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Effect of Solvent on the Lithium−Bromine Exchange of Aryl Bromides: Reactions of *n*-Butyllithium and *tert*-Butyllithium with 1-Bromo-4-*tert*-butylbenzene at 0 °C

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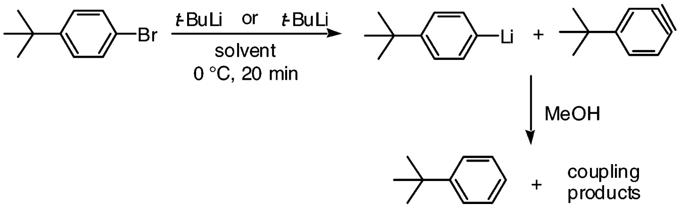

The outcome of reactions of 1-bromo-4-*tert*-butylbenzene (**1**), a representative aryl bromide, with *n*-BuLi or *t*-BuLi at 0 °C in a variety of solvent systems has been investigated. The products of reactions of **1** with *n*-BuLi vary significantly with changes in solvent composition: **1** does not react with *n*-BuLi in pure heptane; the exchange reaction to give (4-*tert*-butylphenyl)lithium, which is slow in pure diethyl ether, is virtually quantitative in heptane containing a small quantity of THF; and the reaction of **1** with *n*-BuLi in THF leads to considerable coupling. Lithium−bromine exchange is the virtually exclusive outcome of reactions of **1** with *t*-BuLi in every solvent studied except pure heptane: the presence of a small quantity of any of a variety of structurally diverse ethers (Et_2O, THF, THP, MTBE) in the predominantly hydrocarbon medium affords (4-*tert*-butylphenyl)lithium, assayed as *tert*-butylbenzene, in yields exceeding 97%. The only side products observed from reactions of **1** with *t*-BuLi are small amounts of benzyne-derived hydrocarbons.

Introduction

We recently reported the results of a study of the reactions of 1-iodooctane, a representative primary alkyl iodide, with *tert*-butyllithium (*t*-BuLi) at 0 °C in a variety of solvent systems composed of heptane and various ethers.[1] An optimal ether−heptane ratio, which varied for each of the ethers studied, was found to maximize the extent of lithium−iodine exchange and minimize side reactions such as coupling and elimination. Prompted by the results of this study, we have extended the investigation to assess the effect of solvent on the outcome of the reactions of 1-bromo-4-*tert*-butylbenzene (**1**), a representative aryl bromide, with *n*-butyllithium (*n*-BuLi) and *t*-BuLi at 0 °C. As detailed below, lithium−bromine exchange to give (4-*tert*-butylphenyl)lithium may be accomplished in virtually quantitative yield at 0 °C by appropriate choice of both solvent and alkyllithium.

Results and Discussion

The reversible metathesis reaction known as the lithium−halogen exchange was first observed in reactions of *n*-BuLi with aryl bromides,[2] and the vast primary literature, detailing both the synthetic utility and mechanistic vagaries of this reaction, has been comprehensively reviewed.[3] The lithium−halogen exchange of an aryl bromide or iodide with an alkyllithium is typically a high-yield process that proceeds rapidly at low temperature and favors the more stable aryllithium at equilibrium.[4] However, nettlesome side reactions, including coupling of the aryllithium with the co-generated alkyl halide and formation of a benzyne intermediate via *ortho*-metalation of the

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[1] Bailey, W. F.; Brubaker, J. D.; Jordan, K. P. *J. Organomet. Chem.* **2003**, *681*, 210.

[2] (a) Wittig, G.; Pockels, U.; Droge, H. *Chem. Ber.* **1938**, *71*, 1903. (b) Gilman, H.; Langham, W.; Jacoby, A. L. *J. Am. Chem. Soc.* **1939**, *61*, 106. (c) It is of some historical interest to note that the lithium−bromine exchange was observed by Marvel and co-workers at least a decade before these reports: treatment of *m*-bromotoluene with *n*-BuLi at room temperature for 4 d in petroleum ether gave an 87% yield of toluene after quench with water, but the implications of this observation were not recognized at the time. See: Marvel, C. S.; Hager, F. D.; Coffman, D. D. *J. Am. Chem. Soc.* **1927**, *49*, 2323.

