contaminated the product and had to be removed by Diels–Alder reaction with maleic anhydride. Homolytic reactions of several alkenyl 1-phenyl esters such as **18** (Scheme 4) were examined.[10] Good yields of cyclized products were obtained along with biphenyl as the benign byproduct.

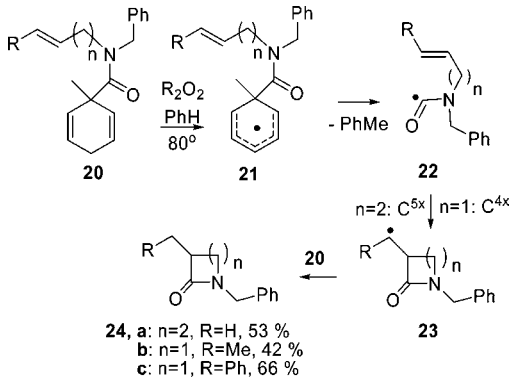
For these precursors, the alternative β-scission of the intermediate cyclohexadienyl radicals would lead to release of phenyl radicals and production of aromatic esters. No such byproducts were observed in any case we studied, that is, the unwanted dissociation was completely suppressed. If a clean and high yielding route to the key precursor 1-phenyl acid **17** could be found, the 1-phenyl esters would be promising alternatives to organotin hydrides.

Amplifying the Theme with Carbamoylcyclohexadienes

In seeking to extend the scope further, we conceived the idea that analogous amides **20** might function as sources of carbamoyl radicals[11] (aminoacyl radicals) **22**. We anticipated that the thermodynamic stability of carbamoyl radicals would prevent decarbonylation from occurring at moderate temperatures, and hence they could be incorporated in radical chain cyclizations.[12a,b] Experiments with amides derived from primary amines were less successful, and therefore *N*-benzyl-protected amides such as **20** were normally utilized. Carbamoyl radicals with butenyl side chains were successfully generated using this methodology and underwent C^{5x} ring closures to give pyrrolidinones, for example, **24a** in yields of 20–55% (Scheme 5).

Use of allyl-amides to promote the much more difficult 4-*exo* cyclizations to β-lactam structural units were also studied. When standard initiation procedures were used, C^{4x} ring closures of carbamoyl radicals with allyl and cinnamyl side chains were achieved giving azetidinones in yields of 30–45% (Scheme 5). Minor amounts of formamides derived from direct H-transfer to carbamoyl radicals **22** were also formed. However, no aromatic amides were observed in any of the reactions indicating

Scheme 5. Preparation of Pyrrolidinones and Azetidinones from Amidocyclohexadienes

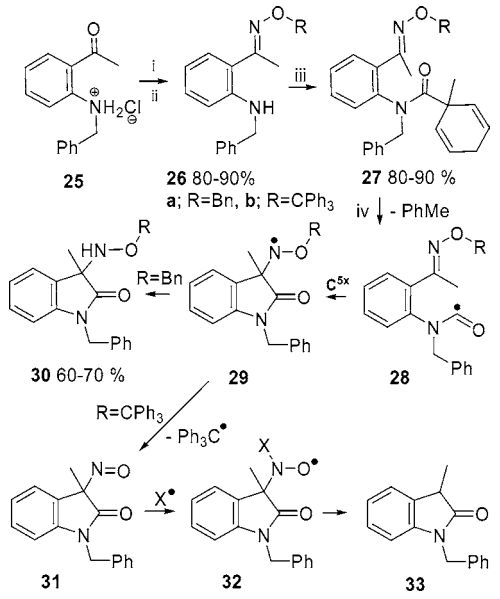


that the undesired fragmentation to Me$^{\bullet}$ radicals was completely suppressed. As expected, a carbamoyl radical with a propargyl side chain cyclized very inefficiently, and no ring closure at all was observed onto the CN group of the cyanomethyl-containing analogue. For these two triply bonded substrates, the main products were just the formamides derived from reduction of the carbamoyl radicals.

