The Reaction of Active Zinc with Organic Bromides

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Abstract: The oxidative addition of highly reactive zinc to organic bromides shows a pronounced structure−reactivity dependence, in contrast to that shown by other metals. The kinetic and LFER studies suggest a mechanism in which electron transfer (ET) is the rate-determining step of the reaction. Experiments carried out with radical clocks as well as the stereochemical outcome of the reaction support the presence of radicals. The reactivity profiles suggest that the ET has an important component of *inner-sphere* process in the reaction with alkyl bromides. In the case of aryl halides, Hammet plots are consistent with the participation of aryl halide radical anions as intermediates. The reaction contemplated here can be ascribed as another example of radical-mediated selective reaction, and it has straightforward synthetic applications. Some synthetic work was done in this direction, to demonstrate how this structure−reactivity dependence can be used to obtain selective organozinc formation in unsymmetrical dibromides.

Introduction

Discovered almost a century ago, the reaction of organic halides with magnesium[1]—and later with lithium[2]—is still the most direct and commonly used method to prepare the corresponding organometallic compounds.[3] These processes have been extensively studied, yet there still remains some degree of uncertainty in several aspects concerning mechanistic details of the reactions.[4] Within some limits, the mechanisms of the formation of organomagnesium and organolithium compounds show great similarities.[5] Another common feature is that neither of these reactions shows much selectivity for the organic structure. As has been stated, "the reaction of organic bromides with magnesium is among the least selective of organic reactions".[6] This lack of selectivity is sometimes attributed to the participation of radicals as key intermediates in the reaction. However, radical-mediated reactions are not necessarily poorly behaved with respect to selectivity, as can be inferred from several recent elegant studies on the topic.[7]

In addition to these metals, zinc has become an important tool for the synthetic organic chemist. Over 100 years ago, zinc metal was found to react with organic iodides to yield organozinc compounds.[8] Recently, considerable attention has been focused on zinc chemistry and its synthetic applications.[9] Organozinc reagents tolerate a broad range of functionalities,[10] and since the introduction of highly reactive zinc,[11] virtually any organozinc reagent can be prepared from the corresponding organic bromide. It is generally accepted that the mechanism of these reactions is similar to those of the analogous reactions of magnesium and lithium.[12] However, few mechanistic studies regarding the formation of organozinc halides are available.

In this work, we present several studies on the reaction of highly reactive zinc with organic bromides. The studies are designed to gain a better understanding of the process and its differences with other related processes. These studies consist of (a) kinetic−structural studies, (b) stereochemical studies of the course of the reaction, (c) indirect detection of intermediates, and (d) linear free energy relationships. The oxidative addition shows a pronounced structure−reactivity dependence, in contrast to that shown by other metals. The stereochemical outcome of

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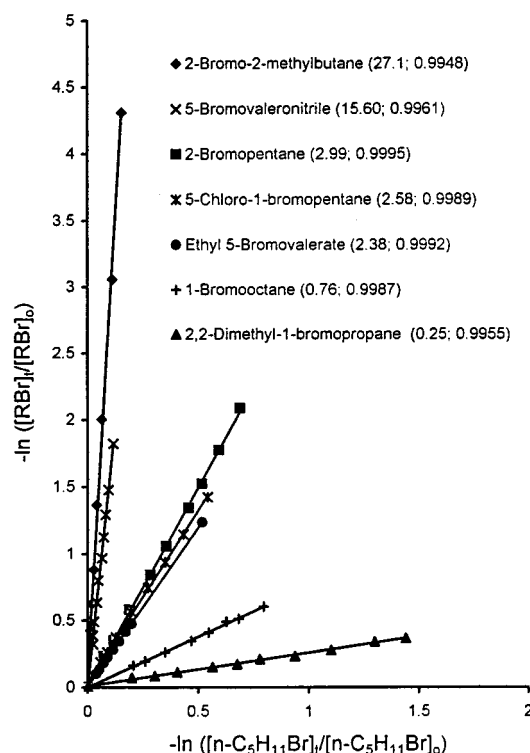
Figure 1. Plots displaying competitive alkylzinc bromide formation according to eq 4. Slopes (k_1/k_2) followed by regression coefficients are in brackets.

the reaction and radical probes however suggest that radicals are taking an active part in the reaction. The reaction contemplated here can therefore be described as another example of a *radical-mediated selective reaction*, and it has straightforward synthetic applications. Some synthetic work was done in this direction, to demonstrate how this structure−reactivity dependence can be used to obtain selective organozinc formation in unsymmetrical dibromides.[13]

Results and Discussion

Competitive Kinetics. The study of the relationship between the structure of a substrate and reactivity exhibited in a given reaction yields extremely valuable information about the nature of the process.[14] It permits, if not to assign a mechanism, to relate a process to others with similar structure−reactivity profiles, so mechanistic inferences can be recognized. When the difference in reaction rates between two different substrates is not too large (this will depend on the limits dictated by the detection/quantification technique utilized), competitive kinetics allow one to obtain reliable rate constant ratios of the reacting substrates.[6] In our case, competitive kinetic methods adapted very well to our purposes, i.e. the study of the rates of reaction of organic halides with highly reactive zinc. The rate of reaction

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Table 1. Relative Rates of Reaction of Alkyl Bromides (k_1/k_2)[a]

	R_1Br	k_1/k_2	R_2Br	$k_1/k_{n\text{-}RBr}$[b]
1.	(structure) Br	*1*	$1\text{-}C_5H_{11}Br$	*1*
2.	(structure) Br	2.99	$1\text{-}C_5H_{11}Br$	2.99
3.	(structure) Br	27.1, 9.58	$1\text{-}, 2\text{-}C_5H_{11}Br$	27.1, *28.6*
4.	(structure) Br	0.25	$1\text{-}C_5H_{11}Br$	0.25
5.	(structure) Br	3.51	$2\text{-}C_5H_{11}Br$	*10.5*
6.	Cl (structure) Br	2.58	$1\text{-}C_5H_{11}Br$	2.58
7.	EtO_2C (structure) Br	2.38	$1\text{-}C_5H_{11}Br$	2.38
8.	NC (structure) Br	15.6	$1\text{-}C_5H_{11}Br$	15.6
9.	NC (structure) Br	8.39	$5\text{-}BrC_4H_8CN$	*131*
10.	(structure) Br	0.17	$2\text{-}C_8H_{17}Br$	*0.42*
11.	(structure) Br	0.76	$1\text{-}C_5H_{11}Br$	*1*
12.	(structure) Br	2.52	$1\text{-}C_8H_{17}Br$	2.52
13.	(structure) Br	31.8, 13.02	$1\text{-}, 2\text{-}C_8H_{17}Br$	31.8, *32.8*

[a] Corresponding to the reaction of two alkyl bromides (R_1Br, R_2Br) with highly reactive zinc. All reactions were carried out in THF at 0 °C. Relative rates were determined by the competitive kinetics technique. [b] k_1/k_2 values for nondirectly measured pairs in italics; n-RBr is 1-bromopentane for entries 1−9 and 1-bromooctane for entries 10−13.

of organic bromides depends, in principle, on the concentration of organic halide, [R_1Br] or [R_2Br], and on some undefined physical characteristics of the metal surface, $f(Zn)$, according to eqs 1 and 2.

$$-d[R_1Br]/dt = k_1[R_1Br]^x f(Zn) \qquad (1)$$

$$-d[R_2Br]/dt = k_2[R_2Br]^x f(Zn) \qquad (2)$$

The simultaneous determination of the concentration of two different organic bromides in solution reacting with the same metallic surface permits eqs 1 and 2 to be simplified. Dividing both, a third expression (eq 3) arises in which two variables, t and $f(Zn)$, are canceled.

$$d[R_1Br]/d[R_2Br] = k_1/k_2([R_1Br]/[R_2Br])^x \qquad (3)$$

$$\ln([R_1Br]_t/[R_1Br]_0) = k_1/k_2 \ln([R_2Br]_t/[R_2Br]_0) \qquad (4)$$

By assuming that $x = 1$ (this will be confirmed later) and integrating eq 3, eq 4 is obtained. The experimental kinetic data fit eq 4 very well (Figure 1). Plots of $\ln([R_1Br]_t/[R_1Br]_0)$ vs $\ln([R_2Br]_t/[R_2Br]_0)$ were linear to elevated conversions (up to >95%). Evaluation of the slope, employing linear regression analysis, yielded k_1/k_2 directly. Each line contains an average of ca. 9 points, with the linear regression coefficients being >0.99 in all cases for alkyl bromides and ca. 0.95 on average for aryl halides. This confirmed our hypothesis that the reaction was first order with respect to the organic halide, in agreement with kinetic data reported for magnesium and lithium.[6b,15] Since the chemical yields of organozinc halides using this procedure are very high,[11a,9b] side reactions represent very small perturbations on the final results.

Alkyl Bromides. Table 1 summarizes the observed ratio of rate constants (k_1/k_2, tetrahydrofuran (THF), 0 °C) for all the pairs of substrates assayed. The reactivity profile correlates with

electron transfer (ET) being the rate-determining step of the reaction, in consonance to analogous processes with magnesium or lithium, as well as with other ET reactions. Other possible mechanisms of the oxidative addition will be discussed later. The reaction shows selectivity toward the nature of the organic moiety. The effect of the alkyl bromide on the rate of the electron transfer is tertiary > secondary > primary (Table 1, entries 2, 3, 12, and 13), roughly in the order 30:3:1. Cyclopentyl bromide has a rate 3.51 times faster than that for 2-bromopentane (Table 1, entry 5), and the 1-adamantyl bromide rate is 5.96 times slower than that for 2-bromooctane (and *77 times* slower than that for 2-bromo-2-methylheptane) (Table 1, entries 10 and 13). These are consistent with the geometric requirements of radical intermediates.[16] The reaction also seems to be slightly sensitive to some degree of steric factors; neopentyl bromide was found to react 4.00 times slower than 1-bromopentane (Table 1, entry 4).[17] The effect of a polar group in the chain is to increase the rate of the reaction (Table 1, entries 6 and 7). In the case of 5-bromovaleronitrile, this effect is notable (15.6 times faster than 1-bromopentane) and may be governed by binding interactions of the nitrile to the metal surface prior to electron transfer or a reduced reduction potential (Table 1, entry 8). When we shorten the chain length by one methylene, much more increased rates were observed (*131* times faster than 1-bromopentane, Table 1, entry 9). Comparative kinetic experiments using 1-bromopentane and 10 equiv of acetonitrile showed little effect on the reaction rate ($k_{THF-AN}/k_{THF} \sim 1.1-1.2$). Neither intramolecular nor intermolecular coordinative stabilization seem to be responsible for the increase in reaction rates observed. Purely inductive effects, which usually vanish rapidly in aliphatic chains, may not provide by themselves a satisfactory explanation. Further studies are in course to determine the cause and scope of the observed selectivity.
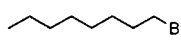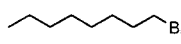
Aryl, Vinyl, Benzyl, and Allyl Bromides. The study of these systems provided important information, for both mechanistic and synthetic purposes. The reactivity of bromobenzene was evaluated against 1-bromooctane by following the same procedure used for alkyl bromides (THF, 0 °C, GLC analysis). It reacts with active zinc ca. 20 times slower than this primary alkyl bromide, and subsequently, *27* times slower than 1-bromopentane, arbitrarily chosen for comparative purposes (Table 2). As an example of a vinylic bromide, 2-bromo-3-methyl-2-butene was tested against bromobenzene in THF at 70 °C. A rate ratio of 0.17 was observed, which corresponds to *160* times slower than 1-bromopentane (Table 2, entry 2).

Benzyl and allyl bromides could not be studied using the normal experimental protocol. The reaction was too fast to adequately monitor by simple sampling at different time intervals. On the other hand, GLC response calibration of benzyl bromide gave inconsistent results.[18] We used a variation of the technique, in which several reactions—one for each point to be plotted—were set up. They were loaded with a previously prepared mixture of bromides/internal standard. A substoichiometric amount of active zinc, different for each reaction, was then injected. The reactions went to completion within minutes. Direct analysis of the unreacted bromides by ^{1}H NMR provided, if not an accurate measurement of the rates ratios, establishment of lower limits for them in these rapid reactions. Benzyl bromide was tested against the fastest organic bromide, whose kinetics were available at that point, i.e. *tert*-pentyl bromide (2-bromo-

Table 2. Relative Rates of Reaction of Aryl, Vinyl, Benzyl, and Allyl Halides (k_1/k_2)[a] (Alkyl−Aryl Halides Link for Tables 1 and 4−5)

	R_1Br	k_1/k_2	R_2Br	$k_1/k_{n\text{-bromopentane}}$[b]
1.	⬡—Br	0.049	∿∿∿Br	*0.037*
2.	=⟨Br	0.17[c]	⬡—Br	*0.0062*[d]
3.	⬡—CH₂Br	≥14	(CH₃)₃C—Br	*≥380*
4.	∿Br	~1-10[e]	⬡—CH₂Br	*>380*
5.	⬡—I	21	∿∿∿Br	*16*

[a] Corresponding to the reaction of two alkyl bromides (R_1Br, R_2Br) with highly reactive zinc. All reactions were carried out in THF 0 °C, unless otherwise stated. Relative rates were determined by the competitive kinetics technique. [b] k_1/k_2 values for nondirectly measured pairs in italics. [c] 70 °C. [d] Calculated from $k_{PhBr}/k_{n-bromopentane}$ at 0 °C. [e] Approximate range (see text).