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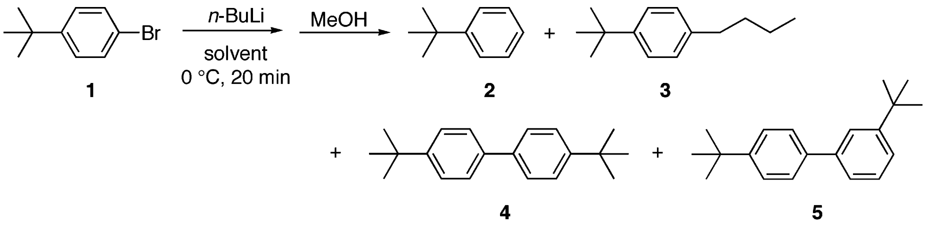
SCHEME 1



aryl halide,[5] are sometimes observed.[3] In an effort to probe the effect of solvent variation on the course of reactions of aryl bromides with *n*-BuLi and *t*-BuLi, 1-bromo-4-*tert*-butylbenzene (**1**) was chosen as a representative substrate: in addition to the practical matter of decreasing the volatility of potential reaction products, the 4-*t*-Bu group serves as a positional marker. We were particularly interested in exploring whether, by appropriate choice of experimental conditions, aryllithiums might be prepared efficiently at 0 °C, a temperature significantly higher than that commonly employed for the exchange reaction.

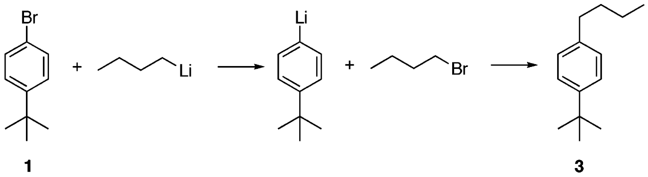
Reactions with *n*-BuLi. Experiments were conducted at 0 °C in solvent systems composed of heptane, diethyl ether, THF, and heptane−THF in various proportions. As detailed in the Experimental Section, solutions of **1** in the appropriate solvent were added at 0 °C over a period of 10 min under an atmosphere of argon to a slight excess (i.e., 1.2 molar equiv) of *n*-BuLi in hexane, and the resulting 0.1 M reaction mixtures were allowed to stand at 0 °C for an additional 20 min before quench with methanol. Crude product mixtures were analyzed by both capillary GC and by GC−MS affording baseline separation of the four products (**2**−**5**), illustrated in Scheme 1, that accounted for essentially the total material balance.[6] The *tert*-butylbenzene (**2**), 1-butyl-4-*tert*-butylbenzene (**3**), and 4,4′-di-*tert*-butylbiphenyl (**4**) products were identified by comparison of their retention times and mass spectra to those of authentic samples; 3,4′-di-*tert*-butylbiphenyl (**5**) was identified on the basis of its reported retention time and mass spectrum.[7] The results of these experiments are summarized in Table 1.

The results presented in Table 1 are likely related to the degree of association of *n*-BuLi in the various solvents that were examined. It is known that *n*-BuLi exists as a hexameric aggregate in hydrocarbons,[8] a tetrameric aggregate in diethyl ether,[9] and as a temperature-dependent equilibrium of dimeric and tetrameric aggregates in THF.[10] It is clear from the results that the hexameric aggregate of *n*-BuLi does not react with the aryl bromide: 99% of **1** is recovered unchanged after treatment with *n*-BuLi in pure heptane (Table 1, entry 1). The lithium−bromine exchange is rather slow in diethyl ether: the yield of (4-*tert*-butylphenyl)lithium, assayed as *tert*-butylbenzene (**2**), is only 80%, and a significant quantity of **1** is recovered (Table 1, entry 2). In THF solution, all of the bromide is consumed, and the products consist primarily of the aryllithium, assayed as **2**, and the coupling product, **3**, as well as small amounts of **4** and **5** (Table 1, entry 5). The formation of **3** is undoubtedly the result, as illustrated below, of lithium−bromine exchange of **1** with *n*-BuLi to give (4-*tert*-butylphenyl)lithium followed by coupling of the aryllithium with the co-generated 1-bromobutane. The ability of THF, in which phenyllithium exists as a dimeric aggregate,[11] to promote coupling of aryllithiums with alkyl halides was noted some time ago by Merrill and Negishi.[12]

