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Radical Transfer Hydroamination with Aminated Cyclohexadienes Using Polarity Reversal Catalysis: Scope and Limitations

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Abstract: The synthesis of various new 1-aminated-2,5-cyclohexadienes is described. These reagents can be used in radical transfer hydroaminations of unactivated and electron-rich double bonds. With thiols as polarity reversal catalysts good yields are obtained. The radical hydroamination occurs with good to excellent anti-Markovnikov selectivity. Many functional groups such as alcohols, silyl ethers, phosphonates, arylbromides, imides, amides, and also acidic protons are tolerated under the reaction conditions. DFT calculations provide insights into the aromatization of silyl, alkyl, and aminyl substituted cyclohexadienyl radicals to generate the corresponding C-, Si-, and N-centered radicals.

Introduction

The hydroamination of olefins has been intensively investigated during the past few years. Most of the hydroaminations successfully conducted are using transition metals as catalysts. Despite the great achievements in this field most of the methods developed are limited to activated olefins.[1] Moreover not many functional groups are tolerated under the conditions applied. This is certainly an important issue for possible applications of the hydroamination in complex natural product synthesis. In terms of functional group compatibility, radical chemistry offers advantages over ionic and transition metal mediated reactions: most of the functional groups are tolerated under radical reaction conditions which makes these processes highly useful in complex natural product synthesis.[2]

However, the radical hydroamination of unactivated olefins is not established. Whereas the addition of N-radicals to alkenes is well-known,[3,4] the H-transfer from N- to C-radicals is not an efficient process. It is the reverse reaction, H-transfer from C to N, occurring in the *Hoffmann−Löffler−Freytag* reaction which is the favored process.[5] Therefore, the direct radical hydroamination via H-transfer reactions using NH compounds is not feasible. N-Radicals are generated via N-halo, N-PTOC (PTOC = *N*-hydroxypyridine-2(1*H*)thione), N-nitroso, and N-SPh derivatives either photochemically or by using a coreducing reagent.[3] However, most of these precursors are unstable and have to be prepared in situ. Moreover, the N-halo and N-SPh reagents can also react as electrophiles with alkenes which may lead to the formation of unwanted side products. Recently, *o*-iodoxybenzoic acid (IBX) has been used for the generation of N-centered radicals.[6]

The group of Walton and we have successfully used substituted 1,4-cyclohexadienes as clean sources for C- and Si-centered radicals.[7] In these reagents the cyclohexadiene moiety also acts as reducing agent. Hence no additional coreducing reagent is necessary to conduct reductive C-radical or Si-radical additions onto olefins using functionalized 1,4-cyclohexadienes.[7] Herein, we present in full detail[8] that aminated 1,4-cyclohexa-

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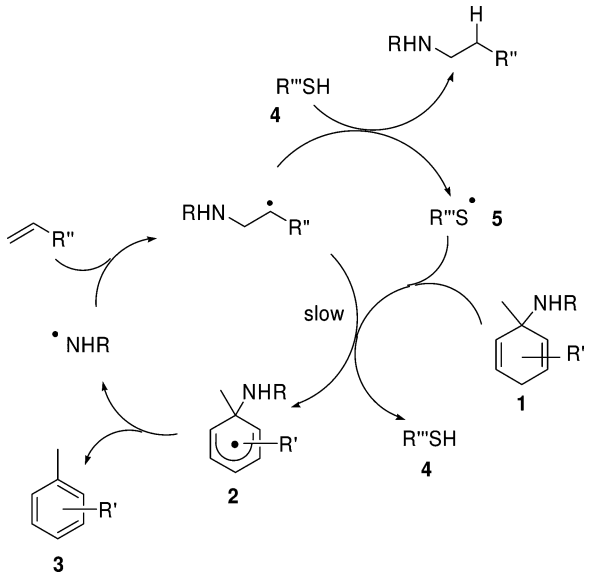
Scheme 1. Radical Transfer Hydroamination − the Concept



