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Reactivity in the upper limits of the reduction potential in solution: arene dianion intermolecular carbolithiation of alkenes

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Dedicated to Professor Henry B. Kagan on the occasion of his 75th birthday

Abstract—Lithium salts of dianions derived from arenes of high reduction potential (biphenyl, naphthalene) can carbometallate terminal alkenes (propene, isobutene) in an intermolecular fashion, affording partially dearomatized alkylated aryl anions, which are susceptible to further functionalization by electrophilic capture. This form of reactivity, specific of the arene dianion, deviates from the typical alkali metal-like reactivity displayed by these complexes, affording in most cases regio- and stereocontrolled products. Simple semiempirical calculations (PM3) help predicting the regiochemical outcome of this reaction, where some of the most inexpensive organic starting materials are involved.

The use of solubilized forms of alkali metals, and in particular of lithium, has seen much success in preparative organic chemistry as ET (electron transfer) reagents, reaching one of the highest exponents in the form of the arene-catalyzed lithiations.[1] Recently, we focused our attention on the differences in reactivity between different species postulated as coexisting in these solutions, namely (for the case of naphthalene) the lithium salts of naphthalene radical anion ($LiC_{10}H_8$) and dianion ($Li_2C_{10}H_8$), in concern with their roles in the mechanism of the arene-catalyzed lithiation.[2] Radical anions, dianions and in general polyanions of aromatic hydrocarbons of high reduction potential are usually regarded as ET reagents, where one or more vacant molecular orbitals of the arene (LUMOs) have been occupied by a number of extra electrons. The resulting π-extended anionic species have thus both very high laying and also highly delocalized electrons. This eventually dictates much of their reactivity, reminiscent of the alkaline metal they originate from. For instance, both $LiC_{10}H_8$ as well as $Li_2C_{10}H_8$ display an ET reactivity profile towards alkyl chlorides.[3] However, intrinsically different electronic configurations between radical anions and dianions (with an open and closed-shell, respectively) anticipate the occurrence of markedly different reactivities when substrates are appropriately chosen. Among the reagents that are capable of discriminating between both reagents, the case of low-strained cyclic ethers has been studied.[2] It is also the case of arene dianions reacting with alkyl fluorides as alkylating reagents, since the corresponding radical anions remain unreactive under identical conditions,[4] except for a few arenes of very high reduction potential. We would like to present here the reaction of lithium dianions derived from three common aromatic hydrocarbons of high reduction potential: biphenyl, naphthalene and, in a lesser extent, phenanthrene, with terminal alkenes, which affords, after electrophilic quenching, regiochemically functionalized alkylated dihydroarenes through an intermolecular carbolithiation as a key step of the synthesis.

A common denominator of the former mentioned arenes is their high reduction potential and their capability to become doubly reduced species, at least to some extent, by $Li_{(s)}$ in THF. A closer look at the reduction potential of these arenes affords subtle differences. From these arenes, biphenyl (**1**) has the highest reduction potential ($E_1^0 = -2.68$ V, $E_2^0 = -3.18$ V) followed by naphthalene (**2**) ($E_1^0 = -2.53$ V) and phenanthrene (**3**) ($E_1^0 = -2.49$ V, $E_2^0 = -3.13$ V), all versus Ag/AgCl under identical experimental conditions.[5] Interestingly,

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Keywords: Arene dianion; Intermolecular carbolithiation; Lithium; Dearomatization; Alkenes.

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the second-reduction-wave in cyclic voltammetry does not follow the same sequence. The biphenyl dianion ($C_{12}H_{10}^{-2}$, **I**) is formed at a less-negative cathodic potential than the corresponding dianion for naphthalene ($C_{10}H_8^{-2}$, **II**), for which the second-reduction potential is beyond the cathodic limit. The effect is interpreted in terms of attainment of Hückel aromatic character for **I**, the opposite being true for **II** (and phenanthrene dianion $C_{14}H_{10}^{-2}$, **III**). Incorporation of two new electrons to **2** (or **3**) has an extra energy penalty as they attain antiaromatic character. This has also been observed as a paratropic NMR shift in the ^{1}H NMR spectrum of **III** and other dianions derived from larger, more easily reducible PAHs (polycyclic aromatic hydrocarbons) of benzenoid structure,[6] which are not ascribed solely to electronic shielding. Semiempirical calculations are a first qualitative approach to the theoretical description of the reactivity of **I**–**III** that proved to be helpful in the past.[4] In the intermolecular carbolithiation the alkene attack takes place at the carbon atom of the arene supporting the highest weight in the HOMO of the dianion, rather than the calculated charge on a given carbon atom (Scheme 1). We have also obtained preliminary results on ab initio calculations that corroborates the main picture given by PM3 calculations. These calculations on isolated highly charged polyanions proved to be far from straightforward. In most cases (including **I**–**III**), the polyanion is unstable with respect to electron loss (even with an extended diffuse function set), so that the high-energy electrons tend to be confined in the space described by the diffuse functions affording meaningless information.[7] This has been confirmed in the past for a number of simple organic,[8] and inorganic dianions,[9] where the use of diffuse functions gave rise to unexpected and unreliable results. According to our preliminary studies, this deleterious effect can be avoided by different means, as the incorporation of a cationic field or the implementation of a continuous solvent model. This will be the subject of upcoming specialized studies.