2-methylbutane). $k_{BnBr}/k_{t-PentBr}$ was found to be ≥14 (THF, 0 °C), the limit being dictated by the sensitivity of the analysis. Consistent with other ET reactions, benzyl bromide showed enhanced reactivity, the rate being *at least 380* times faster than 1-bromopentane (Table 2). The measure of allyl bromide resulted in additional complications. Whereas side reactions were present, but unimportant in the formation of benzylzinc bromide, allyl bromide reacts with extensive homo- and cross-coupling product formation in competitive kinetic experiments with benzyl bromide. A study of the distribution of reaction products as well as unreacted starting materials only permits a rough assignment of reaction rates ratios. With reasonable reliance, we can state that allyl bromide reacts slightly faster than benzyl bromide, but within the same order of magnitude (THF at 0 °C). No attempts were made to determine whether the reaction rates observed for allyl and benzyl bromides are mass-transport-limited or not. Though this may be possible, it does not alter the final conclusions of this work since most substrates assayed fall out of this range.

This set of kinetic data is compiled in Table 3, along with an extensive set of other ET reactions to organic halides, in which reactivity profiles were studied. These are as follows, starting from the left column: $Co(CN)_5^{3-}$ in MeOH−H₂O at 25 °C (RI);[19] $Cr(en)_2^{2+}$ (en = ethylenediamine) in dimethylformamide (DMF)−H₂O at 25 °C (RBr);[20] idem. (RCl);[20] active Zn in THF at 0 °C (RBr);[21] Bu₃Sn• in Et₂O at 35 °C (RCl);[6d] lithium 4,4′-dimethylbenzophenone ketyl in THF at 24 °C (RBr);[6d] Mg in Et₂O at 0 °C (RCl);[6d] (C₅Me₅)₂UCl·THF in benzene at 25 °C (RCl);[22] Bu₃Sn• at 45°/80 °C in chlorobenzene (RBr);[23] electrochemically generated anthracene radical anion in DMF (0.1 M (TBA)BF₄) (TBA = tetrabutylammonium) at 25 °C (RBr);[24] sodium in gas phase (RCl);[25] electrochemically generated benzophenone ketyl in DMF (0.1 M (TBA)BF₄) at 25 °C (RBr);[24] peak potentials (E_p) at glassy carbon electrode in DMF

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Table 3. Relative Rates of Reaction of Organic Halides in Various Electron-Transfer Processes[a]

ET reag.[b] RX	Co(II) RI	Cr(II) RBr	Cr(II) RCl	Zn* RBr	Bu$_3$Sn• RCl	Ar$_2$COLi RBr	Mg RCl	U(III) RCl	Bu$_3$Sn• RBr	Anthr•⁻ RBr	Na$_{(g)}$ RCl	Ph$_2$CO•⁻ RBr	E_p ($E_{1/2}$)[c] RBr	Mg RBr
Me	0.22										0.43		(−1.96)[d]	
n-	1 (Pr)	1 (Bu)	1 (Pr)	1 (Pent)	1 (Pent)	1 (Pent)	1 (Pr)	1 (Bu)	1 (Et)	1 (Bu)	1 (Pr)	1 (Bu)	−2.85 (−2.24) (Bu)	1 (Pr)
sec-	28 (Pr)	10 (Bu)	4.0 (Pr)	3.0 (Pent)	2.9 (Pent)	2.3 (Bu)	3.8 (Pr)	2.1 (Pr)	3.0 (Pr)	2.5 (Bu)	1.3 (Pr)	1.0 (Bu)	−2.63 (−2.34) (Bu)	1.1 (Pr)
tert-	210 (Bu)	41 (Bu)	32 (Bu)	27 (Pent)	19 (Bu)	21 (Hex)	7.7 (Bu)	7.5 (Bu)	7.0 (Bu)	4.4 (Bu)	2.9 (Bu)	2.6 (Bu)	−2.51 (−2.19) (Bu)	1.2 (Bu)
Bn	88000	400[e]	9300[e]	≥380			<92	12	34		4400		(−1.22)	≤1.4
1-adam				0.32				5		0.023			(−2.38)	0.67
neopent				0.25	0.52	0.68	0.22	0.5		0.014			(−2.46)	0.58
c-pent				11	4.3	12	4.2		2.4				(−2.19)	1.2
Ph				0.037				0.05	0.063[f]				(−1.81)[d,g]	0.58
vinyl				0.0062[h]									(−2.46)[i]	0.23[j]
allyl				>380									(−1.24)[d,k]	≤1.8
solvent	MeOH	DMF	DMF	THF	Et$_2$O	THF	Et$_2$O	PhH	PhCl	DMF	−	DMF	DMF	Et$_2$O

[a] All the rates are relative to the corresponding *n*-haloalkane. [b] See text for details and references. [c] Peak potentials, E_p (glassy C, volts) in DMF (0.1 M Bu$_4$NBF$_4$). Half-wave potentials, $E_{1/2}$ (Hg, V, in parentheses) in DMF (0.01 M Et$_4$NBr). Hg electrodes may be chemically involved in the electrochemical reduction of alkyl halides: ref 62. [d] Reference 27b. [e] Estimate: see references in text. [f] 80 °C. [g] DMF (0.02 M Et$_4$NBr). [h] For 2-bromo-3-methyl-2-butene at 70 °C. [i] In 75% dioxane−water (Bu$_4$NI). [j] For 2-bromo-1-butene. [k] In DMSO (0.1 M Et$_4$NClO$_4$).

Scheme 1. Stereochemical Outcome of the Reaction of Zn* with (R)-(+)-2-Bromooctane
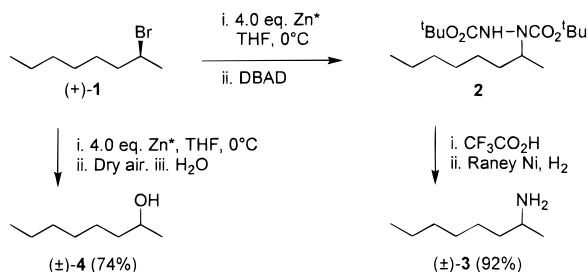
at 10 °C (RBr)[26] and half-wave potentials ($E_{1/2}$) at mercury electrode in different solvents;[27] Mg in Et$_2$O at 0 °C (RBr).[6a] A comparative study of the processes will be discussed later.

Stereochemical Studies. The study of the stereochemical course of a reaction may provide definitive clues on its mechanistic nature. To further explore the oxidative addition step, the reaction of Zn* with an optically active alkyl bromide was investigated. (R)-(+)-2-Bromooctane (**1**)[28] ([α]$_D$25 = + 39.7°, >95% op) (op = optical purity) was prepared and reacted with 4.0 equiv of Zn* at 0 °C. The 2-octylzinc bromide generated was then reacted with 1.0 equiv of di-*tert*-butyl azodicarboxylate (DBAD) at 0 °C.[29] Deprotection and reduction,[30] afforded (±)-2-octylamine (**3**), as shown by [1]H NMR spectroscopy using (S)-(+)-O-acetylmandelic acid as a chiral solvating agent.[31] The use of O$_2$ as an electrophile also resulted in formation of racemic 2-octanol (**4**, ^{1}H/^{19}F NMR spectra of the ester with (R)-(+)-Mosher acid).[32] This is a less reliable reaction since it is possible that racemization might also have taken place during reaction with the oxygen.[33] According to

the kinetics of the isotopic substitution of 2-bromooctane with radioactive bromide ion (Li*Br, acetone, 65.5 °C),[34] racemization attributed to the bromide generated during the reaction may be excluded, without incurring an extensive error (Scheme 1, <5 min of reaction time to completion). On the other hand, configurational stability of a secondary carbon−zinc bond has been previously observed.[35] Accordingly, racemization most likely occurred during the formation of the organozinc reagent.[36]

Radical Detection. The rearrangement of radical probes (radical clocks) has been used extensively to elucidate the nature of the events following ET steps in which the formation of radicals is suspected.[37] Previous studies using 6-halo-1-hexene models suggested radicals as intermediates in the reaction of organic halides with zinc.[38] A difficulty inherent to these radical probes is that the corresponding organometal derivative also cyclizes, although at a much slower rate. It has been demonstrated recently that acyclic organozinc iodides can be prepared from several substituted 6-iodo-1-hexene probes by reaction with zinc, and they only cyclize upon warming.[39] In one example, using (Z)-8-iodo-3-octene and zinc in DMF at 80 °C, cyclization of the corresponding organozinc iodide did not take place to any extent. This observation was clearly inconsistent with a scenario involving radical ring closure. The background depicted above prompted us to examine with caution the study of the

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(27) Casanova, J.; Eberson, L. In *The Chemistry of the Carbon−Halogen Bond*; Patai, S., Ed.; John Wiley & Sons: London-New York, 1973; Part 2, pp 979−1047. (b) Meites, L.; Zuman, P. *CRC Handbook Series in Organic Electrochemistry*; CRC Press: Cleveland, OH, 1977; Vol. I.

(28) Mukaiyama, T.; Hogo, K. *Chem. Lett.* **1976**, 619−622.

(29) Velarde-Ortiz, R.; Guijarro, A.; Rieke, R. D. *Tetrahedron Lett.* **1998**, *39*, 9157.

(30) Evans, D. A.; Britton T. C.; Dorow, R. L.; Dellaria, J. F. *Tetrahedron* **1988**, *44*, 5525.

(31) Parker, D.; Taylor, R. J. *Tetrahedron* **1987**, *43*, 5451.

(32) (a) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543. (b) Sullivan, G. R.; Dale, J. A.; Mosher, H. S. *J. Org. Chem.* **1973**, *38*, 2143.

(33) Radicals on the carbon have been proposed in the reaction of Grignard reagents with oxygen: Lamb, R. C.; Ayers, P. W.; Toney, M. K.; Garst, J. F. *J. Am. Chem. Soc.* **1966**, *88*, 4261.

(34) Evans, C. C.; Sugden, S. *J. Chem. Soc.* **1949**, 270.

(35) Micounin, L.; Oestreich, M.; Knochel, P. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 245.
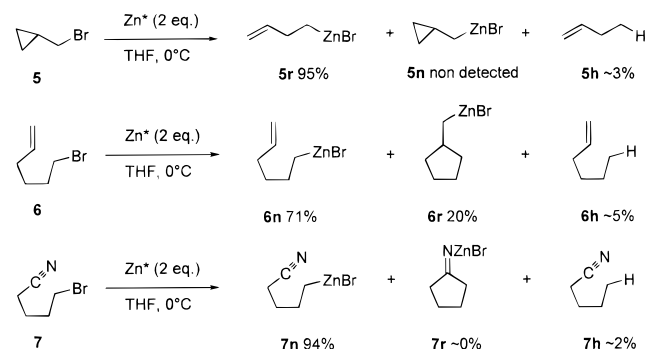
(36) (a) The participation of radicals in the reaction of zinc with alkyl iodides has been suggested: Luche, J. L.; Allavena, C.; Petrier, C.; Dupuy, C. *Tetrahedron Lett.* **1988**, *29*, 5373. (b) Partial loss of the stereochemical integrity was reported for the reaction of zinc with diasteromerical secondary iodides followed by deuteration: Turecek, F.; Veres, K.; Kocovsky, P.; Pouzar, V.; Fajkos, J. *J. Org. Chem.* **1983**, *48*, 2233. NaI S$_N$2 fast exchange and "retention of the configuration in the reduction step" was then proposed. However, substrates nonsusceptible to S$_N$2 equilibration such as *exo-* and *endo*-7-iodonorcarane were found to react with complete loss of their stereochemical integrity: Duddu, R.; Eckhardt, M.; Furlong, M.; Knoess, P.; Berger, S.; Knochel, P. *Tetrahedron* **1994**, *50*, 2415. This and the evidence accumulated in this work point to a radical-induced loss of stereochemistry, rather than retention in the reduction step.