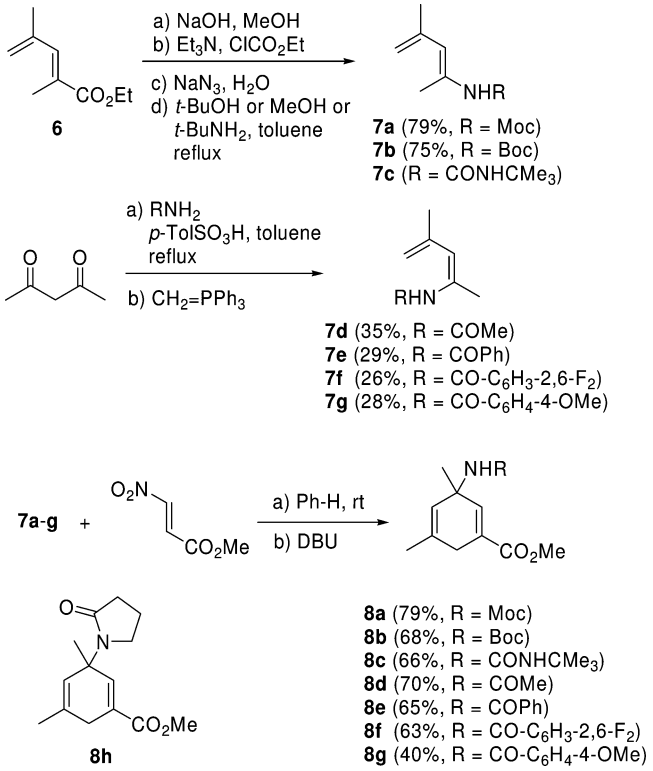
dienes are readily prepared, stable N-radical precursors which can be used as efficient reagents for the transition metal free hydroamination of unactivated olefins. Moreover, the reactions can be conducted without the need of toxic tin hydrides which are often used in radical chemistry.[9] The concept is presented in Scheme 1.

Addition of an N-radical to an alkene will afford the corresponding C-radical which will be reduced with the aminated cyclohexadiene **1** to provide the cyclohexadienyl radical **2** and the desired hydroamination product. Chain propagation occurs via aromatization of the cyclohexadienyl radical **2** to deliver an N-centered radical and arene **3**. The intrinsically difficult H-transfer from N to C is replaced by a known H-transfer process. However, since the reduction of C-radicals with cyclohexadienes is slow,[7] we will show that more efficient chains are obtained using polarity reversal catalysis.[10] In the presence of a catalytic amount of a thiol **4**, the slow reduction of a C-radical with the cyclohexadiene **1** is replaced by an efficient H-transfer from a thiol.[11] The thus formed thiyl radical **5** undergoes H-abstraction from the 1,4-cyclohexadiene **1** to eventually regenerate the catalyst **4** and the cyclohexadienyl radical **2** which is able to propagate the chain by aromatization. In the paper we will also present DFT calculations on the aromatization reaction of the cyclohexadienyl radical **2** to generate the corresponding N-centered radical.

Results and Discussion

Synthesis of the Aminated 1,4-Cyclohexadienes. The ester **6** was readily prepared via Wittig reaction using methacrolein and the corresponding ylide. Saponification and Schmidt type reaction followed by alcoholysis of the intermediate isocyanate provided the dienes **7a** and **b** in good yields. The urea derivative **7c** obtained by treating the isocyanate with *tert*-butylamine was used for the subsequent reaction without purification. The dienes **7d**−**g** were readily synthesized in a two step sequence via enamide formation using acetylacetone and the corresponding amide, with subsequent Wittig methenylation in moderate yields. The Diels−Alder reaction of β-nitroacrylate with the dienes **7a**−**g** followed by DBU induced HNO_2 elimination provided the desired aminated cyclohexadienes **8a**−**g** in moderate to good yields (Scheme 2). Pyrrolidinone derivative **8h** was prepared in analogy as described in the Supporting Information. It is important to note that our method allows the preparation of the dienes in a multigram scale.

Scheme 2. Synthesis of the Cyclohexadienes **8a**−**g**[a]



[a] Boc = *tert*-Butoxycarbonyl, Moc = Methoxycarbonyl.