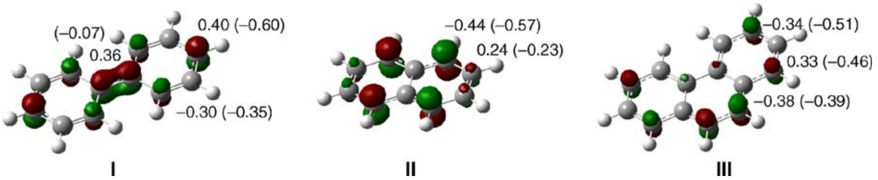
Previous characterization of these highly reduced species has been described elsewhere. **II** was crystallized as a dilithium salt coordinated with TMEDA and its structure determined by X-ray diffraction.[10] Both ^{1}H and ^{13}C NMR spectra of **III** with different alkali counterions have been reported.[6,11] Instead, descriptive work is very scarce for dilithium biphenyl (**I-Li₂**), being mainly limited to the UV and IR spectra of different alkali metal salts of biphenyl in sublimed layers.[12] **I-Li₂** has been suggested as a component of the Li-biphenyl solutions of stoichiometry 2:1 in THF, for which reductive-cleaving properties similar to that of $Li_{(s)}$ are described.[13] Besides that, synthetic exploitation of dianions **I**–**III** is essentially lacking. At this point it is also worth to note that *sec*- and *tert*-alkyllithium reagents react with ethylene to afford carbolithiation products.[14] But, so far no nucleophilic addition of an organoalkali compound to propene or isobutene has ever been reported under mild conditions.

We have observed previously that, in the presence of an excess of Li powder, **2** is doubly reduced in THF or better in THP to its dianion, **II-Li₂**.[2,3] Based on reduction potential criteria,[5] the remaining arenes are also expected to be reduced to the corresponding dianion under the same conditions, according to Eq. 1. Further reaction of the species **I**–**III** with terminal alkenes is described in Scheme 2.

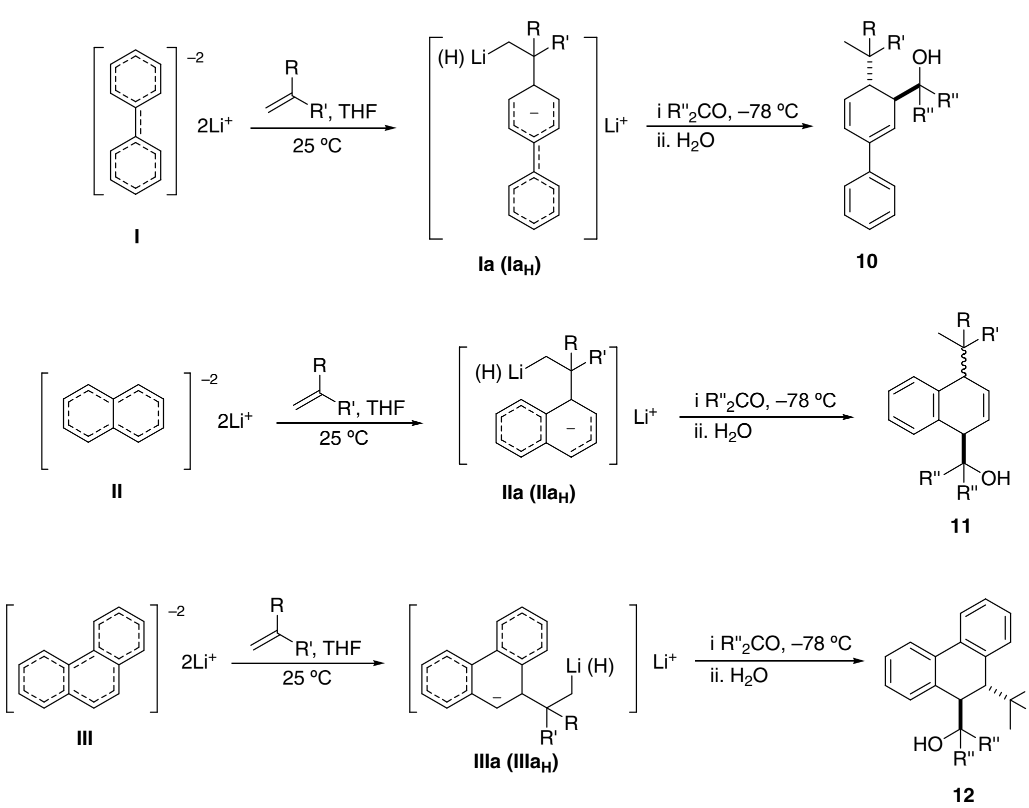
$$\mathrm{Arene}_{(\mathrm{THF})} \xrightleftharpoons{\mathrm{Li}_{(s)}} \mathrm{Arene}^{-\bullet}\,\mathrm{Li}^{+}_{(\mathrm{THF})} \xrightleftharpoons{\mathrm{Li}_{(s)}} \underset{\textbf{I, II or III}}{\mathrm{Arene}^{-2}\,2\mathrm{Li}^{+}_{(\mathrm{THF})}} \qquad (1)$$