(37) Eberson, L. Chapter V. In *Electron Transfer Reactions in Organic Chemistry*; Springer-Verlag: Berlin-Heidelberg, 1987.

(38) (a) Brace, N. O.; Van Elswyk, J. E. *J. Org. Chem.* **1976**, *41*, 766. (b) Samat, A.; Vacher, B.; Chanon, M. *J. Org. Chem.* **1991**, *56*, 3524.

(39) (a) Meyer, C.; Marek, I., Courtemanche, G.; Normant, J.-F. *Synlett* **1993**, 266. (b) Meyer, C.; Marek, I.; Courtemanche, G.; Normant, J.-F. *Tetrahedron Lett.* **1993**, *34*, 6053.

Scheme 2. Indirect Radical Detection in the Reaction of Zn* with Radical Probes

Scheme 3. Oxidative Addition via S_N2 Transition State

Scheme 4. Oxidative Addition via an Ate Complex Transition State/Intermediate

Scheme 5. Oxidative Addition via S_N1 Transition State

reaction of active zinc with radical clocks. Three different radical probes,[40] covering a wide range of radical rearrangement rate constants (k_r, 25 °C), were submitted to test. Bromomethylcyclopropane (**5**) ($k_r = 1.3 \times 10^8$ s^{-1}), 6-bromo-1-hexene (**6**) ($k_r = 1.0 \times 10^5$ s^{-1}) and 5-bromopentanenitrile (**7**) ($k_r = 3.9 \times 10^3$ s^{-1}) were reacted with 2.0 equiv of Zn* at 0 °C in THF. The analysis of products was performed directly on the crude reaction mixture after centrifugation and at the same temperature by 500 MHz ^{1}H NMR (Scheme 2). They reveal a complete rearrangement for the fastest radical clock (**5r**). In contrast, there was essentially total formation of the unrearranged organozinc bromide in the case of the 5-bromovaleronitrile (**7n**).[41] A mixture of both rearranged and nonrearranged products was observed in the case of 6-bromo-1-hexene (**6n**:**6r** ratio = 3.6:1), along with small amounts of the hydrocarbons originated by hydrogen/proton abstraction from the media or during handling (1-hexene (**6h**) and methylcyclopentane (**6h′**) in ~5 and 1−2%, respectively). The reaction was then allowed to warm to room temperature. After 24 h, no substantial change in the ratio of products was observed (3.5:1). In addition, the use of a higher amount of Zn* in the reaction (4 equiv) originated a mixture of compounds enriched in the olefinic component (8.7:1). From all of this, we can conclude that the cyclized products are originated *during* the formation of the organozinc reagent, via radical cyclization. No attempts to measure the reaction rate constant for this second ET were considered. Decay in the reactivity of any powdered metal as the reaction advances adds inherent difficulties to the experiment.
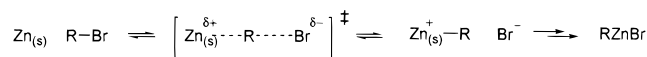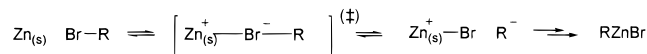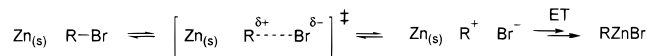
Mechanistic Considerations. Traditionally, we distinguish between one- and two-electron metal redox reagents. In practice, this distinction is only formal, merely reflecting the difficulty of stabilizing certain transient oxidation states. Zinc, with an intermediate oxidation state of low stability (Zn$^+$), is one of these reagents,[42] its two-electron processes being better regarded as two one-electron steps. For the sake of simplicity and symmetry in the following schemes, after any kind of ET, the metallic surface will be referred to as Zn$^+_{(s)}$. It does not imply the presence of an isolated monovalent zinc atom. The entire metallic cluster should be considered to be involved in the stabilization of this electron-deficient entity, until Zn^{2+} ions

neutralize the charge by leaving the surface. Comparison of the reactivity profiles in Table 3 leaves little doubt about the nature of the reaction. However, a complete survey of other mechanisms involving oxidative addition will be considered.[43]

Two-Electron Mechanisms. S_N2. This is a common oxidative addition mechanism. The order of reactivity for this S_N2-type reaction with alkyl halides is primary > secondary > tertiary, which is reversed to that actually observed.[44] Reaction with aryl and vinyl substrates would be also disallowed. The stereochemical outcome of the reaction does not sustain this reaction pathway either. Clearly, this route can be ruled out (Scheme 3).

Ate Complex. Similar to the halogen−lithium exchange, R′Br + RLi → R′Li + RBr, an *ate complex* could be either a transition state or an intermediate of the reaction. The reactivity pattern exhibited does not corroborate this mechanism. Aryl and vinyl bromides would be expected to be more reactive than alkyl bromides. The reverse order of reactivity for the alkyl bromides, would also be expected, i.e. primary > secondary > tertiary. Moreover, stereochemical studies do not show any degree of retention of the configuration at the carbon center either (Scheme 4).

S_N1. An S_N1-like transition state would consists of heterolytic cleavage of the carbon−bromide bond at the transition state of the reaction, followed by electron transfer.[45] Neither the structure−reactivity profile exhibited nor the stereochemical outcome of the reaction is in complete disagreement with this mechanism.[46] Also, radicals might originate in subsequent steps after the rate-limiting step, rendering a positive test for radical presence. However, linear free energy relationship studies with the aryl series, both for bromides and iodides, show that a *negative* charge is being developed at the transition state. Accordingly a positive slope (ρ) is observed in both cases (see below). These results clearly rule out an S_N1 in favor of ET processes (Scheme 5).

One-Electron Mechanisms. The radical clock experiments as well as the stereochemical outcome of the reaction along with the reactivity profiles observed pointed to an ET process as the operating mechanism. Linear free energy relationships were also consistent with this mechanistic pathway (see below). ET may proceed in two ways, usually referred to as *inner-sphere* and *outer-sphere electron transfer*, which can be contemplated as the two extremes of a continuous mechanism.[47] Both

(40) (a) Griller, D.; Ingold, K. U. *Acc. Chem. Res.* **1980**, *13*, 317. (b) Bowry, V. W.; Lusztyk, J.; Ingold, K. U. *J. Am. Chem. Soc.* **1991**, *113*, 5687.

(41) No cyclopentanone could be detected by GLC analysis of the hydrolyzed (2 M HCl) crude reaction mixture.

(42) Very unstable Zn(I) complexes have been produced by pulse radiolysis of solutions of Zn(II) complexes: Weddel, J. K.; Allred, A. L.; Meyerstein, D. *J. Inorg. Nucl. Chem.* **1980**, *42*, 219. (b) Buxton, G. V.; Sellers, R. M. *Coord. Chem. Rev.* **1977**, *22*, 195.

(43) Collmann, J. P.; Hegedus, L. S. *Principles and Applications of Organotransition Metal Chemistry*; University Science Books: Mill Valley, CA, 1980; Chapter 4.

(44) See, for example: Schrauzer, G. N.; Deutsch, E. *J. Am. Chem. Soc.* **1969**, *91*, 3341.

(45) Alignment of the C−X dipole to the potential field gradient near the surface might induce ionization of the bond. This mechanism, suggested in electrochemical reductions, was later discarded: ref 27a, pp 1016−1018.

(46) Bridgehead bicyclic halides, among others, would be expected to be far less reactive: ref 27a, pp 1017−1018.

(47) (a) Sastry, G. N.; Danovich, D,; Shaik, S. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1098. (b) Fawcett, W. R.; Opallo, M. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2131.

Scheme 6. Oxidative Addition via an Outer-Sphere Electron Transfer
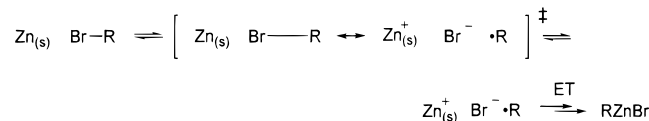
Scheme 7. Oxidative Addition via an Inner-Sphere Electron Transfer
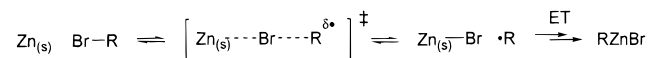
processes are dissociative in nature for alkyl halides and presumably do not involve a discrete radical anion, $RX^{\bullet-}$.[48] The situation may however be different for aryl halides. Radical anions do exist, and aryl halides probably undergo a stepwise reaction with an electron donor to give rise to $RX^{\bullet-}$.[49]

Outer-Sphere Electron Transfer. Also called *nonbonded* ET or simply ET. The term emphasize the low degree of interaction between reacting species in the transition state.[50] The inner coordination shells of the participating metal are intact in the transition state, no ligand-to-metal bond is broken or formed (Scheme 6).

Inner-Sphere Electron Transfer. Also called *bonded* or *halogen transfer*, denoting that the ET occurs within bonding distances between the reactants, through the first coordination sphere of the metal.[51] The ET occurs through a bridged ligand, which is exchanged in the transition state (Scheme 7).

Discerning between both ET mechanisms is not an easy task.[52] Even though there are theoretical models for both processes,[53] the limits of theoretical descriptions have not always been well-substantiated by experimental evidence. Also in some systems it is not clear what kind of theoretical model would be applicable.[54] Those ET reactions in which a single halide bridges the reactant centers at the moment of the electron transfer have been very difficult to treat from a theoretical point of view, owing to ambiguity about the strength of the electronic interactions that accompany the activation process. Estimation of this (often based on spectroscopic data) permits one to estimate the inner-sphere contribution of the process, but this is especially difficult in a heterogeneous system. Table 3 contains data from a vast set of ET reactions in which some structure–reactivity profiles are available. For comparative purposes, we plotted the logarithm of the relative rates of tertiary and secondary vs primary alkyl halides for all of the reactions (Figure 2).[55] The reactions are arranged in such a way that a decrease in selectivity is observed along the "*x*" axis. Among all the ET examples in Figure 2, only the three fist reactions—involving Co(II) and Cr(II) complexes—are fully identified as inner-sphere ET processes.[51] The reactions involving $Bu_3Sn^{\bullet}$ have been ascribed as inner-sphere ET reactions (halogen transfer),[56] but this assumption has not been rigorously proved.[57] Whereas the rate-determining step of the reaction of Bu_3SnH with alkyl chlorides is the halogen transfer, this is not true for alkyl bromides. Hydrogen transfer becomes the determining step of the reaction instead.[58] In a similar way, the reduction of alkyl bromides with lithium 4,4′-dimethylbenzophenone ketyl, considered as an outer-sphere ET process,[59] has by no means been strictly established.[6d,60] It is noticeable that the electrolytically generated benzophenone ketyl shows a much lower degree of selectivity for the structure of the alkyl bromide, indicating that the lithium cation plays an important role in the reaction.[60] The reaction of magnesium with alkyl chlorides, which is not a mass-transport-limited reaction, could not be assigned as either inner- or outer-sphere ET.[6d,4b] Next we find the reduction of alkyl chlorides with an U(III) complex. Originally designated as a halogen-transfer reaction,[22] it was later questioned. Since it was not possible to dismiss its outer-sphere counterpart, the process emerged as a possible *borderline* case of ET.[61] On the other side of the plot, we find the reduction of alkyl halides at an inert electrode and the reaction of alkyl bromides with radical anions, which are considered typical outer-sphere ET reactions.[62] $Na_{(g)}$ is also expected to be an outer-sphere ET reagent in its reaction with alkyl chlorides, based on ergonicity criteria.[63] As the rates of the reactions approach the diffusion-controlled limit, as they are known to for sodium atoms/RCl and Mg/RBr,[25,6b] the selectivity must become slight. Once the nature of these ET reactions has been assigned (tentatively sometimes), one can observe some general features in them. There is a general trend toward a decrease in the selectivity of the reactions, from the left, dominated by inner-sphere processes, to the right, assumed to be outer-sphere processes. There is also an area of non-well-defined processes in which one of them was referred to as *borderline* ET. The activation energy of these processes can thus be regarded as composed of two parts, the inner-sphere contribution and the outer-sphere contribution.[47]

The transfer of an electron occurs under Franck–Condon restrictions.[64] Molecular vibrations are ca. 2 orders of magnitude slower than the transfer of the electron and the position of the atoms remain frozen during the process. According to the

(48) (a) Bertran, J.; Gallardo, I.; Moreno, M.; Savéant, J.-M. *J. Am. Chem. Soc.* **1992**, *114*, 9576. (b) Savéant, J.-M. *Acc. Chem. Res.* **1993**, *26*, 455. (c) Reference 36, Chapter viii. (d) Grimshaw, J.; Langan, J. R.; Salmon, G. A. *J. Chem. Soc., Faraday Trans. 1* **1994**, *90*, 75.