TABLE 1. Reaction of 1-Bromo-4-*tert*-butylbenzene (1) with *n*-BuLi at 0 °C in Various Solvents (Scheme 1)

		products,[a] %				
entry	solvent	2	3	4	5	recovered 1
1	heptane	0.2	tr	tr	tr	98.8
2	Et_2O	80.1	0.3	tr	tr	18.6
3	heptane−THF (99:1 by vol)	96.9	0.8	0.2	0.2	tr
4	heptane−THF (9:1 by vol)	96.1	2.5	tr	tr	tr
5	THF	58.8	39.9	0.2	0.3	tr

[a] Yields were determined by capillary GC; tr indicates that a trace (viz. <0.2%) of material was detected.



Given the outcome of reactions conducted in pure heptane (Table 1, entry 1) and pure THF (Table 1, entry 5), it was somewhat unexpected that addition of a small quantity of THF (1% by vol) to a predominantly heptane reaction medium gave a high yield of **2** (∼97%) accompanied by less than 1% each of the three side products (Table 1, entry 3). Not surprisingly, addition of a larger quantity of THF to the heptane medium

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(4) Applequist, D. E.; O'Brien, D. F. *J. Am. Chem. Soc.* **1963**, *85*, 743.

(5) Hoffmann, R. W. *Dehydrobenzene and Cycloalkynes*; Academic Press: New York, 1967.

(6) No attempt was made to quantitate the amounts, if any, of butane, 1-butene, 1-bromobutane, or octane that may have been produced from extraneous reactions of *n*-BuLi.

(7) Fields, E. K. *J. Org. Chem.* **1978**, *25*, 4705.

(8) Brown, T. L. *Acc. Chem. Res.* **1968**, *1*, 23.

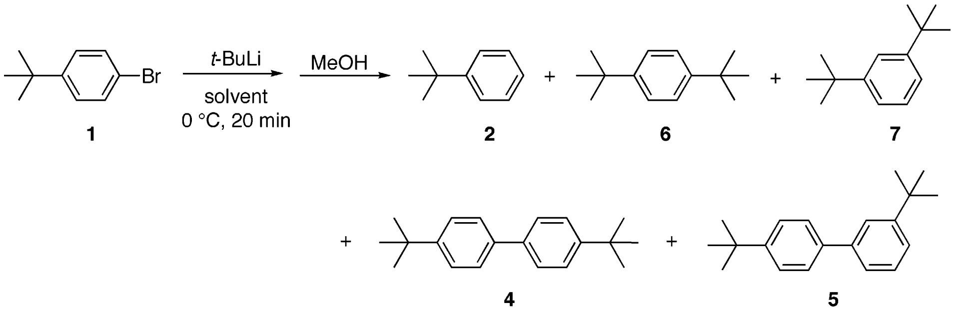
(9) West, P.; Waack, R. *J. Am. Chem. Soc.* **1967**, *89*, 4395.

(10) (a) McGarrity, J. F.; Ogle, C. A. *J. Am. Chem. Soc.* **1985**, *107*, 1805. (b) Bauer, W.; Winchester, W. R.; Schleyer, P. v. R. *Organometallics* **1987**, *6*, 2371.

(11) Reich, H. J.; Green, D. P.; Medina, M. A.; Goldenberg, W. S.; Gudmundsson, B. O.; Dykstra, R. R.; Phillips, N. H. *J. Am. Chem. Soc.* **1998**, *120*, 7201 and references therein.

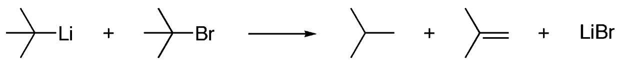
(12) Merrill, R. E.; Negishi, E. *J. Org. Chem.* **1974**, *39*, 3452.