The reactions described in Scheme 2 were carried out using a simple equipment in a one-pot fashion.[15] The carbolithiation step can be followed appropriately by change in color: the arene dianion changes from greenish-blue (**I**), purple (**II**) or dark magenta (**III**) to brown or brownish tones within the times indicated in Table 1, indicating the consumption of **I**–**III**. As electrophiles, symmetric ketones were preferred in order to simplify separations. Regarding the solvent, relatively short reaction times and the convenience of using THF versus THP (mp −45 °C) prompted us to choose THF to the detriment of THP, despite the better stability known for THP in these very reactive media.[2] Two important statements concerning reactivity must be done at this point. First, the reaction of the corresponding arene radical anions with alkenes does not take place at all (0% carbolithiation using a 1:1 Li/arene ratio for **1**–**3**). And second, roughly, for arenes with a second reduction potential less-negative than phenanthrene ($E_2^0 = -3.13$ V), the reaction with terminal alkenes does not proceed in a synthetically useful way (Scheme 3).

The intermediates **Ia**–**IIIa** are postulated after carbolithiation of the corresponding alkenes by **I**–**III**. These species carry two well differentiated organolithiun centers, one primary alkyl-lithium and one highly conjugated organolithium center (benzylic type or both benzyic-allylic type depending on the arene). We have not been able to capture the primary organolithium compound by any means. By the time the carbolithiation is complete, the primary alkyllithium is already quenched by the reaction media. In order to clarify this point, a reaction employing THF-d_8 was carried out. After 3 h of

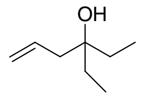


Scheme 1. PM3 HOMO coefficients and Mulliken charges (in parenthesis) for $C_{12}H_{10}^{-2}$ (**I**), $C_{10}H_8^{-2}$ (**II**) and $C_{14}H_{10}^{-2}$ (**III**).

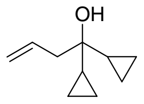


Scheme 2.

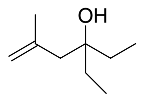
reaction of **I** with propene in THF-d_8 and H_2O hydrolysis, analysis of the crude products showed no deuterium incorporation at all (non-separated mixture of 3,4-dihydrobiphenyl and *trans*- and *cis*-4-isopropyl-1,4-dihydrobiphenyl, **13a–c**, 90%, in ratios **13a**:**13b**:**13c** = 46:33:21). When D_2O was used for quenching, an analogous mixture of monodeuterated products was observed (**13a–c-d_1**, monodeuterium incorporation >99.5%, natural isotopic abundance for $C_{15}H_{17}D$ corrected). Deuterium incorporation took place exclusively at the ring, as could be determined both by ^1H NMR and MS (Scheme 2). The reaction employing biphenyl-d_{10} was examined at this point. After reaction with $Li_{(s)}$ in THF and methylenecyclopentane (2 h), and electrophilic capture with 3-pentanone, **10f-d_{10}**, with all-10 D in the rings was isolated and characterized, proving that biphenyl or subsequent intermediates were not the source of quenchable protons in this reaction (Scheme 4). The only remaining source of protons is the alkene. Indirect evidence of the alkene participation in the protonation step **Ia**–**IIIa** → **Ia$_H$**–**IIIa$_H$** (Scheme 2) was obtained upon detection of alcohols **14**–**19** as side-products in variable yields in the reaction crudes. The presence of these side-products was confirmed by independent synthesis of **14**–**19** and quantitatively assessed by reexamination of the corresponding reaction crudes.