(49) (a) Andrieux, C. P.; Blocman, C.; Dumas-Bouchiat, J.-M.; M'Halla, F.; Savéant, J.-M. *J. Am. Chem. Soc.* **1980**, *102*, 3806. (b) Andrieux, C. P.; Blocman, C.; Dumas-Bouchiat, J.-M.; Savéant, J.-M. *J. Am. Chem. Soc.* **1979**, *101*, 3432. (c) Reference 36, pp 122–123. (d) Pierini, A. B.; Duca, J. S. Jr. *J. Chem. Soc., Perkin Trans. 2* **1995**, 1821.

(50) Eberson, L. *New J. Chem.* **1992**, *16*, 151.

(51) Kochi, J. K. *Organometallic Mechanisms and Catalysis*; Academic Press: New York, 1978; pp 139–146, 153.
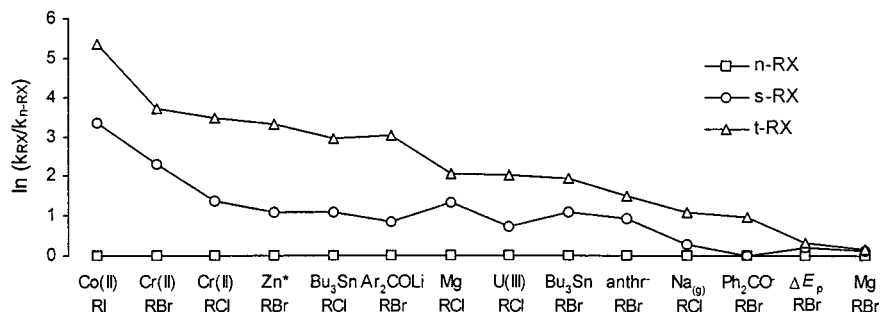
(52) (a) Cannon, R. D. *Electron Transfer Reactions*; Butterworth: London, 1980; Chapter 5.

(53) (a) Marcus, R. A. *Pure Appl. Chem.* **1997**, *69*, 13. (b) Sutin, N. *Prog. Inorg. Chem.* **1983**, *30*, 441.

(54) For example, the Marcus theory for outer-sphere ET was applied to alkyl halide reductions by inner- and outer-sphere reagents with reasonable success: Eberson, L. *Acta Chem. Scand.* **1982**, *B36*, 533.

(55) For electrochemical reduction of alkyl bromides, $\Delta E_p = E_p(RBr) - E_p(n\text{-}RBr)$.

(56) (a) Neumann, W. P. *The Organic Chemistry of Tin*; Interscience: London, New York, 1970; pp 114–115. (b) Kuivila, H. G. *Acc. Chem. Res.* **1968**, *1*, 299.

(57) (a) Polar resonant structures [... ↔ $R^{\bullet}Br^{-+}SnBu_3$ ↔ ...] were used to describe the transition state: ref 56. (b) An outer-sphere ET cannot be totally ruled out: ref 6d.

(58) The measure of the disappearance of a pair of halides in a competitive process, however, yields the ratio of rate constants of halogen abstraction by $Bu_3Sn^{\bullet}$: (a) Carlsson, D. J.; Ingold, K. U. *J. Am. Chem. Soc.* **1968**, *90*, 7047. (b) Reference 6d. This is true provided that the halogen transfer, $Bu_3Sn^{\bullet} + RBr \rightarrow Bu_3SnBr + R^{\bullet}$, is an irreversible step. An equilibrium seems reasonable for this step. Indeed, ΔH is only slightly exothermic in these halogen transfers: Nash, G. A.; Skinner, H. A.; Stack, W. F. *Trans. Faraday Soc.* **1965**, *61*, 640, 2122. This would explain why this reaction is abnormally positioned toward the right in Figure 2.

(59) (a) Garst, J. F.; Smith, C. D. *J. Am. Chem. Soc.* **1976**, *98*, 1520. (b) Holy, N. L. *Chem. Rev.* **1974**, *74*, 243.

(60) Lund, H.; Daasbjerg, K.; Lund, T.; Occhiliani, D.; Pedersen, S. U. *Acta Chem. Scand.* **1997**, *51*, 135. Reaction of RBr with $Ar_2CO^-Li^+$ might involve inner-sphere transfer through bridging halogen and metal ion: [$Ar_2CO\cdots Li\cdots BrR$]. This was suggested in ref 6d and is now reinforced with the previous observation.

(61) Eberson, L. *Acta Chem. Scand.* **1982**, *B36*, 533.

(62) (a) Andrieux, C. P.; Gallardo, I.; Savéant, J.-M. *J. Am. Chem. Soc.* **1989**, *111*, 1620. (b) Reference 26.

(63) Reference 37, Chapter vii.

(64) Reynolds, W. L.; Lumry, R. W. *Mechanisms of Electron Transfer*; Ronald Press: New York, 1966.

Figure 2. Structure−reactivity profiles for the reactions of a set of ET reagents with primary, secondary, and tertiary alkyl halides. Inner-sphere processes dominate the left side of the plot, whereas outer-sphere processes are dominant in the right.

Scheme 8. Oxidative Addition via a Radical-Anion Intermediate
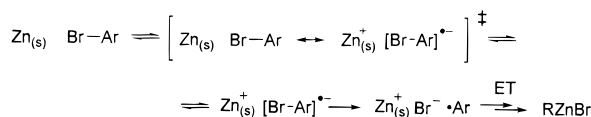
definition of outer-sphere ET, the interaction between donor and acceptor is weak in the transition state.[50] Electronic interactions <1 kcal mol^{-1} define this ET, yet the inner-sphere ET must be assumed to possess a respectable donor/acceptor interaction, >5 kcal mol^{-1}. Stronger interactions with the donor in the transition state, i.e. inner-sphere ET, should be accompanied with a higher degree of rehybridization (or C−X weakening) at the carbon center. It consequently may accommodate better the incipient radical which is being formed. It is at this stage that structure−reactivity relationships are displayed, following the normal order of thermodynamical stability of carbon-centered radicals. As we saw before, there are several cases of well-established inner-sphere ET. They all show pronounced dependence of the reactivity to the structure of the organic halide (or *selectivity*). However, in the case of outer-sphere ET, despite the fact that they follow the same general trend, none was found to show a high degree of selectivity. The presented results so far suggest, but do not prove, an important contribution of an inner-sphere ET in the oxidative addition of active zinc to alkyl bromides.[65] It is not clear that structure−reactivity studies may resolve this problem without the aid of supporting evidence.[66] The most straightforward proof of inner-sphere mechanism comes from the analysis of products.[51] In these processes, the halogen atom must remain bonded to the metal ion after the ET takes place. Presently, this can only be demonstrated when the metal ion is inert toward ligand substitution, which Zn^{2+} is not.[67]

Linear Free Energy Relationships (LFERs). The use of LFERs for mechanistic assignment is a fundamental tool of

physical organic chemistry and can be applied to the characterization of ET mechanisms as well. As previously mentioned, the ET to aryl halides may not be of a dissociative nature, in contrast to that of alkyl halides. A radical anion, ArX$^{•-}$, is generated, which subsequently evolves to products (Scheme 8). The study of the electronic demand of the reaction Zn* + ArX can provide important clues about the structure of the transition state, linking it to an ET process or any other conceivable mechanism. A series of substituted aryl bromides, as well as aryl iodides—which are very convenient precursors of arylzinc halides when mild reaction conditions are needed—were submitted to competitive kinetic analysis in a similar way as described for alkyl bromides. Tables 4 and 5 summarize the observed ratio of rate constants (k_1/k_2) for all the substrates assayed. The most important fact derived from this set of data is that a notable grade of selectivity is again observed for the substrates examined, bearing in mind that a heterogeneous ET is, most likely, the key step of the reaction. Rates range from $k_1/k_2 = 700$ for 4-bromobenzonitrile/4-bromo-*N,N*-dimethylaniline in refluxing THF and go up to >*1000* when 4-bromobenzonitrile is measured at 0 °C (the reaction of 4-bromo-*N,N*-dimethylaniline is too slow to be conveniently monitored at 0 °C) (Table 4). In the case of aryl iodides, this range is smaller, $k_1/k_2 = 300$ for 4-iodobenzonitrile/4-iodo-*N,N*-dimethylaniline in THF at 0 °C, but still significant (Table 5). Comparison with other related processes leaves little doubt about the singularity of the reaction and its possible synthetic applications. Magnesium (and consequently lithium) shows little or no selectivity in its reaction with substituted aryl bromides and iodides.[6c] The rates summarized in Tables 4 and 5 were correlated with substituent effects using Hammett σ parameters.[68] Hammett plots for the reactions of Zn* with aryl bromides (THF, 70 °C), aryl iodides (THF, 0 °C), Mg with aryl bromides (Et$_2$O, THF, 0 °C), and aryl iodides (Et$_2$O, 0 °C)[69] are represented in Figure 3. The wide range of reactivity exhibited and σ values covered, as well as the good fitting of the lines for the Zn* reactions, permit an estimation a priori of the difference in reaction rates of two potentially reactive centers, by simply reading the plot. A hypothetical molecule bearing several aryl bromides in different electronic environments could thus be selectively metalated.
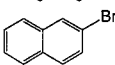
On the other hand, reaction constants for these plots, ρ, can be compared to a number of other reactions, heterogeneous or not, for which ρ values are available. For comparison, reaction constants, ρ, for these and other reactions involving *halogen transfer* (ArBr + Bu$_3$Sn$^•$,[6c] ArI + Ph$^•$),[70] heterogeneous ET to aryl halides (polarographic reduction of ArCl, Br, and I at mercury electrode in DMF),[71] homogeneous ET (Ni(0) com-

(65) "The formations of Grignard reagents and organolithium compounds are examples of the reduction of alkyl halides directly by metals.... It is not clear whether *inner-* or *outer-sphere* processes are involved since the reactions occurring on a metal surface offer only a limited number of probes": Kochi, J. K. *Free Radicals*; John Wiley & Sons: New York, 1973; 663.

(66) The rate−structure profiles for the reaction of Mg with alkyl chlorides, Bu$_3$SnH with alkyl chlorides, Ar$_2$CO$^-$Li$^+$ with alkyl bromides, and $E_{1/2}$ (C, alkyl chlorides) are all linearly correlated: ref 6d. It was also pointed that in better defined inorganic ET reactions, inner- and outer-sphere processes may exhibit linearly correlated rate−structure profiles. Linearly correlated reactions can have different selectivities however, the slope of the log k_{rel} plot for both reactions being a measure of the relative selectivity.

(67) (a) Prince, R. H. In *Comprehensive Coordination Chemistry*; Wilkinson, G., Ed.; Pergamon Press: Oxford-New York, 1987; Vol. 5, pp 983−985. (b) For a conductrimetric study of the equilibrium ZnCl$_2$ + Cl$^-$ ⇌ ZnCl$_3^-$ in THF: Folest, J.-C.; Troupel, M.; Perichon, J. *Bull. Soc. Chim.* **1980**, *I*-181.

(68) σ values; (a) Hine, J. *Physical Organic Chemistry*; McGraw-Hill: New York, 1962. (b) Isaacs, N. S. *Physical Organic Chemistry*; Longman Scientific & Technical: Harlow Essex, England, 1987.

(69) Calculated from kinetic data in ref 6c.

(70) Dannen, W. C.; Saunders: D. G. *J. Am. Chem. Soc.* **1969**, *91*, 5924.

Table 4. Relative Rates of Reaction of Aryl Bromides (k_1/k_2)[a]

	R_1Br	k_1/k_2	R_2Br	Temp. (°C)	σ[b]	k_1/k_{PhBr}[c]
1.	4-CN	7.8, 7.0	n-C$_8$H$_{17}$Br, 4-EtO$_2$CC$_6$H$_4$Br	0°, 70°	0.70	*160, 105*[d]
2.	4-COMe	37	PhBr	70°	0.48	37
3.	4-CO$_2$Et	15	PhBr	70°	0.45	15
4.	3-CO$_2$Et	8.3	PhBr	70°	0.35	8.3
5.	3-OMe	2.2	PhBr	70°	0.11	2.2
6.	H	*1*	PhBr	-	0	*1*
7.	4-Me	0.59	PhBr	70°	-0.17	0.59
8.	4-OMe	0.39	PhBr	70°	-0.28	0.39
9.	4-NMe$_2$	0.15	PhBr	70°	-0.63	0.15
10.	(1-bromonaphthalene)	5.0	PhBr	70°		5.0
11.	(2-bromonaphthalene)	1.6	PhBr	70°		1.6

[a] Corresponding to the reaction of two organic bromides (R$_1$Br, R$_2$Br) with Zn*. All reactions were carried out in THF at the given temperature. Relative rates were determined by the competitive kinetics technique. [b] Substituent constants from ref 68. [c] k_1/k_2 values for nondirectly measured pairs in italics. [d] The difference reflects the difference in experiment temperature.