SCHEME 2



(viz. 10% by vol) leads to an increase in the extent of coupling of the aryllithium with 1-bromobutane to give **3** (Table 1, entry 4).

Reactions with *t*-BuLi. Experiments involving *t*-BuLi were run at 0 °C in solvent systems composed of heptane−dialkyl ethers in various proportions. The reactions were conducted as described above for the case of *n*-BuLi with one significant difference: 2.2 equiv of *t*-BuLi in heptane were used per mol of **1**. As illustrated below, the second equivalent of *t*-BuLi consumes the *t*-BuBr generated in the exchange to give isobutane, isobutylene, and LiBr.[13]



GC and GC−MS analysis of product mixtures afforded baseline separation of the five products (**2**, **4**, **5**, **6**, and **7**), illustrated in Scheme 2, that accounted for the total material balance. The 1,4-di-*tert*-butylbenzene (**6**) and 1,3-di-*tert*-butylbenzene (**7**) products were identified by comparison of their retention times and mass spectra to those of authentic samples.[14] The results of these experiments are summarized in Table 2.

The most striking feature of the results presented in Table 2 is their monotony: the yield of the aryllithium, assayed as **2**, is virtually quantitative (>97% yield) in every solvent system examined except for pure heptane. The failure to observe any significant exchange in pure heptane (Table 2, entry 1), a solvent in which *t*-BuLi is known to exist as a tetrameric aggregate,[8,15] was not unexpected.[13a] However, the acute sensitivity of the exchange reaction to the presence of very small quantities (1% by vol) of any of a variety of structurally diverse ethers (Et_2O, THF, tetrahydropyran (THP), or MTBE) was unanticipated. It is clear from the results summarized in Table 2 that addition of any of the ethers studied, in any proportion from 1% to 10% by volume,[16] to the predominantly hydrocarbon medium provides a reactive *t*-BuLi solvate. Given that *t*-BuLi exists as a dimeric aggregate in Et_2O[17] and primarily as a solvated monomer in THF,[18] the outcome of the exchange reaction between **1** and *t*-BuLi is apparently indifferent to the aggregation state of ether-solvated *t*-BuLi. As a practical matter, to the extent that **1** is representative of its class, the lithium−bromine exchange between *t*-BuLi and an aryl bromide may be conducted at 0 °C in a predominantly hydrocarbon solvent containing a small quantity of virtually any ether.

TABLE 2. Reaction of 1-Bromo-4-*tert*-butylbenzene (1) with *t*-BuLi at 0 °C in Heptane−Ether Solvent (Scheme 2)

		products,[a] %					
entry	solvent	**2**	**6**	**7**	**4**	**5**	recovered **1**
1	heptane	5.4			tr	tr	93.3
2	heptane−Et_2O (99:1 by vol)	97.7	0.2	tr	0.8	0.5	
3	heptane−Et_2O (19:1 by vol))	97.2	0.2	tr	0.6	0.4	
4	heptane−Et_2O (9:1 by vol)	97.6	0.2	0.2	0.5	0.4	
5	heptane−THF (99:1 by vol)	98.7			0.3	0.4	
6	heptane−THF (19:1 by vol)	98.4			0.3	0.4	
7	heptane−THF (9:1 by vol	96.9			0.3	0.4	
8	heptane−THP (99:1 by vol)	97.8	tr	0.2	0.5	0.4	
9	heptane−THP (19:1 by vol)	97.3	0.2	0.2	0.5	0.7	0.2
10	heptane−THP (9:1 by vol)	97.9	0.2	tr	0.4	0.6	
11	heptane−MTBE (99:1 by vol)	97.0	0.2	tr	0.8	0.5	
12	heptane−MTBE (19:1 by vol)	97.1	0.2	0.2	0.5	0.3	
13	heptane−MTBE (9:1 by vol)	97.9	tr	0.2	0.4	0.3	

[a] Yields were determined by capillary GC; tr indicates that a trace (viz. <0.2%) of material was detected.