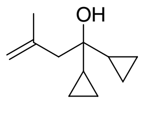
14 (20%)



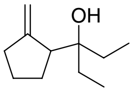
15 (55%)



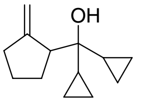
16 (29%)



17 (32%)



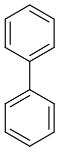
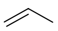
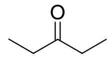
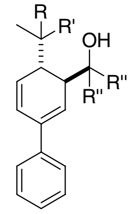
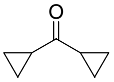
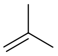
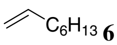
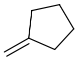
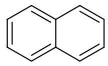
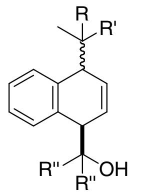
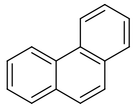
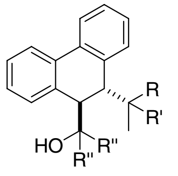
18 (27%)



19 (25%)

In conclusion, unprecedented reactivity patterns have been identified for lithium dianions of polycyclic arenes of high reduction potential. Largely unexplored, the reactivity displayed by these highly reduced species (**I**–**III**) other than ET is notable and has straightforward synthetic uses. Through an intermolecular carbolithiation, the presented reaction is an example of synthesis of highly elaborated, regiochemically and stereochemically well defined products obtained after processing of among some of the most low-costing organic starting materials. The reaction involves partial dearomatization and produces doubly functionalized 2-phenyl-1,3-cyclohexadienes as well as functionalized 1,4-dihydronaphthalenes and 9,10-dihydrophenanthrenes when starting from biphenyl, naphthalene and phenanthrene, respectively. Besides the synthetic scope, the relevance of this work can be understood from its advances in two fronts. From one side, as a reaction in which arene radical anion and dianion display clear-cut different reactivity. From the other side, as one of the first reactions of arene dianions of high reduction potential displaying reactivity profiles other than alkali metal-like soluble forms. Interestingly, this form of reactivity is manifested before

Table 1. Alkene carbolithiation plus electrophilic capture of arene dianions **I–III**

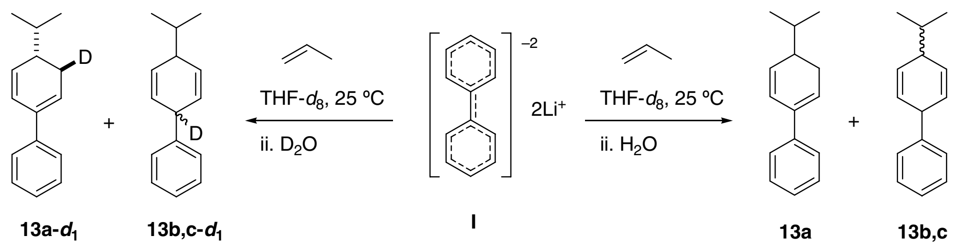
Arene	Alkene	*t* (h)	Electrophile	R	R′	R″	Isolated product[a]	%[b]
 **1**	 **4**	1	 **8**	H	Me	Et	 **10a**	62
1	**4**		 **9**	H	Me		**10b**	80
1	 **5**	1.5	**8**	Me	Me	Et	**10c**	63
1	**5**		**9**	Me	Me		**10d**	76
1	 **6**	1.5	**8**	H	Hx	Et	**10e**[c]	67
1	 **7**	1.5	**8**	[CH$_2$]$_4$		Et	**10f**	58
1	**7**		**9**	[CH$_2$]$_4$			**10g**	59
 **2**	**4**	2	**8**	H	Me	Et	 **11** (*t*-/*c*- 78:22)[d]	58
 **3**	**4**	2.5	**8**	H	Me	Et	 **12**	20

[a] All compounds were isolated (>94% purity by GLC and/or 300/500 MHz ^{1}H NMR) giving consistent NMR spectra and correlations (^{1}H, ^{13}C, DEPT, COSY, HSQC and HMBC), as well as HRMS and IR spectra. Stereochemistry was determined on the basis of NOESY experiments. Compounds **10** and **12** were obtained as single diastereomers.