Table 5. Relative Rates of Reaction of Aryl Iodides (k_1/k_2)[a]

	R_1I	k_1/k_2	R_2I[b]	σ[c]	k_1/k_{PhI}[d]
1.	4-CN	4.4	4-EtO$_2$CC$_6$H$_4$I	0.70	*18.5*
2.	4-CO$_2$Et	4.2	PhI	0.45	4.2
3.	3-CO$_2$Et	3.1	PhI	0.35	3.1
4.	3-OMe	1.2	PhI	0.11	1.2
5.	H	*1*	PhI	0	*1*
6.	4-Me	0.41	PhI	-0.17	0.41
7.	4-OMe	0.25, 5.2	PhI, n-C$_8$H$_{17}$Br[b]	-0.28	0.25
8.	4-NMe$_2$	0.25	4-MeOC$_6$H$_4$I	-0.63	*0.062*

[a] Corresponding to the reaction of two aryl iodides (R$_1$I, R$_2$I) with Zn* in THF at 0 °C. Relative rates were determined by the competitive kinetics technique. [b] 4-Bromoanisole was also measured vs n-bromooctane to link with the bromides series. [c] Substituent constants from ref 68. [d] k_1/k_2 values for nondirectly measured pairs in italics.

plexes + ArCl, −Br, and −I)[72] and nucleophilic substitutions (ArCl + MeO$^-$)[73] are included in Table 6. Unfortunately, linear free energy relationships between log k and log K (the Hammett plots being one of these cases) cannot be taken as evidence for common outer-sphere or inner-sphere mechanisms for a series of related reactions. These plots may be linear for *atom-transfer* reactions as well as for ET reactions.[74] Indeed, the reaction of Mg with ArBr in ether (Table 6, entry 5) correlates equally well with rates of bromine abstraction by Bu$_3$Sn$^•$[75] and polarographic reduction potentials.[76] The reaction of Ni(PEt$_3$)$_4$ with aryl halides (Table 6, entries 12−14) was interpreted as outer-sphere ET and is linearly correlated with $E_{1/2}$, as well as with σ.[77] σ correlates itself well with the reaction ArBr + Bu$_3$Sn$^•$.[6c] It is not surprising that the reaction of Zn* with aryl bromides also shows reasonable correlations vs $E_{1/2}$(ArBr) and Bu$_3$Sn$^•$ + ArBr (0.92 of correlation coefficients in both cases). These facts can be taken only as a reinforcement of the hypothesis of an ET process as the rate-determining step of the reaction, but do not

provide further evidence about its nature in a deeper level. However, comparison of the slopes for (supposedly) homogeneous *halogen-transfer* processes (ρ = 1.4, 0.57, Table 6, entries 7−8) and (supposedly) homogeneous outer-sphere ET processes (ρ = 4.4, 2.2; Table 6, entries 13−14) denotes a higher degree of charge separation in the transition state for the latter ones, in good agreement with the mechanism. The electronic demand of our reaction suggests the participation of an intermediate of the type ArX$^{•-}$, much like those proposed for the analogous reaction with other reducing agents (Scheme 8).[48a,49] Differences in selectivity can thus be explained in terms of an *early* ET transition state for Mg vs a *late* ET transition state for Zn*, the latter having an increased ionic character and therefore displaying the observed reactivity. The proposed mechanism is equally valid for substituted ArBr and ArI, with [ArI]$^{•-}$ having the shortest lifetime, since both series of halides are also correlated (0.96 of linear regression coefficient, eight different substituents), indicating only minor differences in their mechanistic pathways.

Other possibilities for the transition state, like carbanions, [Ar$^-$]‡ or concerted insertion of Zn in the C−Br bond [C−Zn−Br]‡, seem unlikely. The moderate ρ value does not indicate the development of a carbanion or a carbon−zinc bond in the transition state. In such a case, the carbon would bear a large negative charge and larger value for ρ would be expected.[78]

To conclude with all of these mechanistic considerations, we have to point out that the experimental evidence collected, both for alkyl and aryl systems, goes against the possibility of multiple mechanisms.[79] Radicals have been detected on primary carbons. No sign of inversion (or retention) was detected in the

(71) Sease, J. W.; Burton, F. G.; Nickol, S. L. *J. Am. Chem. Soc.* **1968**, *90*, 2595.

(72) Tsou, T. T.; Kochi, J. K. *J. Am. Chem. Soc.* **1979**, *101*, 6319.

(73) Exner, O. *Correlation Analysis of Chemical Data*; Plenum Press: New York, 1988; 72−73.

(74) Chipperfield, J. R. In *Advances in Linear Free Energy Relationships*; Chapman, N. B., Shorter, J., Eds.; Plenum Press: London-New York, 1972; p 340.

(75) Studies of tin hydride reductions of bridgehead aliphatic halides have been interpretated as indicating little or no charge separation in the transition state: Fort, R. C., Jr.; Hiti, J. *J. Org. Chem.* **1977**, *42*, 3968. However, positive slope of the Hammett plot, ρ = 1.4 points toward some participation of ET with partial negative charge generation at the transition state.

(76) Electrochemical reductions have been referred to as "compulsory ET processes" and for inert smooth Pt and some C electrodes is assumed to be outer-sphere ET. For a dropping Hg electrode, which is the case considered here, the situation has been discussed: ref 37, p 79.

(77) With some restrictions, see Table 6, footnote g.

(78) Compare with ArH + NH$_3^-$/NH$_{3 (l)}$ ⇌ [Ar$^-$] → ... (ρ ∼ 6): Shatenshtein, A. I. *Adv. Phys. Org. Chem.* **1963**, *1*, 155, and reaction in Table 6, entry 15.
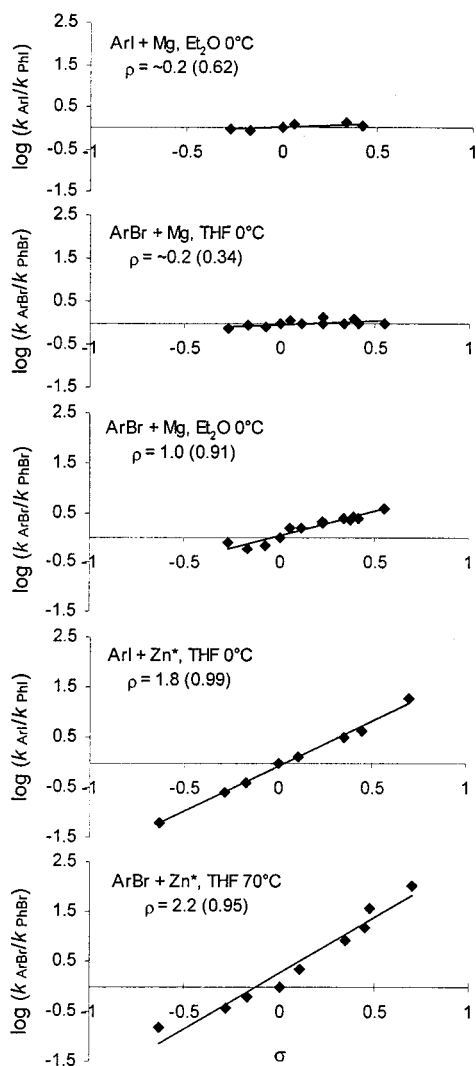
Figure 3. Hammett plots for the reactions ArI/Mg (Et$_2$O), ArBr/Mg (THF, Et$_2$O), ArI/Zn* (THF), and ArBr/Zn* (THF). Reaction constants, ρ; regression coefficients are in parentheses.

Table 6. Hammett Constants (ρ) for Some ET Reactions (1−14) and One S$_N$ (15) Involving Aryl Halides

	reaction[a]	solvent (T, °C)	ρ
1	ArBr + Zn*	THF (70)	2.2
2	ArI + Zn*	THF (0)	1.8
3	ArCl + Mg	Et$_2$O (23)	($\sim$2)[b,c]
4	ArBr + Mg	THF (0)	($\sim$0.2)[b,d]
5	ArBr + Mg	Et$_2$O (0)	1.0[e]
6	ArI + Mg	Et$_2$O (0)	($\sim$0.2)[b,d]
7	ArBr + Bu$_3$Sn$\cdot$	Et$_2$O (0)	1.4
8	ArI + Ph$\cdot$	CCl$_4$ (60)	0.57
9	ArCl + e$^-$	DMF (25)	0.8[f]
10	ArBr + e$^-$	DMF (25)	0.57[f]
11	ArI + e$^-$	DMF (25)	0.35[f]
12	ArCl + Ni(PEt$_3$)$_4$	THF (25)	5.4[g]
13	ArBr + Ni(PEt$_3$)$_4$	THF (25)	4.4[g]
14	ArI + Ni(PEt$_3$)$_4$	THF (25)	2.0[g]
15	ArCl + NaOMe	MeOH (50)	8.47[h]

[a] See text for details and references. [b] Nonlinear Hammett plots. [c] Insufficient number of points and σ range covered. [d] Mass transport limited. [e] Obtained after data process of ref 6c. No statistical correction in dihalides was applied. [f] Slopes of the plots $E_{1/2}$ vs σ. [g] Only Me, Ph, H, and Cl substituents are included. *p*-MeO and *p*-MeOCO give deviations. [h] σ^-.

Scheme 9
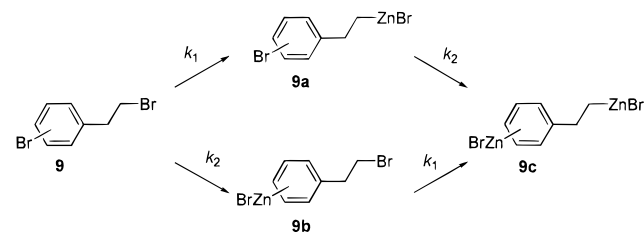
monobrominated monoorganozinc bromides in good yields from the corresponding starting materials **8**−**13**. These intermediates showed remarkable stability (Table 7, entry 9, footnote l) and could be conveniently reacted either after transmetalation or directly (Table 7, entries 1, 3, 4, 6−8, 11 and 2, 5, 9, 10, respectively) with a variety of electrophiles (CH$_2$=CClCH$_2$Cl, D$_2$O, ^{t}BuO$_2$CN=NCO$_2$Bu^t, PhCOCl, 2-cyclohexenone, AcOH).

The reaction products derived from the metalation of the *less* reactive bromide in the molecule were not analyzed, their concentration being expected to be very low. The more advantageous cases to detect minor reaction products correspond to those with the less favorable ratio of rate constants. Table 7, entry 2 is one of these cases. Let us consider this case in detail (Scheme 9). The estimated ratio of constants for this reacting system is $k_{n-\text{alkyl}}/k_{p-\text{tolyl}} = 45.8$. If we assume a statistical distribution of products, i.e. k_1/k_2 remains constant for all of the reacting species including intermediates, the rate laws that define this system (eqs 5−7) permit an evaluation of the composition of the crude reaction. Numerical integration yields the concentration of each species, **9**−**9c**, which are represented in Figure 4 vs the amount of active zinc reacted.[82]

$$\frac{d[\mathbf{9a}]}{d[\mathbf{9}]} = \frac{[\mathbf{9a}] - x[\mathbf{9}]}{(x+1)[\mathbf{9}]} \tag{5}$$

$$\frac{d[\mathbf{9b}]}{d[\mathbf{9}]} = \frac{x[\mathbf{9b}] - [\mathbf{9}]}{(x+1)[\mathbf{9}]} \tag{6}$$

$$\frac{d[\mathbf{9c}]}{d[\mathbf{9}]} = \frac{[\mathbf{9a}] + x[\mathbf{9b}]}{-(x+1)[\mathbf{9}]}, \quad \text{where } x = k_1/k_2 \tag{7}$$

The experimental results, however, show better conduct of the reaction than that merely predicted by mathematical argu-

(79) Depending on the nature of the substrate, e.g. S$_N$2 for primary bromides and ET for hindered systems: Zhou, D.-L.; Walder, P.; Scheffold, R.; Walder, L. *Helv. Chim. Acta* **1992**, *75*, 995.

(80) Truce, W. E.; Lindy, L. B. *J. Org. Chem.* **1961**, *26*, 1463. It was also prepared by reduction of γ-phenylbutyrolactone with LiAlH$_4$ and bromination using the procedure described for **12** (68%).

(81) Grinberg, S.; Shaubi, E. *Tetrahedron* **1991**, *47*, 2895. The crude reaction mixture was distilled under vacuum, and an intermediate fraction (61% *p*-isomer/39% *o*-isomer) was used in the reaction with active zinc.