Table 1. Stability Studies (Conditions: Perdeuterated Benzene in a Sealed Tube at 140 °C for 18 h)

entry	reagent	R	stability test (% decomposition)[a]
1	**8a**	C(O)OMe	< 2
2	**8b**	C(O)O*t*Bu	< 2
3	**8c**	$CONHCMe_3$	100
4	**8d**	COMe	8
5	**8e**	COPh	15
6	**8f**	$CO\text{-}C_6H_3\text{-}2,6\text{-}F_2$	12
7	**8g**	$CO\text{-}C_6H_4\text{-}4\text{-}OMe$	40

[a] Determined by ^1H NMR spectroscopy.

Stability Studies. To test the thermal stability of the reagents (elimination of the RNH substituent to form methyl 2,4-dimethylbenzoate and RNH_2), the dienes **8a**−**g** were stirred in perdeuterated benzene in a sealed tube at 140 °C (oil bath temperature) for 18 h. By ^1H NMR analysis the amount of methyl 2,4-dimethylbenzoate and RNH_2 formed was readily determined. No other side products were identified in these stability tests. The results of the decomposition studies are presented in Table 1. Decomposition was not observed for the carbamates **8a** and **b** (entries 1, 2). The urea derivative **8c** was the least stable compound in the series (entry 3). Complete decomposition of the reagent occurred within 18 h. The acetate

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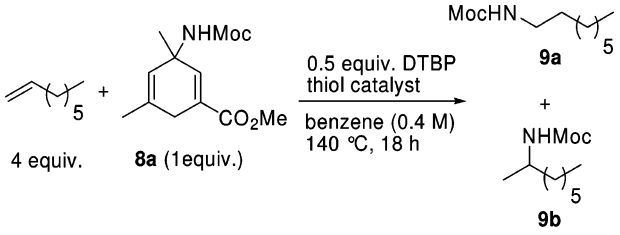
Table 2. Hydroamination of 1-Octene: Variation of the Thiol Catalyst

entry	thiol	equiv of thiol	yield[a] (%)
1	none	–	10
2	$HSCH_2CH_2SH$	0.15	12
3	$HSCH_2CF_3$	0.15	42
4	$HSCH_2CH_2OH$	0.15	41
5	$HSCH_2CO_2Me$	0.15	39
6	$HSCPh_3$	0.15	14
7	$HSCHMe_2$	0.15	32
8	$HSSiPh_3$	0.15	47
9	b-HS-naphthyl	0.15	38
10	HSPh-4-OMe	0.15	43
11	HSC_6F_5	0.15	47
12	HSPh	0.15	51
13	HSPh	0.05	26
14	HSPh	0.10	39
15	HSPh	0.20	50
16	HSPh	0.30	34

[a] The products were formed as a 7:1 mixture of regioisomers **9a** and **9b**.

Scheme 3. Hydroamination of 1-Octene Using Polarity Reversal Catalysis



8d was rather stable (8% decomposition, entry 4), whereas for the benzoate **8e** 15% decomposition product was identified (entry 5). The better leaving group ability of the benzamide as compared to the acetamide is probably the reason for the decreased stability of **8e** with respect to **8d**. A similar stability was observed for the difluoro derivative **8f** (12% decomposition, entry 6). To our surprise, the para-methoxy benzamidyl substituted cyclohexadiene **8g** underwent a fast decomposition (40% decomposition, entry 7). The pyrrolidinone **8h** was more stable (10% decomposition; not shown in the table) as compared to the benzamide derivatives **8e**–**g**. This result correlates well with the leaving group ability of pyrrolidinone compared to the RNH groups in **8e**–**g**.

Hydroamination of 1-Octene with Reagent 8a – Variation of the Thiol Catalyst. As a test reaction we first studied the difficult hydroamination of 1-octene using various polarity reversal catalysts (PRCs). To this end, 1-octene (4 equiv), the reagent **8a** (1 equiv), di-*tert*-butyl peroxide (DTBP, 0.5 equiv), and the catalyst were dissolved in benzene (0.4 M). In a sealed tube the reaction mixture was heated to 140 °C (oil bath temperature) for 18 h. Yields were determined based on isolated material. The hydroamination product was formed as a 7:1 mixture of regioisomers **9a** and **9b**. As expected for a radical reaction, the anti-Markovnikov product **9a** was formed as the major regioisomer (Scheme 3).