The cinnamyl-substituted amide **20c** was chosen to expedite the difficult C^{4x} step, because resonance stabilization in the cyclized radical **23c** should favor this. However, initiation with DTBP or benzoyl peroxide gave low yields of **24c** (12–15%) probably because of difficult H-atom abstraction by the delocalized species **23c**. We reasoned that addition of a good H-atom donor would promote easier trapping of radical **23c**. Use of lauroyl peroxide as initiator, together with methyl thioglycolate (RSH) as H-donor, led to a greatly improved yield of **24c**. It is likely that polarity reversal catalysis[13] played a part in enhancing this yield. The azetidinylbenzyl radical **23c** will be resonance stabilized and nucleophilic. Hence, a polar effect should favor H-abstraction from the electronegative RSH. The electrophilic thiyl radical (RS$^{\bullet}$) generated in this way will, in turn, H-abstract more readily from the cyclohexadienyl site of **20c**, thus regenerating RSH and continuing the chain.

Cyclizations onto the oxime ether functional group are regiospecific for the C-atom of the C=N bond[14] and give rise to much higher radical cyclization rates than analogous alkene acceptors.[15a–c] Moreover, a useful N-functional group remains available for further synthetic elaboration. We envisaged that amido-cyclohexadienes, suitably functionalized with oxime ether radical acceptors, would be mild precursors for preparations of indolones with N-functionality at the 3-position. We prepared several precursors of type **26** with *O*-benzyl- and *O*-trityl oxime ether acceptors (Scheme 6). When **27a** was refluxed in benzene with lauroyl peroxide and a catalytic amount of RSH, dihydroindol-2-one **30a** was isolated in 68% yield.[16] Observations on the cyclohexadienyl radical and cyclized radical **29a** by electron paramagnetic resonance (EPR) spectroscopy showed the process to be very rapid. This protocol amounts to a clean route leading from 2-aminoacetophenones to 1,3-dihydroindol-2-ones in four steps.

Scheme 6. Oxime Ether Substituted Cyclohexadienes and Indolone Preparation[a]



[a] Conditions: (i) $RONH_2$, EtOH, 12 h; (ii) concentrated HCl; (iii) **7**, pyridine, DMAP, reflux; (iv) lauroyl peroxide, RSH, PhH, reflux.

An interesting sequence of reactions took place with the *O*-trityl analogue **27b**. EPR spectroscopy showed that the corresponding cyclohexadienyl radical cyclized to afford aminyl radical **29b**. However, ring closure was quickly followed by another β-scission step that released the persistent trityl radical and 3-nitrosoindolone **31**. The latter then acted as an efficient spin trap for other radicals in the system and yielded a series of nitroxides **32**. End product analysis showed a mixture of products including **33** from which the 3-N-functionality had been lost. This was accounted for in terms of a further β-scission of **32** yielding a nitroso-compound (X−N═O) together with a resonance-stabilized indolonyl radical, which was reduced to indolone **33**.

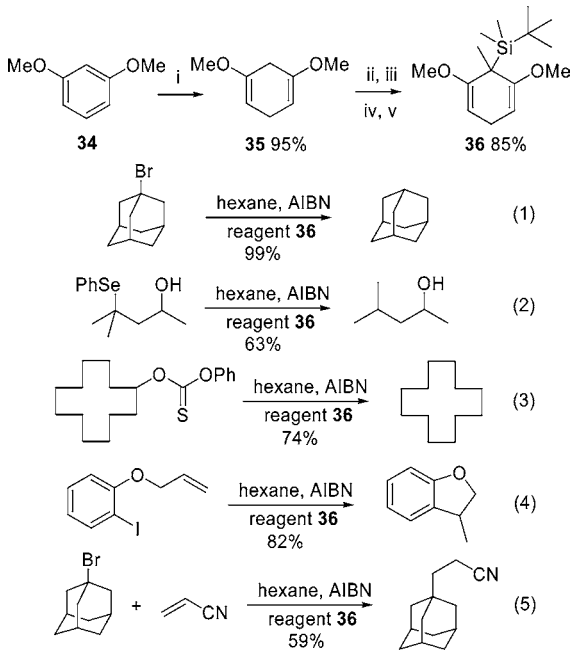
CHD Radical Precursors in Synthesis—Generation of Heteroatom-Centered Radicals

So far the generation of C-centered radicals using the cyclohexadiene approach has been described. As an extension of the concept we assumed that the generation of heteroatom-centered radicals should also be feasible from functionalized cyclohexadienes. In the following sections, we will briefly discuss the successful application of pro-aromatic compounds for the generation of Si-, Sn-, and N-centered radicals.