(82) The steady-state approximation, applied to eq 4, gave, without the aid of a computer, a reasonable estimate of the distribution of products. Nonetheless, to compare with experimental results, exact numbers were preferred.

Table 7. Synthetic Applications

Entry	Starting material[b]	N° (%)[c]	Reaction Conditions[a]		Product[f]	N° (%)[g]
			Zn*[d]	Electrophile[e] (Catalyst)[e]		
1.	[PhCH(Br)CH₂CH₂Br]	**8** (68)	1.1 0°C 10 min	(10% CuCN·2LiBr) CH₂=CClCH₂Cl	[product structure]	**14** (64)
2.	[BrC₆H₄CH₂CH₂Br]	**9**[h] (80)	1+1 rt, 3+2h	D₂O	[product structure, –D]	**15**[h,i] (96)
3.	**9**	9	"	(5% CuCN·2LiBr) CH₂=CClCH₂Cl	[product structure]	**16**[h] (65)
4.	[CH₂=C(Br)(CH₂)₄CH₂Br]	**10** (90)	3 rt, 3 h	(10% CuCN·2LiBr) CH₂=CClCH₂Cl	[product structure]	**17** (96)
5.	**10**	10	"	^{t}BuO₂CN=NCO₂Bu^{t}	[product structure, NHCO₂^{t}Bu / N–CO₂^{t}Bu]	**18** (91)
6.	[BrC₆H₄CH₂Br]	**11**[j] (-)	1.0 0°C,1h	(5% CuCN·2LiBr) CH₂=CClCH₂Cl	[product structure]	**19** (96)
7.	**11**	11	1.2 0°C, 1h	(CuCN·2LiBr) PhCOCl	[product structure, Ph / O]	**20** (89)
8.	[structure with Br]	**12** (92)	1.1 rt, 10h	(Li[(2-Th)CuCN]) 2-cyclohexenone 2eq. TMSCl	[cyclohexanone product]	**21** (65)
9.	**12**	12	1.1 rt, 12h	AcOH[k]	[product structure]	**22** (81)[l]
10.	**12**	12	1.1 rt, 10h	^{t}BuO₂CN=NCO₂Bu^{t}	^{t}BuO₂CN–NHCO₂^{t}Bu [product]	**23** (65)
11.	[long chain structure with Br Br]	**13** (95)	"	(Li[(2-Th)CuCN]) 2-cyclohexenone 2eq. TMSCl	[cyclohexanone product]	**24** (63)

^{a} All the reactions were carried out in THF. ^{b} See experimental for procedures. ^{c} Overall yield for the synthesis of the starting material. ^{d} Equivalents of Zn*; several additions and/or excess were used to minimize reaction times. Reaction time and temperature. ^{e} 1.0 equiv unless otherwise noted. ^{f} All products were pure (≥95%) and fully characterized by spectroscopical means (IR, ^{1}H and ^{13}C NMR, HRMS). ^{g} Based on the dibrominated starting materials **8**−**13**. ^{h} 61/39 *p-/o*-mixture of regioisomers (^{1}H NMR, GLC). ^{i} >98% D incorporation (^{1}H NMR). ^{j} Commercially available. ^{k} Distilled under Ar. ^{l} The organozinc intermediate did not decompose extensively after 12 h at room temperature.
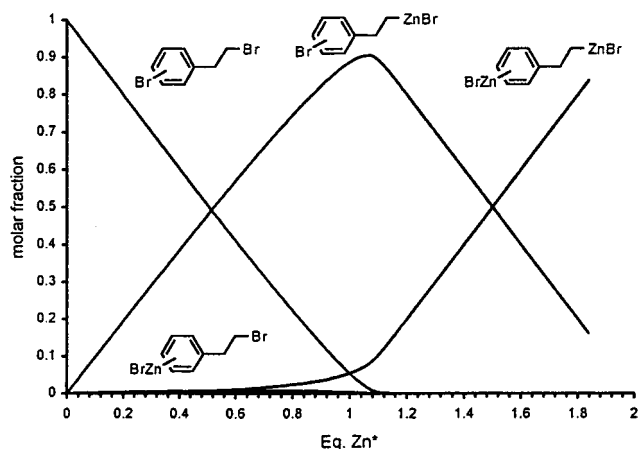
Figure 4. Calculated distribution of products for the reaction of **9** with Zn* as a function of the equivalents of zinc reacted (Scheme 9). Some selected values (Zn*, **9**, **9a**, **9b**, **9c**) are (a) 1 equiv of Zn* (1.0000, 0.0550, *0.8864*, 0.0036, 0.0550), (b) absolute (and relative) maximum for **9a** (1.0545, 0.0198, 0.9042, 0.0018, 0.0742), (c) absolute maximum for **9b** (0.6459, 0.3671, 0.6119, 0.0080, 0.0130); the yield of **9b** was always ≤0.80%.

ments. This reaction can be easily monitored by GLC, and it was allowed to react until ca. 1.0 equiv of zinc was consumed. The yield of the monometalated product **9a** was found to be 96%, after deuteriolysis. The expected yield according to Figure 4 would be 88.64%. The origin of this apparent contradiction

has to be found in the initial hypothesis of constancy of k_1/k_2. In other words, the experimental evidence provided suggest that *deactivation mechanisms* are operative after the first oxidative addition, preventing, to some extent, the monometalated intermediates from proceeding any further. Under these circumstances, the ratio of products (**9a/9b**) will tend to equal the ratio of rate constants, $k_1/k_2 = 45.8$, which corresponds to yields of ca. 97.86% of **9a** and 2.14% of **9b**. Indeed, GLC analysis after hydrolysis showed only traces of the expected second major product according to Figure 4 (ethylbenzene), which was not quantified. 2-Bromoethylbenzene (from hydrolysis of **9b**) was not detected.[83]

A rough classification of the organic bromides, attending to their reactivities resulted in three main groups: (a) benzyl/allyl bromides, (b) alkyl bromides, and (c) aryl and vinyl bromides. Benzylic and allylic bromides can be selectively reacted with Zn* in the presence of alkyl bromides. One example of this kind is presented in Table 7, entry 1. An estimate for this process is $k_{benzyl}/k_{n-alkyl} > 380$, provided that the reaction centers act independently. Presumably, this can be also extended to secondary alkyl bromides ($k_{benzyl}/k_{s-alkyl} > 120$) and other bromides (Table 1). In a similar way, alkyl bromides can be selectively reacted in the presence of aryl bromides (provided that no electron-withdrawing groups are present on the aromatic

(83) The reported difference between experimental and calculated yields cannot be attributed exclusively to small differences between the assigned k_1/k_2 (*45.8*) and the actual for **9**, which exact value is unknown. A $k_1/k_2 \geq$ 135 would be required to yield 96% of **9a**.
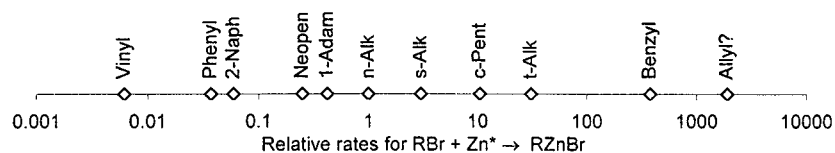
Figure 5.

ring), as well as vinyl bromides. As examples, compounds **9** and **10** were synthesized (Table 7, entries 2 and 4). $k_{n-\text{alkyl}}/k_{p-\text{tolyl}} = 45.8$ and $k_{n-\text{alkyl}}/k_{\text{vinyl}} = 160$ are the expected selectivities to be observed. Compounds **19** and **20** were prepared after selective reaction of the benzylic bromide in **11**. The selectivity expected is $k_{\text{benzyl}}/k_{p-\text{tolyl}} > 17\,000$.

Selective reactions are also possible inside the same group. Wide ranges of reactivity have already been mentioned for substituted aryl bromides and iodides. In the alkyl series, selective insertion of Zn* in a tertiary bromide, leaving intact a primary one was achieved in compounds **12** and **13** with good yields (Table 7, entries 8–11). As we saw, the estimated selectivity for these processes is $k_{t-\text{alkyl}}/k_{n-\text{alkyl}} = 31.8$.

Finally, the overall spectrum of reactivity for the reaction of active zinc with organic bromides cover a range of $k_1/k_2 \sim 7 \times 10^5$, with allylic and benzylic bromides in one extreme and vinyl and aryl bromides (carrying electron-donating groups) in the other (Figure 5). Since preparation of the corresponding organozinc bromides can be accomplished for most substrates in good yields, including deactivated aryl bromides and vinyl bro-mides,[11a,29] sequential cycles of metalation–reaction with electrophile are theoretically feasible in multibrominated starting materials.

Conclusions

In conclusion, we have established that our highly reactive zinc exhibits unusual structure-dependent reactivity that can be used to elaborate complex molecules containing more than one bromine atom. The kinetic and LFER studies suggest a mechanism in which ET is the rate-determining step of the reaction. Experiments carried out with radical clocks as well as the stereochemical outcome of the reaction support the presence of radicals. The reactivity profiles suggest that the ET has an important component of inner-sphere process in the reaction with alkyl bromides. In the case of aryl halides, Hammett plots are consistent with the participation of aryl halides radical anions as intermediates of the reaction. In addition, the use of the schemes described herein constitutes a new contribution to the current strategies in organic synthesis. Active zinc emerges out of this as a singular metal whose selectivity in these processes markedly distinguishes itself from other synthetically relevant metals.

Experimental Section

Preparation of Starting Materials 8–13. Compounds **8**[80] and **9**[81] were prepared following reported procedures. **11** was commercially available.

2,7-Dibromo-1-heptene (10). Active zinc (2.35 g, 36 mmol)[11a] in 23.5 mL of tetrahydrofuran was injected into a 100 mL flask containing dry tetrahydrofuran (20 mL) and 1-bromo-4-chlorobutane (5.15 g, 30 mmol) at room temperature under an Ar atmosphere. After overnight reaction, the excess of zinc was allowed to settle. The clear solution was then cannulated to a separate flask and cooled at −30 °C under an Ar atmosphere, containing a solution of CuCN·2LiBr in tetrahydrofuran (10%, 3 mmol in 3 mL). The mixture was stirred for 5 min at this temperature, and 2,3-dibromopropene (6.00 g, 30 mmol) was injected. Stirring was continued for 1 h, and the reaction was allowed to warm

to 0 °C, quenched with 2 M hydrochloric acid, extracted (hexanes), dried (MgSO₄), and concentrated. The crude product was transferred to a 500 mL flask provided with a Friedrich condenser, containing 1-methyl-2-pyrrolidinone (150 mL), ethyl bromide (45 mL, 15 equiv), and NaBr (620 mg, 0.2 equiv). The reaction was refluxed at 50 °C for 24 h. After the mixture was cooled, hexanes were added (200 mL), the upper phase was washed with water (3 × 150 mL) and dried (MgSO₄), solvents and excess of reagents were removed (15 Torr), and the crude product was distilled to afford 90% of **10**: bp 70−1 °C (0.5 Torr); IR (cm⁻¹) 2940, 2860, 1630, 1458, 1429, 1224, 887, 641; ¹H NMR (300 MHz) 1.40−1.53 (m, 2H, C*H*₂CH₂CH₂Br), 1.53−1.66 (m, 2H, C═CBrCH₂C*H*₂), 1.89 (quintet, $J = 7.1$ Hz, 2H, CH₂C*H*₂CH₂Br), 2.44 (t, $J = 7.1$ Hz, 2H, C═CBrCH₂), 3.42 (t, $J = 7.1$ Hz, 2H, CH₂Br), 5.41 (d, $J = 1.2$ Hz, 1H, H*H*C═C), 5.58 (d, $J = 1.2$ Hz, 1H, *H*HC═C); ¹³C NMR (75 MHz) 27.55, 27.65, 33.1, 34.25, 41.8, 117.35, 134.9; HRMS calcd for C₇H₁₂Br (M − Br)⁺ 175.0122, found 175.0119.