The hydroamination in the absence of a thiol catalyst afforded only 10% of the hydroamination products **9a**,**b** (Table 2, entry 1). By using ethanedithiol (0.15 equiv) as an additive only a slightly better yield was obtained (entry 2). The thiol catalyst is probably destroyed by disulfide formation. Pleasingly, the yield increased to 42% upon using $HSCH_2CF_3$ as a PRC documenting the beneficial effect of the thiol on the radical hydroamination (entry 3). This result clearly shows that the slow reduction of a C-radical with the aminated 1,4-cyclohexadiene **8a** can be replaced by a fast reduction using a thiol thus proving our concept. A similar result was obtained with the less acidic $HSCH_2CH_2OH$ showing that the acidity of the thiol does not influence the reaction outcome to a large extent (entry 4). With methyl thioglycolate as a PRC, **9a**,**b** were isolated in a 39% combined yield (entry 5). The catalyst $HSCPh_3$ did not provide a large effect on the hydroamination (entry 6). We believe that $HSCPh_3$ is consumed during the reaction because the corresponding thiyl radical generated after H-transfer probably undergoes the S-neophyl type rearrangement to give the stable $Ph_2(PhS)C$ radical.[12] The reaction with 2-propanethiol as a catalyst afforded a moderate yield of the hydroamination product (entry 7). A good result was achieved with $HSSiPh_3$ (47%, entry 8). β-Thionaphthol (entry 9) and the electron-rich *p*-methoxythiophenol (entry 10) provided moderate results. An improvement of the yield was noticed upon using the electron-poor perfluorothiophenol (47%, entry 11). The best result was achieved with the cheap commercially available thiophenol (51%, entry 12). Therefore, all further experiments were conducted using thiophenol.

We next varied the catalyst loading. Decreasing the amount of HSPh to 0.05 equiv resulted in a sharp decrease of the yield (26%, entry 13). A slight improvement was observed upon using 0.10 equiv of the catalyst (39%, entry 14). With 0.20 and 0.15 equiv of HSPh similar yields were obtained (51 and 50%, respectively; compare entries 12 and 15), and using 0.30 equiv of the catalyst provided a decrease of the yield (34%, entry 16). Hence, the following experiments were performed using either 0.15 or 0.20 equiv of the thiol catalyst.

Table 3. Hydroamination of Norbornene with the Cyclohexadienes **8a**–**g**

entry[a]	reagent	R	product	yield (%)
1	**8a**	C(O)OMe	**10a**	57
2	**8b**	C(O)O*t*Bu	**10b**	56
3	**8c**	$CONHCMe_3$	**10c**	8
4	**8d**	COMe	**10d**	41
5	**8e**	COPh	**10e**	13
6	**8f**	$CO\text{-}C_6H_3\text{-}2,6\text{-}F_2$	**10f**	15
7	**8g**	$CO\text{-}C_6H_4\text{-}4\text{-}OMe$	**10g**	9

[a] Conditions: 0.5 equiv of DTBP, 0.15 equiv of PhSH, benzene (0.4 M), 140 °C, 18 h.

Hydroamination of Norbornene – Variation of the Reagent. Hydroaminations of norbornene (2.5 equiv) were performed in sealed tubes using the aminated cyclohexadienes **8a**–**h** (1 equiv), DTBP (0.5 equiv), and PhSH (0.15 equiv) in benzene (0.4 M) at 140 °C (oil bath temperature) for 18 h. It was found that the yield of the hydroamination product correlates well with the reagent stability (see Table 1). Hence, for the perfectly stable carbamate derivatives **8a** and **b** highest yields were obtained (Table 3; **10a**: 57%, **10b**: 56%; entries 1,2). Not surprisingly, only the exo-hydroamination products were formed. It has previously been shown that radical additions onto norbornene occur with perfect exo-selectivity.[13] Using the reagent **8d**, which showed rather good stability, the exo-