The robust nature of the aryl bromide exchange with *t*-BuLi at 0 °C stands in contrast to the more complex behavior of primary alkyl iodides when treated with *t*-BuLi under these conditions. As noted above, the reaction of a primary iodide with *t*-BuLi at 0 °C in hydrocarbon−ether solution affords a mixture of exchange, coupling, and elimination products whose composition varies with changes in both the quantity and nature of the ether cosolvent.[1] The only side products detected in the reactions of **1** with *t*-BuLi are small quantities (i.e., <1%) of **4**, **5**, **6**, and **7** (Scheme 2, Table 2). As illustrated in Scheme 3, the formation of these hydrocarbons is undoubtedly the result of *ortho*-lithiation[19] of **1** followed by rapid loss of LiBr to give a 4-*tert*-butylbenzyne intermediate[5] that then adds either *t*-BuLi, to afford **6** and **7**, or (4-*tert*-butylphenyl)lithium to give **4** and **5**.

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[14] Okada, T.; Karaki, I.; Mataga, N. *J. Am. Chem. Soc.* **1982**, *104*, 7191.

[15] Thomas, R. D.; Clarke, M. T.; Jensen, R. M.; Young, T. C. *Organometallics* **1985**, *5*, 1851.

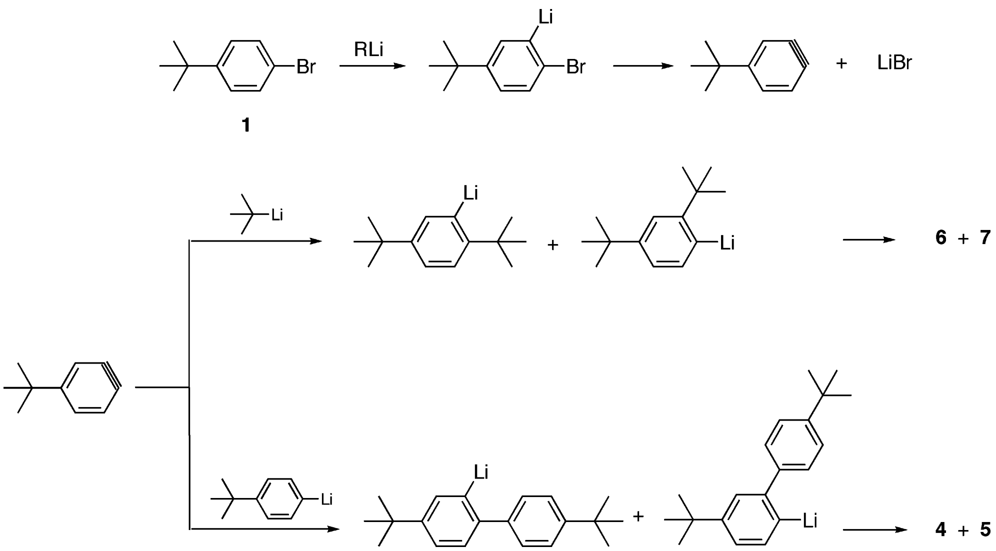
[16] In light of the fairly rapid consumption of *t*-BuLi by proton abstraction from various ethers at 0 °C, the exchange reaction between **1** and *t*-BuLi in solvent containing more than 10% by volume of an ether was not investigated. The half-life of *t*-BuLi in various solvents has been reported; see: Stanetty, P.; Mihovilovic, M. *J. Org. Chem.* **1997**, *62*, 1514.

[17] Bates, T. F.; Clarke, M. T.; Thomas, R. D. *J. Am. Chem. Soc.* **1988**, *110*, 5109.

[18] Bauer, W.; Winchester, W. R.; Schleyer, P.v. R. *Organometallics* **1987**, *6*, 2371.

[19] Snieckus, V. *Chem Rev.* **1990**, *90*, 879 and references therein.