Enlarging the Theme with Silylated Cyclohexadienes

Silylated cyclohexadiene **36** was readily prepared starting from commercially available resorcin dimethyl ether (**34**) by Birch reduction (→ **35**) and subsequent one-pot silylation−methylation (Scheme 7).[17] The Si-group can readily be varied by employing different silylation reagents. We anticipated that the cyclohexadienyl radical

Scheme 7. Silylated Cyclohexadiene 36 in Different Radical Chain Reductions[a]



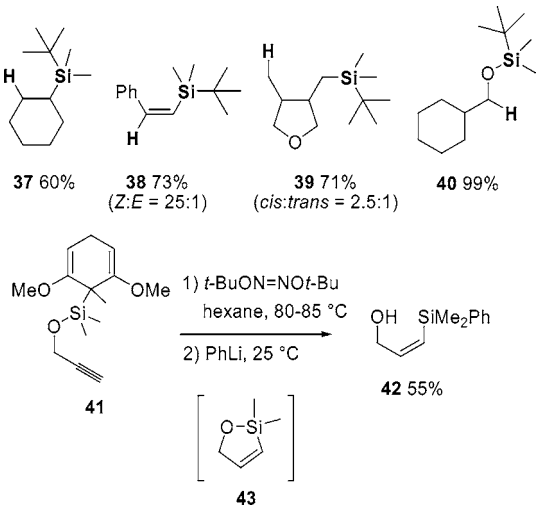
[a] Conditions: (i) Na, NH_3, EtOH; (ii) *t*-BuLi, TMEDA; (iii) *t*-$BuMe_2SiCl$; (iv) BuLi; (v) $(MeO)_2SO_2$.

derived from **36** would re-aromatize with selective Si-radical generation, that is, that methyl radical release would be slow. Indeed, we were very pleased to observe that cyclohexadiene **36** is a nearly perfect environmentally benign tin hydride substitute.

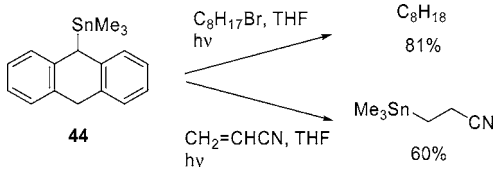
Typical radical reactions such as dehalogenations (eq 1), deselenations (eq 2), deoxygenations (eq 3), cyclizations (eq 4), and Giese-type additions (eq 5) can be performed with Si-reagent **36** under standard radical conditions. Yields are similar to those obtained using toxic trialkyltin hydrides. Recently, reagent **36** was successfully used for a reductive radical deselenation in a complex natural product synthesis.[18]

Furthermore, these silylated cyclohexadienes can also be used in radical hydrosilylation reactions.[19] These hydrosilylations can formally be regarded as *transfer hydrosilylations*, since reagent **36** is transformed to the corresponding arene in a reverse hydrosilylation process. The driving force of these transfer hydrosilylations is the resonance energy of the arene. Some examples are depicted in Scheme 8. Reactions were performed with Si-reagent **36** (1.5-fold excess) and the radical acceptor (1 equiv) using α,α′-azobisisobutyronitrile (AIBN) as initiator. Cyclohexene (→ **37**), phenyl acetylene (→ **38**), and cyclohexane carboxaldehyde (→ **40**) were successfully hydrosilylated using this method. Radical silylation/cyclization is also possible with **36** as shown for the transformation of bisallyl ether to give **39**. We were also able to conduct the first 5-*endo-dig* radical cyclization using cyclohexadiene **41**.[20] Phenyllithium treatment of the intermediately formed hydrosilylation product **43** provided stereoselectively *cis*-vinyl silane **42**.