1,6-Dibromo-6-methylheptane (12). Methylmagnesium bromide (20 mL, 3 M) in diethyl ether was added via cannula to a 250 mL round-bottom flask containing diethyl ether (150 mL) under argon. Caprolactone (2.30 g, 20 mmol) in diethyl ether (10 mL) was slowly injected into the ether solution with stirring (ca.15 min) at room temperature. The reaction was allowed to stir for 15 additional min. Then it was quenched with water and carefully neutralized with 2 M hydrochloric acid. The organic layer was removed, and the aqueous phase was extracted with ethyl acetate (2 × 100 mL), evaporated to dryness (70 °C overnight), and extracted with acetone (2 × 100 mL). This second extraction over the solid inorganic salts afforded ca. 20% of the overall weight. The combined organic layers were dried over magnesium sulfate, and the solvents were removed (15 Torr). The oil obtained was poured in a addition funnel and was dropped slowly (ca. 1 h) into a 500 mL three-necked flask heated at 100 °C and was vigorously stirred while a stream of hydrogen bromide was passed into the flask. After the addition was completed the reaction was allowed to stir for an additional 30 min. The crude mixture was diluted with pentane (100 mL), shaken with concentrated sulfuric acid (50 mL), washed with 0.2 M phosphate buffer (100 mL), and dried over magnesium sulfate. Removal of pentane afforded 1,6-dibromo-6-methylheptane (92%), which did not required any further purification for most applications. A sample was distilled under vacuum for analytical purposes. **12**: bp 85−86 °C (1 Torr); IR (cm⁻¹) 2963, 2937, 2863, 1465, 1454, 1369, 1240, 1101, 730, 648; ¹H NMR (300 MHz) 1.40−1.60 (m, 4H, C*H*₂CH₂-CH₂CH₂Br), 1.75 (s, 6H, (CH₃)₂CBr), 1.72−1.82 (m, 2H, (CH₃)₂-CBrC*H*₂), 1.84−1.95 (m, 2H, CH₂C*H*₂CH₂Br), 3.42 (t, $J = 6.8$ Hz, 2H, CH₂Br); ¹³C NMR (75 MHz) 25.4, 28.0, 32.5, 33.7, 34.15, 34.25, 47.2, 68.05; HRMS calcd for C₈H₁₅Br⁸¹Br (M − H)⁺ 270.9520, found 270.9518. Anal. Calcd for C₈H₁₆Br₂: C, 35.32; H, 5.93. Found: C, 35.5; H, 6.2.

1,15-Dibromo-15-methylhexadecane (13). The same procedure described for **12**, using ω-pentadecalactone afforded pure **13** (95%): mp 13−4 °C (neat); IR (cm⁻¹) 2905, 2860, 1467, 1369, 722, 646; ¹H NMR (300 MHz) 1.20−1.35 (m, 18H, CH₂(C*H*₂)₉CH₂CH₂CH₂Br), 1.35−1.55 (m, 4H, C*H*₂(CH₂)₉C*H*₂CH₂CH₂Br), 1.75 (s, 6H, (CH₃)₂-CBr), 1.75−1.85 (m, 2H, (CH₃)₂CBrC*H*₂), 1.80−1.92 (m, 2H, C*H*₂-CH₂Br), 3.40 (t, $J = 6.9$ Hz, 2H, CH₂Br); ¹³C NMR (75 MHz) 26.25, 28.15, 28.75, 29.4, 29.5, 29.55 (6C), 32.8, 33.95, 34.2, 34.2, 47.55, 68.65. Anal. Calcd for C₁₇H₃₄Br₂: C, 51.27; H, 8.60. Found: C, 51.5; H, 8.9.

Preparation of Products 14−24. 7-Bromo-2-chloro-4-phenyl-1-heptene (14). Active zinc (1.5 mL, 2.2 mmol)[11a] as a tetrahydrofuran suspension ($c = 10$ g/100 mL) was added via disposable syringe under argon atmosphere to a 50 mL centrifuge tube containing 1,4-dibromo-1-phenylbutane (**8**, 584.1 mg, 2.0 mmol) in anhydrous tetrahydrofuran (10 mL) at 0 °C and equipped with stirring bar and septum. The reaction

was stirred at 0 °C for 10 min (Table 7, reaction conditions). The organozinc reagent was centrifuged (2500 rpm, 2 min), and the content of the tube was cannulated to a two-necked 100 mL flask containing copper(I) cyanide (17.9 mg, 0.2 mmol) and lithium bromide (17.4 mg, 0.4 mmol) in anhydrous tetrahydrofuran (10 mL) at −30 °C. 2,3-Dichloropropene (222 mg, 2.0 mmol) was added immediately to the flask. After 3 h, temperature was allowed to rise to room temperature and stirring was maintained for an additional 3 h. After this, hexanes (50 mL) were added, the mixture was hydrolyzed (1 M hydrobromic acid) and extracted (hexanes, 2 × 50 mL), the organic phases were dried over magnesium sulfate, and the solvents were removed (15 Torr, 30 °C). **14** (64%) was purified from the crude reaction mixture by Kugelrohr distillation: IR (cm^{-1}) 1635, 1453, 910, 884, 761, 735, 701, 647; ^{1}H NMR (300 MHz) 1.61−2.00 (m, 4H, CH_2CH_2CH$_2$Br), 2.56−2.70 (m, 2H, C=CClCH$_2$), 2.94−3.10 (m, 1H, PhCH), 3.36 (app t, J = 6.4 Hz, 2H, CH$_2$Br), 4.99 (app d, J = 1.0 Hz, 1H, HHC=C), 5.10 (app d, J = 1.0 Hz, 1H, HHC=C), 7.14−7.38 (m, 5H, ArH); ^{13}C NMR (75 MHz) 30.55, 33.65, 33.65, 42.5, 46.65, 114.0, 126.55 (2C), 127.45, 128.45 (2C), 140.5, 143.1; HRMS calcd for C$_{13}$H$_{16}$BrCl 286.0124, found 286.0128.

4- and 2-Bromo-(2-deuterioethyl)benzene (15). Active zinc (1.3 mL, 2.0 mmol)[11a] as a tetrahydrofuran suspension (c = 10 g/100 mL) was added via disposable syringe under argon atmosphere to a 50 mL centrifuge tube charged with a 61/39 mixture 4- and 2-bromo-(2-bromoethyl)benzene (**9**, 527.9 mg, 2.0 mmol) in anhydrous tetrahydrofuran (10 mL) equipped with stirring bar and septum at room temperature. The reaction was stirred at room temperature for 3 h and another 1 equiv of active zinc was added in the same way, stirring for 2 h more (Table 7, reaction conditions). Deuterium oxide (48.1 mg, 2.4 mmol) in anhydrous tetrahydrofuran (1 mL) was then added. After 1 h, hexanes (50 mL) were added and the mixture was hydrolyzed (2 M hydrochloric acid) and extracted (hexanes, 2 × 50 mL). The organic phases were dried over magnesium sulfate and the solvents removed (15 Torr, 30 °C). The crude product was a 61/39 mixture of 4-Br/2-Br isomers (^{1}H NMR and GLC). **15** (96%) was purified from the crude reaction mixture by Kugelrohr distillation for analytical purposes: IR (cm^{-1}) 2964, 2936, 1487, 1470, 1073, 1021, 1011, 814, 751, 656; ^{1}H NMR (300 MHz), 4-Br (mayor) isomer: 1.15−1.32 (m, 2H, CH$_2$D), 2.61 (app t, J = 7.3 Hz, 2H, ArCH$_2$), 7.09 (app d, J = 8.2 Hz, 2H, ArH$_o$), 7.42 (app d, J = 8.2 Hz, 2H, ArH$_m$). 2-Br (minor) isomer: 1.15−1.32 (m, 2H, CH$_2$D), 2.78 (app t, J = 7.4 Hz, 2H, ArCH$_2$), 7.02−7.11 (m, 1H, 4-ArH), 7.22−7.29 (2m, 2 × 1H, 5- and 6-ArH), 7.55 (app d, J = 7.9 Hz, 1H, 3-ArH); ^{13}C NMR (75 MHz) of 4-Br (mayor) isomer 15.85 (t, J_{CD}= 19.2 Hz), 28.95, 119.95, 130.35 (2C), 132.0 (2C), 143.8; ^{13}C NMR (75 MHz) of 2-Br (minor) isomer 14.65 (t, J_{CD}= 19.8 Hz), 30.0, 125.0, 128.05, 128.2, 130.2, 133.35, 143.95; HRMS calcd for C$_8$H$_8$BrD 184.9949, found 184.9943. Anal. Calcd for C$_8$H$_8$BrD (corrected for D incorporation): C, 51.64; H + D, 4.89. Found: C, 51.6; H + D, 4.9.

4- and 2-Bromo-(4-chloro-4-penten-1-yl)benzene (16). Compound **9** was reacted with active zinc using the same procedure as described for **15**. Then, following the procedure described for **14**, the organozinc intermediate was coupled with 2,3-dichloropropene to afford **16** (65%) as a 61/39 mixture of 4-Br/2-Br isomers: IR (cm^{-1}) 2955, 1634, 1489, 1470, 1073, 1011, 882, 751, 696; ^{1}H NMR (300 MHz) of 4-Br (mayor) isomer 1.83−1.98 (m, 2H, CH$_2$CH_2CH$_2$), 2.37 (app t, J = 7.3 Hz, 2H, C=CClCH$_2$), 2.60 (app t, J = 7.8 Hz, 2H, ArCH$_2$), 5.15 (app s, 1H, HHC=C), 5.22 (app s, 1H, HHC=C), 7.08 (app d, J = 8.4 Hz, 2H, ArH$_o$), 7.42 (app d, J = 8.4 Hz, 2H, ArH$_m$); ^{1}H NMR (300 MHz) of 2-Br (minor) isomer 1.83−1.98 (m, 2H, CH$_2$CH_2CH$_2$), 2.44 (app t, J = 7.4 Hz, 2H, C=CClCH$_2$), 2.77 (app t, J = 7.8 Hz, 2H, ArCH$_2$), 5.20 (app s, 2 × 1H, H$_2$C=C), 7.05−7.15 (m, 1H, 4-ArH), 7.20−7.30 (2m, 2 × 1H, 5- and 6-ArH), 7.55 (app d, J = 7.9 Hz, 1H, 3-ArH); ^{13}C NMR (75 MHz) of 4-Br (major) isomer 28.5, 33.9, 38.35, 112.45, 119.6, 130.15 (2C), 131.4 (2C), 140.5, 142.35; ^{13}C NMR (75 MHz) of 2-Br (minor) isomer: 27.25, 34.95, 38.6, 112.35, 124.4, 127.4, 127.65, 130.3, 132.8, 141.0, 142.3; HRMS calcd for C$_{11}$H$_{12}$BrCl 257.9811, found 257.9802. Anal. Calcd for C$_{11}$H$_{12}$BrCl: C, 50.90; H, 4.66. Found: C, 50.9; H, 4.7.

2-Bromo-9-chloro-1,9-decadiene (17). By adapting the procedure described for **14** to the reaction conditions described in Table 7, **10**

was reacted with active zinc (3.0 mmol) at room temperature (3 h) and the organozinc intermediate was coupled with 2,3-dichloropropene to afford **17** (96%): IR (cm^{-1}) 2898, 2849, 1629, 1428, 1175, 879, 639, 616; ^{1}H NMR (300 MHz) 1.26−1.40 (m, 4H, CH$_2$CH$_2$CH_2CH$_2$CH$_2$CH$_2$), 1.50−1.63 (m, 4H, CH$_2$CH_2 CH$_2$CH$_2$CH_2CH$_2$), 2.33 (t, J = 7.4 Hz, 2H, C=CClCH$_2$), 2.41 (t, J = 7.4 Hz, 2H, C=CBrCH$_2$), 5.11 (app t, J = 1.0 Hz, 1H, cis-HHC=CCl), 5.13 (app s, 1H, trans-HHC=CCl), 5.38 (app d, J = 1.2 Hz, 1H, cis-HHC=CBr), 5.55 (app d, J = 1.2 Hz, 1H, trans-HHC=CBr); ^{13}C NMR (75 MHz) 26.95, 27.7, 28.0, 28.1, 39.0, 41.25, 111.85, 116.3, 134.7, 142.95; HRMS calcd for C$_{10}$H$_{16}$Br (M − Cl)$^+$ 215.0435, found 215.0430. Anal. Calcd for C$_{10}$H$_{16}$BrCl: C, 47.74; H, 6.41. Found: C, 47.7; H, 6.6.