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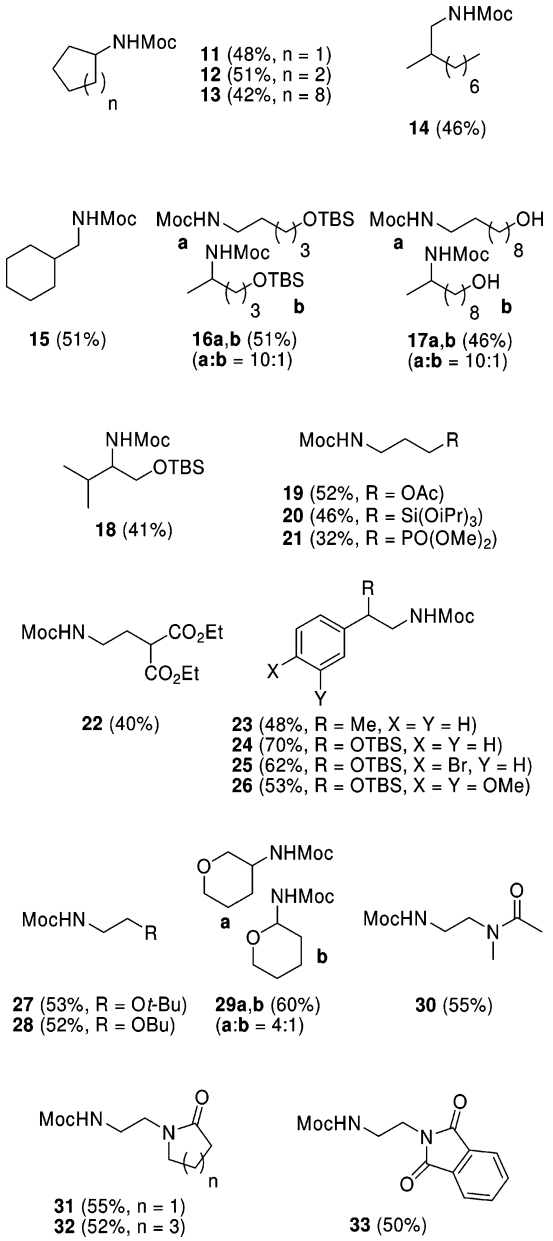
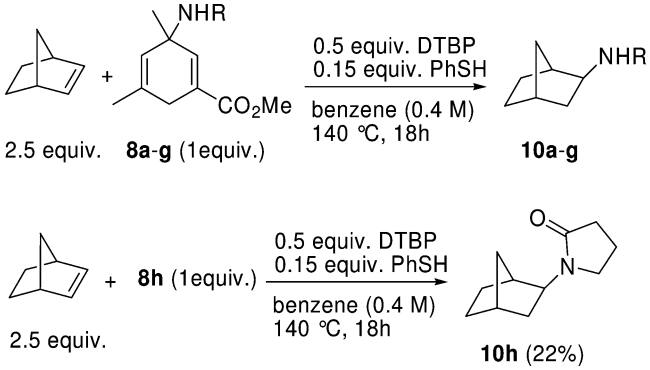


Figure 1. Hydroamination of various olefins with the reagent **8a** under the optimized conditions (2.5−6.0 equiv of olefin, 1 equiv of **8a**, 0.5 equiv of DTBP, and 0.15−0.20 equiv of PhSH in benzene (0.4 M) for 18 h at 140 °C).

hydroamination product **10d** was isolated in 41% yield (entry 4). All the other reagents turned out to be too unstable to deliver the corresponding hydroamination products **10c** and **10e**−**g** in satisfactory yields (entries 3, 5−7). A similar result was obtained using the pyrrolidone reagent **8h** where the transfer hydroamination product **10h** was isolated in a low yield (22%, Scheme 4).

Although the nature of the N-substituent affects the reactivity of the N-centered radical, as nicely shown by Newcomb for N-radical cyclizations,[14] the main influence of the protecting group in the intermolecular transfer hydroamination probably lies on the reagent stability. We will show below by DFT calculations that the activation energy for the aromatization of cyclohexadienyl radicals of type **8** to generate the corresponding N-centered radicals is not altered to a large extent upon switching from the amide to the carbamate group.