Scheme 8. Radical Hydrosilylation Using Silylated Cyclohexadiene 36



Scheme 9. Sn-Radical Generation from Dihydroanthracene 44



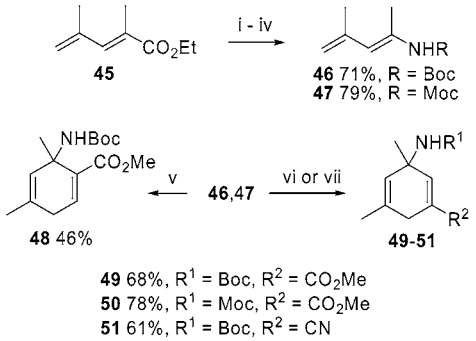
Retrogression to Toxic Stannyl Radicals Using Pro-Aromatic Stannanes

Although the goal of our cyclohexadiene research is to develop environmentally benign free radical chemistry, we will briefly mention the possibility of generating stannyl radicals from pro-aromatic compounds. Back in the late 1980s, Neumann showed that trimethylstannyl-substituted dihydroanthracene **44** delivers the Me_3Sn radical upon photoirradiation.[21] Reagent **44** can be used in reductive radical chain reactions. Dehalogenation of octyl bromide was successfully achieved with this method (Scheme 9). Moreover, radical hydrostannylation of acrylonitrile was performed with **44**. Addition of THF as a solvent led to improved yields. This is an indication that **44** is not a good H-donor and reduction occurs to a large extent by THF.

Amidyl Radicals from N-Functionalized Cyclohexadienes

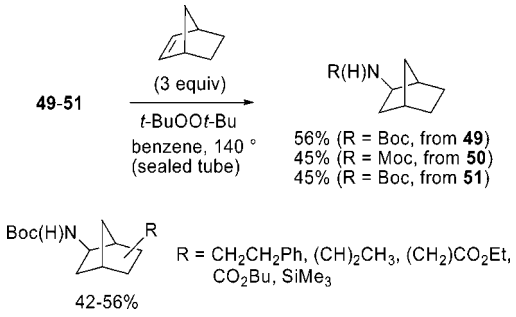
N-Centered radicals are generally obtained via N-halo, N-PTOC (PTOC = *N*-hydroxypyridine-2(*1H*)thione) and N-SPh derivatives either photochemically or by using a co-reducing agent.[22] However, most of these precursors are unstable and have to be prepared in situ. We conceived that aminyl- or amidyl-substituted cyclohexadienes might serve as stable alternatives for the generation of N-centered radicals under neutral conditions. As for the Si-reagents discussed above, the N-substituted cyclohexadienes should be suitable for radical transfer–hydroamination reactions. It is important to note that the transition metal-mediated hydroamination of olefins has been intensively investigated during the past few years.[23] Despite these efforts, the methods developed so far are still limited to activated systems.

Scheme 10. Synthesis of N-Substituted Cyclohexadienes[a]



[a] Conditions: (i) NaOH, MeOH; (ii) Et_3N, ClC(O)OEt; (iii) NaN_3, H_2O; (iv) *t*-BuOH or MeOH, toluene, reflux; (v) methyl propiolate, dioxane, 110 °C; (vi) 3-nitro methylacrylate, Ph-H,, then DBU; (vii) 3-nitroacrylonitrile, Ph-H, then DBU.

Scheme 11. Hydroamination of Norbornene with N-Substituted Cyclohexadienes



The aminated cyclohexadienes can readily be prepared by Diels–Alder reaction of dienes **46** and **47** using methyl propiolate, 3-nitro methylacrylate, or 3-nitro acrylonitrile. In the case of nitroolefin additions, the cyclohexadienes **49**–**51** were eventually formed upon nitrite elimination of the Diels–Alder adducts (Scheme 10).[24] Dienes **46** and **47** were prepared by saponification of readily available ester **45** and subsequent Schmidt-type reactions. It turned out that cyclohexadiene **48** is not stable at elevated temperatures in apolar solvents. However, **49**–**51** showed high stability in various solvents.