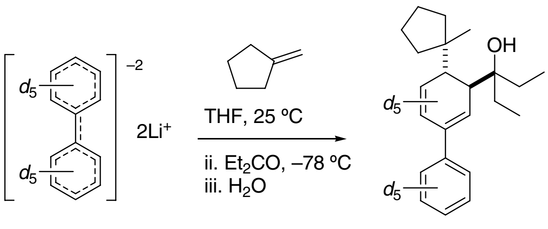
[b] Isolated yield based on arene **1**–**3**.

[c] 1:1 mixture of diastereomers corresponding to the two possible configurations of the 1-methylheptyl moiety.

[d] Separated trans- and cis-stereoisomers in 78:22 ratio.



Scheme 3.



I-d_{10}

60% **10f-d_{10}**

Scheme 4.

alkenes, in particular before propene an isobutene, which only very seldom undergo nucleophilic substitution processes. Mechanistic considerations and further theoretical studies to shed light onto the principles driving this reaction will be further explored.

Acknowledgements

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15. Representative example: preparation of compound **10a**. To a deeply colored solution of biphenyl (3 mmol) and lithium powder (Li$_{(s)}$, 12 mmol) in dry THF (10 ml) at 25 °C with vigorous stirring under Ar, propene was delivered using a balloon (approx. 3 l, 1 atm). Proper evacuation of Ar is critical for the reaction with gaseous alkenes in order to not lengthen unnecessarily the reaction times. After ca. 1 h, the initial greenish-blue color of **I** turned brown. The reaction was then cooled down to −78 °C. THF was chosen as solvent instead of THP (of improved stability towards reductive cleavage, see Ref. 2) to prevent freezing at this point. 3-Pentanone (**8**, 6 mmol) was then added. After 15 min the reaction was hydrolyzed (H$_2$O) and worked up as usual (3×20 ml diethyl ether, Na$_2$SO$_4$, 15 Torr), purifying **10a** by flash chromatography (silica gel, Hx/EtOAc). A 0.5 wt % of hydroquinone was added for storage (see Ref. 2). *3-[(1RS,6SR)-6-Isopropyl-3-phenylcyclohexa-2,4-dienyl]pentan-3-ol* (**10a**): $R_f = 0'36$ (9:1 hexane/ethyl acetate); IR (film): $\nu\,(\mathrm{cm}^{-1}) = 3583$, 3486, 3032, 2963, 2879, 1599, 1494, 1461, 1447, 1384, 1367, 1123, 948, 917, 771, 750, 697; ^{1}H NMR (300 MHz, CDCl$_3$): $\delta_H = 0'88$ (t, 3H, $J = 7.6$, CH_3CH$_2$), 0′92 (d, 3H, $J = 6.6$, CH_3CH), 0′93 (d, 3H, $J = 6.9$, CH_3CH), 0′95 (t, 3H, $J = 7.7$, CH_3CH$_2$), 1.49 (br s, 1H, OH), 1.51–1.70 (m, 5H, $2 \times$ CH_2CH$_3$, CH$_3$CHCH$_3$), 2.42–2.48 (2m, 2×1H, C=CHCHCOH and CH=CHCH^iPr), 5.82 (app. d, $J = 6.4$ Hz, 1H, C=CHCHCOH), 5.88 (app. dd, $J =$ 10.0 Hz, $J = 6.2$ Hz, 1H, CH=CHCH^{i}Pr), 6.28 (app. d, $J = 9.8$ Hz, 1H, CH=CHCPh), 7.24–7.42 (m, 5H, Ph); ^{13}C NMR: $\delta_C = 7.6$, 7.9 ($2 \times$ CH$_3$CH$_2$), 18.45, 19.45 (CH$_3$-CHCH$_3$), 27.1, 28.0 ($2 \times C$H$_2$CH$_3$), 34.7 (CH$_3C$HCH$_3$), 38.4 (CH=CHCH^{i}Pr), 43.1 (C=CHCHCOH), 78.8 (COH), 122.55 (C=CHCHCOH), 124.35 (CCH=CHCH^{i}Pr), 125.5 (2C, Ph$_{Co}$), 127.0 (Ph$_{Cp}$), 128.4 (2C, Ph$_{Cm}$), 130.7(CH=CHCH^{i}Pr), 136.1 [CH=C(Ph)CH], 140.8 (Ph$_{Ci}$); MS: m/z (%): 266 (<1%, M$^+$−18), 198 (34), 155 (100), 154 (32), 87 (34). HRMS: calcd for C$_{20}$H$_{28}$O: 284.2140; found 284.2092.