SCHEME 3



Conclusions

The results presented above (Table 2) demonstrate that lithium−bromine exchange of an aryl bromide may be accomplished in high yield at 0 °C, a temperature significantly higher than that normally used for the process,[3] by using 2 molar equiv of *t*-BuLi in heptane in a predominantly hydrocarbon medium containing a small (1% by vol) to modest (10% by vol) quantity of any of a variety of ethers (Et_2O, THF, THP, or MTBE). The only side products detected from experiments conducted under these conditions were small amounts of benzyne-derived hydrocarbons (Scheme 2 and Table 2). The outcome of reactions of *n*-BuLi with 1-bromo-4-*tert*-butylbenzene (**1**) 0 °C is rather more sensitive to variation in solvent. The exchange reaction between **1** and *n*-BuLi, which is slow in pure diethyl ether (Table 1, entry 2), proceeds in high yield in a hydrocarbon medium containing a small amount (1% by vol) of THF (Table 1, entry 3), but coupling of the aryllithium with co-generated 1-bromobutane occurs to a significant extent in pure THF (Table 1, entry 5).

Experimental Section

The concentrations of *t*-BuLi in heptane (FMC) and *n*-BuLi in hexane (FMC) were determined prior to use by the method of Watson and Eastham.[20] A sample of 1-butyl-4-*tert*-butylbenzene (**3**),[21] isolated from the coupling of 1-bromobutane with (4-*tert*-butylphenyl)lithium in THF (Table 1, entry 5), displayed the following properties: $n^{23}{}_{D} = 1.4924$ (lit.[21] $n^{20}{}_{D} = 1.4898$); ^{1}H NMR δ 0.92 (t, $J = 4.34$ Hz, 3H), 1.28−1.41 (overlapping multiplet and singlet, 11H), 1.55−1.63 (m, 2H), 2.57 (t, $J = 8.0$ Hz, 2H), 7.10 (dt, $J = 8.67$, $J = 1.96$, 2H), 7.29 (dt, $J = 8.32$, $J = 2.22$, 2H); ^{13}C NMR δ 14.2, 22.7, 31.7, 33.9, 34.5, 35.3, 125.3, 128.3, 140.0, 148.5. A mixture of 1,4-di-*tert*-butylbenzene (**6**) and 1,3-di-*tert*-butylbenzene (**7**) was prepared following a literature procedure[14] and analytically pure samples of **6** [mp 77−78 °C (lit.[14] mp 77.7 °C)] and **7** [^{13}C NMR δ 31.7, 35.0, 122.4, 122.6, 127.8, 150.8] were isolated by preparative gas chromatography on a 10-ft, 20% SE-30 on Anakrom A (60/80 mesh) column.

Reactions of 1-Bromo-4-*tert*-butylbenzene (1) with *n*-BuLi or *t*-BuLi at 0 °C. A flame-dried, septum-capped, 10-mL flask was kept under a positive pressure of argon and charged with an accurately weighed quantity (ca. 1 mmol) of 1-bromo-4-*tert*-butylbenzene (**1**). A separate flame-dried, septum-capped, 25-mL round-bottomed flask was charged under a positive pressure of argon with either 1.2 molar equiv of *n*-BuLi in hexane or 2.2 molar equiv of *t*-BuLi in heptane. The amount of solvent used for each reaction was determined by calculating the total amount of heptane and dialkyl ether needed to make a 0.1 M solution of **1** in the desired solvent ratio: **1** was dissolved in half of the solvent volume, including all of the ether and the appropriate amount of heptane, and the alkyllithium was diluted with the remaining heptane. The alkyllithium solution was cooled to 0 °C and the solution of **1** in the appropriate solvent was added dropwise via a Teflon cannula over a period of 10 min. Upon completion of the addition, the mixture was allowed to stir at 0 °C for an additional 20 min and then quenched with MeOH. The organic layer was washed with water and dried ($MgSO_4$), and the crude products were analyzed by GC on a 25 m × 0.2 mm × 0.33 μm DB-5 cross-linked 5% phenyl methyl silicone capillary column and by GC−MS on a 25 m × 0.2 mm × 0.25 μm HP-5 cross-linked 5% phenyl methyl silicone capillary column. The results of these experiments are summarized in Tables 1 and 2.

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(21) Hennion, G. F.; Auspos, L. A. *J. Am. Chem. Soc.* **1943**, *65*, 1943.