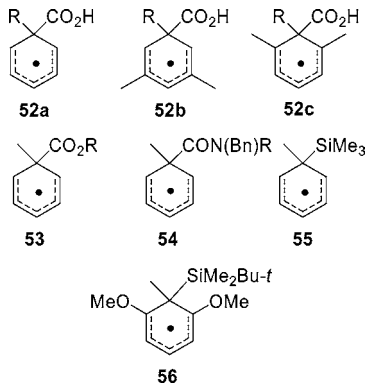
Pleasingly, reaction of reagent **49** with norbornene afforded the desired hydroamination product in an acceptable yield under radical conditions (Scheme 11). Slightly lower yields were observed using reagents **50** and **51**. The method could be extended to other norbornene derivatives. Yields ranging from 42% to 56% were obtained. We have to admit that norbornenes belong to the class of activated olefins and are therefore rather easy to hydroaminate. However, we also showed that 1-octene underwent hydroamination with reagent **50**. Although the yield is not yet satisfactory (17%), we believe that upon tuning the reactivity of the N-centered radical, hydroamination of unactivated olefins should be feasible using our approach. Experiments along this line are currently under way.

Kinetics of Cyclohexadienyl Chain Propagation

The two chain propagation steps are, first, dissociation of the cyclohexadienyl radical (k_d) and, second, H-atom abstraction from the precursor cyclohexadiene (k_H). The progress of many cyclohexadiene-based reactions could be monitored by EPR spectroscopy as a function of temperature. For selected precursors, the concentrations of the cyclohexadienyl radicals and the released C- or Si-centered radicals were determined using this technique. For CHD intermediates that dissociated predominantly by a single mode, this enabled serviceable $k_d/2k_t$ ratios to be obtained, where $2k_t$ refers to the termination process.[25] Termination under EPR spectroscopic conditions was by bimolecular reactions of the cyclohexadienyl or released radicals or both, all of which were small to medium sized. As a consequence, termination was diffusion-controlled, and the well-established $2k_t$ value of Fischer[26] could be employed, corrected for differences in solvent viscosity.[27] Dissociation data for 1-alkyl-1-carboxylic acid-substituted species,[28] 1-methyl-1-carboxylic esters, 1-methyl-1-amides,[29] and silylated cyclohexadienes[17b] are summarized in Table 1.

The data for the cyclohexadienyls containing only a 1-methyl substituent in the ring (apart from the leaving group) show that dissociation rates increase in the order: $-CO_2R \approx -CO_2H < -CONHR < -CON(Bn)R \approx -SiMe_3$. Extrusion of alkoxycarbonyl substituents was most difficult, followed only marginally more rapidly by the formate radical. Carbamoyls with mono-N-substitution (CONHBn) were extruded more slowly than carbamoyl radicals with di-N-substitution (CON(Bn)R) by a factor of about 7, but both were extruded at least an order of magnitude more rapidly than alkoxycarbonyls. The data indicate that the $SiMe_3$ group is ejected at about the same rate as carbamoyls. The most extensive series of data, for the 1-substituted acids **52**, showed that the ease of dissociation increased dramatically with the degree of branching associated with the C−C bond undergoing β-scission. In fact, release of the *t*-Bu radical was about 5 orders of magnitude faster than primary alkyl radical ejection. The rate constants increased as follows for release of delocalized radicals: *n*-Pr$^\bullet$ < N≡CCH$_2^\bullet$ < CH≡CCH$_2^\bullet$ < PhCH$_2^\bullet$ < CH$_2$=CHCH$_2^\bullet$. The k_d for allyl was more than 5 orders of magnitude greater than the k_d for *n*-Pr ejection. The extent of delocalization/resonance stabilization in these radicals increases along the same series, so it follows that electron delocalization in the released radical is a second important factor in controlling the fragmentation rates. It is worth noting that the relative rates of β-scission of these CHD-radicals parallel the classic work of Walling on the β-scission of alkoxyl radicals.[30] 3,5-Dimethyl substitution of the CHD ring caused a small reduction in k_d for *i*-Pr release, but surprisingly, 2,6-dimethyl substitution led to a diminished dissociation rate, possibly because the 2,6-Me groups led to enhanced stabilization of the cyclohexadienyl radical. Values of k_d were obtained for amides of type **54** with several substituents (R) (not shown), and they implied that k_d was practically independent of R (except for R = H). Rate constants were not obtained for the silyl-cyclohexadienes, but the temperature ranges in which dissociation set in (Table 1) reveal that **55** extruded a $SiMe_3$ radical at about the same rate as a carbamoyl radical. The most dramatic effect was observed for the 2,6-dimethoxy-substituted reagent (**56**) for which ejection of the $SiMe_2$Bu-*t* radical was greatly accelerated making chain propagation far more efficient.