Scheme 4. Hydroamination of Norbornene Using Various Reagents



Hydroamination of Various Alkenes with Reagent 8a under the Optimized Conditions. To study the scope and limitations of the new hydroamination method, various olefins were reacted with the reagent **8a** under the optimized conditions. All yields were determined based on isolated material. In Figure 1 the hydroamination products **11**−**33** successfully prepared from the corresponding olefins are depicted. Yields are given in brackets.

Satisfactory yields resulted for the radical hydroamination of cyclic olefins. The products **11**−**13** were isolated in 42−51% yield. Perfect anti-Markovnikov selectivity was achieved for β,β-disubstituted olefins: the Moc-protected amines **14** and **15** were isolated in 46 and 51% yield, respectively. Silyl ethers are tolerated under the applied conditions as shown for the transformation of 5-*tert*-butyldimethylsilyloxy-1-pentene to give **16a,b** in 51% combined yield (ratio **16a**/**16b** = 10:1). The hydroamination can be conducted in the presence of free alcohols (→ **17a**,**b**, 46%; **17a**/**17b** = 10:1), and the reaction of silylated prenyl alcohol occurred with perfect regioselectivity (→ **18**).

Due to the radical nature of the hydroamination reaction, many functional groups are tolerated. Hence, allylacetates, allylsilanes, and allylphosphonates can be transferred to the corresponding Moc-protected amines in moderate to good yields (→ **19**−**21**). Acidic protons are tolerated as documented for the highly regioselective amination of diethyl allylmalonate (see **22**). To our delight, β-substituted styrene derivatives undergo amination with perfect anti-Markovnikov selectivity in good yields. Thus, biologically important aminoalcohol derivatives are readily synthesized by this new method starting from the corresponding readily prepared silyl enol ethers (→ **24**−**26**). It is important to note that bromides are tolerated under the reaction conditions. Aryl bromides are substrates for tin hydride mediated radical reactions and are also substrates in transition metal mediated coupling processes. As expected, electron-rich double bonds of vinyl ethers, vinyl esters, and vinyl amides are readily hydroaminated (→ **27**−**33**). To conclude these substrate scope studies we can state that our method is generally applicable for the hydroamination of unactivated and of activated electron-rich double bonds. However, electron-poor olefins such

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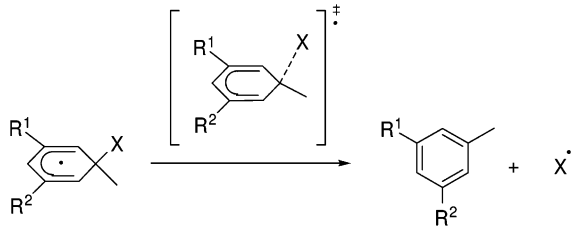
Scheme 5. Aromatization of the Cyclohexadienyl Radicals **34a**−**e** and **35a**−**e**[a]



[a] For specification of X, R^1, and R^2, see Table 4.

Table 4. Reaction Barriers and Reaction Energies (PBE/TZVPP) for the Aromatization Reaction of **34a**−**e** and **35a**−**e**[a]

X	R^1	R^2	compound	$E^{\ddagger}$ (kcal mol^{-1})	E_R (kcal mol^{-1})
CH_3	H	H	**34a**	+20.8	+12.5
SiH_3	H	H	**34b**	+8.9	+7.9
NH_2	H	H	**34c**	+15.0	+12.8
$NH(CO)CH_3$	H	H	**34d**	+11.5	+7.0
$NH(CO)OCH_3$	H	H	**34e**	+12.5	+10.9
CH_3	CH_3	CO_2CH_3	**35a**	+20.6	+12.3
SiH_3	CH_3	CO_2CH_3	**35b**	+8.8	+7.7
NH_2	CH_3	CO_2CH_3	**35c**	+14.3	+11.7
$NH(CO)CH_3$	CH_3	CO_2CH_3	**35d**	+11.3	+6.3
$NH(CO)OCH_3$	CH_3	CO_2CH_3	**35e**	+12.4	+10.9

[a] All energies refer to 0 K and are not corrected for zero-point vibrational energies.

as acrylates and acrylonitriles are not hydroaminated using our new protocol. Importantly, many functional groups are tolerated, and the products are obtained with good to excellent anti-Markovnikov selectivity. In addition, the products are delivered as protected amines: product purification does not cause any problems. Moreover, the Moc- and the Boc-group are N-protecting groups which have found widespread application in organic synthesis.