Di-*tert*-butyl (6-Bromo-6-hepten-1-yl)hydrazine-*N,N′*-dicarboxylate (18). Compound **10** was reacted with active zinc using the same procedure as described for **17**. The resulting organozinc was centrifuged (2500 rpm, 2 min), and the content of the tube was cannulated under argon atmosphere to a 50 mL flask at 0 °C. Di-*tert*-butyl azodicarboxylate (460.6 mg, 2.0 mmol) in dry tetrahydrofuran (4 mL) was added to the flask at 0 °C, leaving the mixture to react for 10 min. The reaction was hydrolyzed (0.2 M phosphate buffer, 10 mL), extracted (ethyl acetate, 3 × 30 mL), and dried (magnesium sulfate), the solvents were removed (15 Torr, 30 °C), and the crude reaction mixture was purified by flash chromatography (Florisil, hexanes/ethyl acetate) to afford **18** (91%): IR (cm^{-1}) 3312, 2971, 2925, 1712, 1630, 1394, 1369, 1254, 1157, 885, 856, 781, 759; ^{1}H NMR (300 MHz) 1.20−1.35 (m, 2H, CH_2CH$_2$CH$_2$N), 1.43 (s, 9H, (CH$_3$)$_3$C, 9H), 1.44 (s, (CH$_3$)$_3$C, 9H), 1.48−1.62 (2m, 2 × 2H, CH_2CH$_2$CH_2CH$_2$N) 2.39 (t, J = 7.3 Hz, 2H, C=CBrCH$_2$), 3.40 (br t, J = 6.2 Hz, 2H, CH$_2$N), 5.35 (app s, 1H, cis-HHC=CBr), 5.52 (app s, 1H, trans-HHC=CBr), 6.17, 6.35 (2 br s, 1H, NH); ^{13}C NMR (75 MHz) 25.4, 27.15 (br), 27.5, 28.15 (br, 6C), 42.2, 49.2 (br), 81.0 (br, 2C), 116.4, 134.5, 155.35 (br, 2C); HRMS calcd for C$_{17}$H$_{31}$N$_2$O$_4$BrLi (M + Li)$^+$ 413.1628, found 413.1627.

4-Bromo-(3-chloro-3-buten-1-yl)benzene (19). By adapting the procedure described for **14** to the reaction conditions described in Table 7, **11** was reacted with active zinc (1.0 mmol) at 0 °C (1 h) and the organozinc intermediate was coupled with 2,3-dichloropropene to afford **19** (96%): IR (cm^{-1}) 1634, 1489, 1072, 1011, 884, 813, 619; ^{1}H NMR (300 MHz) 2.60 (app t, J = 7.5 Hz, 2H, C=CClCH$_2$), 2.85 (app t, J = 7.5 Hz, 2H, ArCH$_2$), 5.05 (app d, J = 1.0 Hz, 1H, HHC=C), 5.15 (app d, J = 1.0 Hz, 1H, HHC=C), 7.07 (app d, J = 8.2 Hz, 2H, ArH$_o$), 7.41 (app d, J = 8.2 Hz, 2H, ArH$_m$); ^{13}C NMR (75 MHz) 32.95, 40.75, 113.05, 119.95, 130.2 (2C), 131.45 (2C), 139.35, 141.4; HRMS calcd for C$_{10}$H$_{10}$BrCl 243.9654, found 243.9654. Anal. Calcd for C$_{10}$H$_{10}$BrCl: C, 48.91; H, 4.10. Found: C, 48.9; H, 4.2.

4-Bromobenzyl Phenyl Ketone (20).[84] Compound **11** was reacted with active zinc using the same procedure as described for **19**. The organozinc reagent was then centrifuged (2500 rpm, 2 min), and the content of the tube was cannulated to a two-necked 100 mL flask containing copper(I) cyanide (179 mg, 2 mmol) and lithium bromide (174 mg, 4 mmol) in anhydrous tetrahydrofuran (10 mL) at −30 °C. The mixture was stirred for 15 min, allowing the temperature to rise to 0 °C. Then it was cooled back to −30 °C and benzoyl chloride (281.14 mg, 2.0 mmol) was added. After 3 h, the temperature was allowed to rise to room temperature. The reaction mixture was hydrolyzed (aqueous NaHCO$_3$) and extracted (ethyl acetate, 2 × 50 mL and benzene, 2 × 50), the organic phases was dried over magnesium sulfate, and the solvents were removed (15 Torr, 30 °C). **20** (89%) was purified from the crude reaction mixture by recrystallization: mp 148−148.5 °C (hexanes/ethyl acetate); ^{1}H NMR (300 MHz) 4.25 (s, 2H, COCH$_2$), 7.14 (app d, J = 8.6 Hz, 2H, 4-BrArH$_o$), 7.46 (app d, J = 8.6 Hz, 2H, 4-BrArH$_m$), 7.45−7.52 (m, 2H, PhH$_m$), 7.54−7.63 (m, 1H, PhH$_p$), 7.98−8.05 (m, 2H, PhH$_o$); ^{13}C NMR (75 MHz) 44.7, 120.9, 128.5 (2C), 128.7 (2C), 131.25 (2C), 131.7 (2C), 133.35, 133.4, 136.35, 196.95.

3-(6-Bromo-1,1-dimethylhexyl)cyclohexanone (21). Active zinc (2.9 mL, 2.2 mmol) as a tetrahydrofuran suspension (c = 5 g/100 mL)[11a] was added via disposable syringe under argon atmosphere to a 50 mL centrifuge tube charged with anhydrous tetrahydrofuran (10 mL) and equipped with stirring bar and septum. A solution of 1,6-dibromo-6-

(84) Kim, S.-H.; Rieke, R. D. *J. Org. Chem.* **1998**, *63*, 6766.

methylheptane (**12**, 544.1 mg, 2.0 mmol) in tetrahydrofuran (0.5 mL) was added in the same way. The reaction was stirred at room temperature for ca. 10 h. Meanwhile 2-thienyllithium (2 mL, 1.0 M in tetrahydrofuran) was added to a two-necked 100 mL flask containing anhydrous tetrahydrofuran (10 mL) and copper(I) cyanide (179.1 mg, 2.0 mmol) at −30 °C which was then stirred for 30 min. The organozinc reagent was centrifuged (2500 rpm, 2 min), and the content of the tube was cannulated to the Li(2-Th)CuCN containing flask at −30 °C. A solution of 2-cyclohexenone (202.40 mg, 2.0 mmol) and chlorotrimethylsilane (438.9 mg, 4.0 mmol) (distilled and kept over Mg turnings) in dry tetrahydrofuran (1 mL) was immediately added to the flask. The temperature was allowed to rise to room temperature, and stirring was maintained for 1 day. An additional 0.5 equiv of the electrophilic mixture (1 mmol of 2-cyclohexenone + 2 mmol of chlorotrimethylsilane) was then added, allowing the reaction to stir for 2 days more. After this, the mixture was hydrolyzed with 2 M hydrochloric acid and extracted with diethyl ether (2 × 100 mL), the organic phases were dried over magnesium sulfate, and the solvents were removed (15 Torr, 30 °C). Impure 3-(6-bromo-1,1-dimethylhexyl)cyclohexanone was isolated from the crude reaction mixture by column chromatography (Florisil, hexanes/ethyl acetate). Byproducts were removed by shaking a hexane solution of the impure compound (50 mL) with a methanolic solution of mercurium(II) acetate (ca. 0.25 M, 25 mL) for 5 min. No degradation of the desired compound was detected under these purification conditions by ^{1}H NMR. Addition of water (50 mL) and extraction with ether (2 × 100 mL) afforded, after drying (magnesium sulfate) and elimination of solvents, pure **21** (65%): IR (cm^{-1}) 2959, 2937, 1711, 645; ^{1}H NMR (300 MHz) 1.15−1.45 (m, 6H, (CH$_2$)$_2$C-(C*H*$_2$)$_3$), 1.25−1.65 (3m, 3 × 1H, 2 × *c*-CH*H* and *c*-CH), 1.79−1.91 (m, 2H, C*H*$_2$CH$_2$Br), 1.81−1.92 (m, 1H, *c*-CH*H*), 2.07 (app t, *J* = 13.4 Hz, CHC*H*HCO), 2.06−2.16 (m, 1H, *c*-CH*H*), 2.16−2.30 (m, 1H, C*H*HCO), 2.31−2.42 (2m, 2 × 1H, 2 × CH*H*CO), 3.40 (t, *J* = 6.8 Hz, 2H, CH$_2$Br); ^{13}C NMR (75 MHz) 23.45, 25.0, 25.15, 26.35, 26.4, 29.75, 33.45, 34.6, 35.65, 40.8, 42.05, 43.95, 47.75, 213.65; HRMS calcd for C$_{13}$H$_{22}$BrO (M − CH$_3$)$^+$ 273.0854, found 273.0842.

1-Bromo-6-methylheptane (22).[85] Compound **12** was reacted with active zinc using the same procedure as described for **21**. Dibenzyl (182.3 mg, 1.0 mmol, internal GLC and ^{1}H NMR standard) was also added along with the reagents. After the reaction finished, acetic acid (2 mL, deoxygenated by reaction with 50 mg of Mg powder and distilled under argon) was injected and the crude reaction was extracted (pentane/water, 10/10 mL) and quantitatively analyzed by GLC (81%) and 500 MHz ^{1}H NMR (**22**, 80%) using dibenzyl as a internal standard.

(85) Bestmann, H. J.; Vostrowsky, O.; Stransky, W. *Chem. Ber.* **1976**, *109*, 3375.

A sample was purified by distillation (lit.[85] bp 74−77 °C, 17 Torr): bp 71−74 °C (15 Torr); ^{1}H NMR (500 MHz) 0.90 (d, *J* = 6.4 Hz, 6H, 2 × CH$_3$), 1.17−1.23 (m, 2H, CHC*H*$_2$), 1.29−1.37 (m, 2H, CHCH$_2$C*H*$_2$), 1.40−1.47 (m, 2H, C*H*$_2$CH$_2$CH$_2$Br), 1.50−1.62 (m, 1H, CH), 1.88 (app quintet, *J* = 6.9 Hz, 2H, C*H*$_2$CH$_2$Br), 3.43 (t, *J* = 6.9 Hz, 2H, CH$_2$Br).

Di-*tert*-butyl (6-Bromo-1,1-dimethylhexyl)hydrazine-*N,N′*-dicarboxylate (23). Compound **12** was reacted with active zinc using the same procedure as described for **21**. Then, following the procedure described for **18**, the organozinc intermediate was reacted with di-*tert*-butyl azodicarboxylate to afford **23** (65%): IR (cm^{-1}) 3338, 3271, 3161, 2975, 2930, 1711, 1390, 1365, 1340, 1251, 1158, 763, 734, 647; ^{1}H NMR (500 MHz) 1.15−1.60 (m, 4H, NCH$_2$C*H*$_2$CH$_2$), 1.24 (br s, 3H, C*H*$_3$CNCH$_3$), 1.40 (br s, 3H, CH$_3$CNC*H*$_3$), 1.44 (s, 9H, (CH$_3$)$_3$CO), 1.46 (s, 9H, (CH$_3$)$_3$CO), 1.60−1.68 (m, 1H, NCC*H*H), 1.85 (app quintet, *J* = 7.3 Hz, 2H, C*H*$_2$CH$_2$Br), 1.88−1.96 (m, 1H, NCCH*H*), 3.37 (t, *J* = 6.9 Hz, 2H, CH$_2$Br), 5.80−6.30 (br s, 1H, NH); ^{13}C NMR (75 MHz) 23.5, 26.3, 26.9, 28.15, 28.25, 28.35, 32.6, 33.75, 39.9, 61.85, 80.5, 80.6, 154.65, 156.0; HRMS calcd for C$_{18}$H$_{35}$BrN$_2$O$_4$Li (M + Li)$^+$ 429.1940, found 429.1941.

3-(15-Bromo-1,1-dimethylpentadecyl)cyclohexanone (24). The same procedure described for **21**, using **13** as a starting material afforded, directly after column chromatography, pure **24** (63%): IR (cm^{-1}) 2923, 2850, 1711, 1468, 722, 645; ^{1}H NMR (300 MHz) 1.12−1.45 (m, 24H, (CH$_3$)$_2$C(C*H*$_2$)$_{12}$), 1.30−1.65 (3m, 3 × 1H, 2 × *c*-C*H*H and *c*-CH), 1.79−1.91 (m, 2H, C*H*$_2$CH$_2$Br), 1.81−1.93 (m, 1H, *c*-CH*H*), 2.06 (app t, *J* = 13.4 Hz, CHC*H*HCO), 2.05−2.16 (m, 1H, *c*-CH*H*), 2.16−2.30 (m, 1H, C*H*HCO), 2.31−2.43 (2m, 2 × 1H, 2 × CH*H*CO), 3.40 (t, *J* = 6.9 Hz, 2H, CH$_2$Br); ^{13}C NMR (75 MHz) 23.5, 24.35, 24.5, 25.7, 25.75, 28.15, 28.75, 29.4, 29.5, 29.6 (4C), 29.65, 30.6, 32.8, 34.05, 34.95, 40.35, 41.4, 43.25, 47.05, 213.2; HRMS calcd for C$_{23}$H$_{44}$BrO (M + H)$^+$ 415.2576, found 415.2540.

Supporting Information Available: General information, kinetic methods, procedures, and spectra for the studies on the stereochemical course of the reaction and detection of radicals and IR, ^{1}H NMR, and ^{13}C NMR for all new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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