Table 1. Kinetic Parameters for Dissociation of Functionalized Cyclohexadienyl Radicals



precursor	released radical R	temp range, K	$10^{-3}k_d$, s^{-1} (300 K)	E_d^{13},[a] kcal/mol
52a	Me	>380	≤0.001	≥18
52a	Et	330−360	0.04	15.0
52a	*n*-Pr	340−370	0.02	16.0
52a[b]	CO_2H		∼0.002	∼17.5
52c	*n*-Pr	>370		
52b	Me_2CHCH_2	300−330	0.53	14.1
52a	*i*-Pr	250−290	0.96	13.8
52b	*i*-Pr	250−290	0.28	14.5
52a	*c*-C_5H_{11}	280−305	1.3	13.6
52a	*t*-Bu	180−210	1070	9.6
52a	allyl	185−220	4450	8.7
52a	propargyl	195−235	23	11.9
52a	$NCCH_2$	270−300	1.5	13.5
52a[c]	$PhCH_2$	165−205	1300	9.5
53	$PhCH_2$	>370	<0.001	>18
54	H	>350	<0.008	>17
54	*n*-Bu	300−340	0.06	15.4
55	$SiMe_3$	>325[d]		
56	$SiMe_2$Bu-*t*	>145		

[a] Based on an assumed log(A/s^{-1}) = 13. [b] R = *n*-Pr. [c] Pentadeuteriocyclohexadiene ring. [d] Based on the appearance of *t*-Bu$^\bullet$ from reaction of R_3Si-radical with *t*-BuBr.

Rate constants (k_H) for H-atom abstractions from functionalized cyclohexadienes were determined by using the C^{5x} cyclization of 5-hexenyl as a radical clock.[25,31] 1-(Hex-5-enyl)cyclohexa-2,5-diene-1-carboxylic acid[8] and 5-hexenyl 1-methylcyclohexa-2,5-diene-1-carboxylate[7] were employed, as were silylated reagents **55**−H and **36** in conjunction with 1-bromohex-5-ene.[17b] A few k_H values were also derived from EPR spectroscopic radical concentration measurements.[28]

Table 2 shows that the silylated reagents transfer H-atoms at least 55 times more slowly than Bu_3SnH, and about an order of magnitude more slowly than tris(trimethylsilyl)silane. The 2- and 6-methoxy substituents of **36** should extend the resonance stabilization of radical **56** and hence would be expected to augment the rate of H-donation. Thus, the somewhat smaller k_H value for