Theoretical Studies on the Elimination Reaction. Electronic reaction barriers $E^{\ddagger}$ and reaction energies E_R for the aromatization reaction of the cyclohexadienyl radicals **34a**−**e** ($R^1 = R^2 = H$) and **35a**−**e** ($R^1 = CH_3$, $R^2 = COOCH_3$) were calculated with density functional theory (DFT). All DFT calculations were performed with the TURBOMOLE package.[15] The GGA-type functional PBE[16] was used for all geometry optimizations together with a triple-ζ quality basis set (TZV)[17] with three (2df,-2pd) sets of polarization functions. Transition structures were optimized with TURBOMOLE after a numerical calculation of the Hessian matrix with the SNF program.[18]

The results for the unsubstituted cyclohexadienyl radicals **34a**−**e** are in good qualitative agreement with the experimental findings: all reaction barriers and energies allow the elimination process under the reaction conditions employed.[7] As expected, the CH_3 radical is the worst leaving radical due to a high barrier and unfavorable reaction energy. For the silyl-substituted cyclohexadienyl radical **34b** we calculated the lowest barrier toward elimination. Indeed, we have previously shown that C−Si bond cleavage in silylated cyclohexadienyl radicals can occur even at low temperatures.[19] Although the C−C bond cleavage as compared to the C−NH_2 cleavage is a higher energy pathway, the formation of the NH_2 radical is the most endergonic process in this series. A separately calculated hydrogen transfer from NH_3 to $^{\bullet}CH_3$ is endothermic by +2.9 kcal mol^{-1} with PBE/TZVPP, in good agreement with high level G3 calculations.[20]

Clearly, carbonyl substitution at nitrogen stabilizes the N-centered radicals (already in the TS). Therefore, especially with the acyl function as a protecting group ($X = NHCOCH_3$), the aromatization is least endothermic and has the lowest barrier among the N-substituted cyclohexadienyl radicals **34c**−**e**. The computational results for the substituted cyclohexadienyl radicals **35a**−**e** support that there is no significant intrinsic electronic (or steric) effect that changes the relative reactivity of the intermediates between the unsubstituted dienes **34** and the substituted dienes **35**. As a general trend, barriers are lower by 0.1−0.7 kcal mol^{-1} and reaction energies are lower by 0.0−1.1 kcal mol^{-1} for the substituted cyclohexadienyl radicals **35a**−**e** as compared to the analogous aromatizations of the unsubstituted cyclohexadienyl radicals **34a**−**e**.

Conclusions

We presented a new generally applicable method for the radical hydroamination of various unactivated and electron-rich double bonds. The reagents are readily prepared at a large scale, and the hydroaminations are easy to conduct. Importantly, the reagents are stable compounds which are readily stored for months. In contrast to most of the known transition-metal-mediated hydroaminations, the method presented herein tolerates many functional groups. Moreover, metal-catalyzed hydroaminations of unactivated olefins generally deliver the Markovnikov hydroamination products.[21] Our method is complementary to these metal-mediated reactions since high anti-Markovnikov selectivities are obtained. It is important to note that the radical hydroaminations described herein are environmentally benign tin-free processes. Theoretical calculations on the aromatization of functionalized cyclohexadienes to form the corresponding radicals show that aromatizations under generation of C-radicals, Si-radicals, and N-radicals are endothermic processes. In agreement with the experimental results, the lowest barriers are obtained for the Si-radical generation.[7,22] As compared to the C-radical generation from alkylated cyclohexadienyl radicals,[23] the formation of N-radicals from aminated cyclohexadienyl radicals is more efficient.

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