Table 2. Kinetic Data for H-Abstraction from 1-[1]R,1-[2]R-substituted Cyclohexa-2,5-dienes and Other H-Atom Donors in Solution

abstracting radical (R•)	[1]R, [2]R[a] or donor	temp, K	$10^{-5}k_H$ M^{-1} s^{-1}	ref
t-BuO	H, H	295	540	32
Me	H, H	300	1.3	33
Et	H, H	300	0.6	33
Et	HO_2C, Et (**52a**-H)	340	0.14	28
H5e[b]	H, H	323	2.3	34
H5e[b]	Me, O_2CR^c (**53**−H)	413	0.8	6
H5e[b]	HO_2C, R^c (**52a**-H)	421	0.2	8
primary	Me, $SiMe_2Bu$-*t* (2,6-di-MeO, **36**)	343	1.0	17b
primary	Me, $SiMe_2Bu$-*t* (**55**−H)	343	0.7	17b
primary	Bu_3SnH	343	55	35
primary	$(Me_3Si)_3SiH$	343	11	36
primary	Bu_3GeH	297	1.0	37
i-Pr	HO_2C, *i*-Pr (**52a**-H)	270	0.003	8
t-Bu	H, H	300	0.09	33

[a] Substituents at C(1) of the cyclohexadienyl ring. [b] H5e = 5-hexenyl. [c] R = 5-hexenyl.

55−H (which lacks the methoxy substituents) is in accord with expectation. The k_H values for other **52** derivatives are even smaller suggesting that the 2,6-methoxy substituents significantly enhance the H-donation ability of **36**. A large reduction in k_H along the series Me• > Et• ≈ *n*-Pr• > *i*-Pr• > *t*-Bu• is evident for C-centered alkyl radicals. This is easily explained in terms of the decreasing strength of the R−H bond being formed across the series.

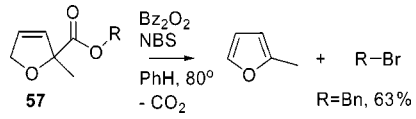
The dissociation data show that silyl, resonance-stabilized, tertiary-alkyl, secondary-alkyl, and carbamoyl radicals were all released sufficiently rapidly for chain propagation to proceed efficiently. Release of primary-alkyl radicals was slower, and temperatures significantly above 300 K would be needed. The rate of H-atom donation by cyclohexadienes to branched radicals (and probably resonance stabilized radicals) is comparatively slow, and hence the second propagation step would not be very effective for these species. We conclude that the most useful cyclohexadienes will release silyl, carbamoyl, or branched C-centered radicals but that ideally these should be transformed during propagation to primary C-centered, vinyl or O-centered radicals by cyclization, addition, etc. reactions to ensure that the H-transfer step is fast enough to maintain functioning chains. Methyl substituents attached to the cyclohexadiene ring had only minor effects on k_d and k_H, but 2,6-dimethoxy substitution enhanced both steps of chain propagation.

Cyclohexadiene Analogues and Spin Off

Several dihydroheteroarene systems were examined in the hope that they might offer advantages over the cyclohexadiene derivatives. 2,5-Dihydrofuran carboxylates **57** might be better H-atom donors than cyclohexadienes because of a polar effect from the adjacent O-atom. Reagents **57** did indeed generate C-centered radicals, but it was found that they offered no significant advantages, affording comparable product yields plus significant amounts of byproducts (Scheme 12).[7]

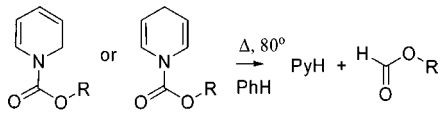
N-Alkoxycarbonyldihydropyridines **58** were more convenient to make, because Birch reduction/alkylation in liquid ammonia was avoided. Moreover, a blocking group, to prevent H-abstraction of the "wrong" H-atom, was not needed at the 3-valent N-atom (Scheme 13). EPR spectroscopy showed some radical formation, but it was found that the main products from both 1,2-dihydropyridines **58a** and 1,4-dihydropyridines **58b** were pyridine and formate esters derived from thermal, nonradical 1,2- and 1,4-elimination reactions.[38]

Scheme 12. Dihydrofuran Carboxylates as C-Radical Precursors



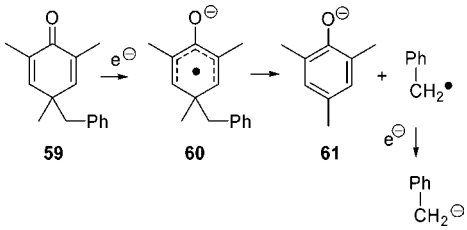
57

Scheme 13. Formate Elimination from *N*-Alkoxycarbonyldihydropyridines



58a 58b

Scheme 14. SET-Induced Processes of Cyclohexadienones



59 60 61

The idea that single electron transfer (SET) to a suitably substituted cyclohexadienone **59** would produce a pro-aromatic, delocalized ketyl radical anion **60**, which should readily dissociate to a phenolate anion **61** and release a useful radical, was also investigated (Scheme 14).[39] Product studies showed that photoelectron transfer to **59** with $Et_3N/h\nu$ generated benzyl radicals, as did electrochemical reductions, but product yields were low. Cyclic voltammograms in CH_3CN, with $TBAPF_6$ as supporting electrolyte, showed an irreversible reduction wave for **59** (E_p^c = −2.42 vs ferrocene; i.e., −1.77 vs SHE). Interestingly, this was a two-electron wave suggesting that release of the benzyl radical was followed by its immediate reduction to the benzyl anion. A preparative reduction with Na/liq NH_3 ($E'^\circ = -2.25$) gave toluene and mesitol as essentially the only products. However, reduction with and Li/liq NH_3 ($E'^\circ = -2.64$) gave additional products attributed to benzyl anion attack on the starting dienone. It is likely that released benzyl radicals, which have a comparatively low reduction potential (ca. −1.2 V vs SHE), were immediately reduced to benzyl anions. Primary and secondary alkyl radicals have larger reduction potentials (ca. −2.0 vs SHE), and therefore processes starting with 5-alkenyl-substituted cyclohexadienones might give viable radical reactions with the Na/liq NH_3 reductant.

Recently, Rossi and co-workers reported that irradiation of dienolates in the presence of α-bromophenyl allyl ether provided benzofurans in excellent yield. The reaction occurs via SET from the enolate to the arylbromide

generating the corresponding aryl radical, which undergoes fast 5-*exo* cyclization.[40]

Conclusions and Future Prospects

The two key features that have given organotin hydrides such wide scope and flexibility, that is, their ability to release radicals and their facile donation of H-atoms, are both mimicked effectively by cyclohexadiene derivatives, but without the toxic byproducts. Currently, to generate a C-centered radical from an alcohol, an ester with 1-phenylcyclohexa-2,5-diene-1-carboxylic acid (e.g., **18**) is probably the best bet. Likewise, the scope is wide for generation of carbamoyl radicals from amines via the corresponding amides with 1-methylcyclohexa-2,5-diene-1-carboxylic acid (e.g., **20** or **27**). On the other hand, silylated reagent **36** is near ideal for use in conjunction with halides, selenides, and esters of thiocarbonic acid. Hydrogen donation by cyclohexadienes is slower than that with organotin hydrides or tris(trimethylsilyl)silane. Research with reagent **36** indicated that 2,6-dimethoxy substituents improved the rate of H-donation, and further work is needed to transfer this substitution pattern to other CHD reagents. For ester and amide type reagents, H-atom transfer to branched and resonance stabilized radicals is comparatively slow. However, it is usually possible to arrange for the released radical to be converted to a primary, vinyl- or oxygen-centered radical by means of a cyclization or intermolecular addition, prior to the H-transfer step. Even when this cannot be achieved, the H-transfer chain propagation step can be fortified via polarity reversal catalysis by inclusion of a thiol. The comparatively slow H-atom donation by CHD reagents has advantages in that it enables premature reduction of initial radicals, before they can take part in addition, cyclization, or cascade processes, to be avoided. Cyclohexadiene-based reagents exhibit exceptional scope and offer clean alternatives to organotin reagents that enable many types of carbocyclic and heterocyclic compounds to be accessed. The pro-aromatic principle is a "surplus of meaning" concept that is likely to find fruitful future adaptability as a driver for still to be discovered processes.

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