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A Study of *N*-Nitrosoamide-Mediated Friedel−Crafts Type Benzylation of Benzene−Toluene and Benzene−Anisole[1a]

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Nitrogen-separated carbocation−carboxylate ion pairs were employed as sources of carbocations in the alkylation of aromatic compounds. The *N*-nitrosoamide approach to these nitrogenous-molecule-separated ion pairs is an excellent alternative to the standard acid-catalyzed Friedel−Crafts approach for studies of the alkylation because of the following variables: high reactivity of the electrophile, stability of the products, strict kinetic control, homogeneity, lack of overalkylation, straightforward chemistry, and good product balance. In deaminative benzylations of benzene−toluene and anisole−benzene mixtures, the values of k_X/k_B and % *meta* isomer are significantly different from those observed in the standard benzylations in a manner that indicates the deaminative electrophiles are more reactive than those generated by the standard Friedel−Crafts approach. The reactions show a direct proportionality between inter- and intramolecular selectivities and thus follow the Brown selectivity relationship (BSR). The benzylation of 2,4,6-trideuteriotoluene provided no evidence for deuterium rearrangements (or coupled benzyl rearrangements) in the arenium ion intermediate. Kinetic isotope effects were not detected. The methyl substituent on toluene appears to affect intermolecular selectivity (k_T/k_B) and intramolecular selectivity (*o*, *m*, *p* distribution) to similar degrees. A mechanism is proposed in which both selectivities are determined by activation energy differences in the transition states leading to the σ-complex intermediates. The observation that most standard Friedel−Crafts benzylations do not follow the BSR is discussed in terms of possible systematic errors in those cases. Silver ion-assisted Friedel−Crafts benzylations were performed under dry, basic conditions to investigate whether the standard approach could lead to data that obey the BSR.

Introduction

Standard Friedel−Crafts Alkylation. The standard Friedel−Crafts (F−C) alkylation of aromatic compounds is a Brønsted or Lewis acid catalyzed reaction of an aromatic substrate with alkyl halides, alkyl esters of strong acids, with alcohols, or with unsaturated compounds. The reaction has wide synthetic use, and its mechanism remains the subject of lively debate.[2−5] In the generally accepted mechanism,[3] the electrophile reacts with the aromatic nucleus via a high energy σ-type transition state to form a σ-complex (or Wheland intermediate or arenium ion).[3] This σ-complex may be preceded by a lower energy π-complex in which the electrophile is loosely bonded to the π-system of the arene, but the formation of the latter is not rate-determining.[3] The π-complex is probably an oriented entity since the electrophile should prefer to be near the positions of higher electron density on the ring.[3a,c] The final step of the reaction is a rapid, rearomatizing deprotonation of the arenium ion to generate a substituted arene. Thus the formation of each isomer may be traced through a distinct π-complex and a distinct σ-complex.

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† This paper is dedicated to the memory of Professor Emil H. White, 1926−1999.

(1) (a) Publication 3 in a series on benzylation of benzene/aromatic cosolvent systems via deaminatively generated carbenium ions. Previous publication is ref 1b. (b) Darbeau, R. W.; White, E. H.; Song, F.; Darbeau, N. R.; Chou, J. *J. Org. Chem. Soc.* **1999**, *64*, 5996. (c) Darbeau, R. W. Ph.D. Thesis, The Johns Hopkins University, Baltimore, Maryland, 1996. (d) White, E. H.; Darbeau, R. W.; Chen, Y.; Chen, D.; Chen, S. *J. Org. Chem.* **1996**, *61*, 7986.

(2) (a) Olah, G. A., Ed.; *Friedel−Crafts and Related Reactions*; Wiley: New York, 1963−1965; Vols. 1−4, (b) Lowry, T. H.; Richardson, K. S. *Mechanism and Theory in Organic Chemistry*, 3rd ed.; Harper and Row: New York, 1987; p 626.[16b] (c) White, E. H. *Tetrahedron Lett.* **1997**, *38*, 7649.

(3) (a) Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry Part A.; Structure and Mechanisms*, 3rd ed.; Plenum Press: New York and London, 1993; Chapter 10. (b) Sykes, P. *A Guidebook to Mechanism in Organic Chemistry*, 5th ed.; Longman: London and New York, 1981; Chapter 6. (c) Lowry, T. H.; Richardson, K. S. *Mechanism and Theory in Organic Chemistry*, 3rd ed.; Harper and Row Publishers: New York, 1987; Chapter 7.

(4) (a) Olah, G. A.; Kuhn, S. J.; Flood, S. H. *J. Am. Chem. Soc.* **1962**, *84*, 1688. (b) Diphenylmethanes in the presence of Lewis acids may generate overalkylated products such as "benzyhydryldiphenylmethane derivatives...in the high-boiling residues of the isomerizations". (Olah, G. A.; Olah, J. A. *J. Org. Chem.* **1967**, *32*, 1612−1614). (c) Olah, G. A.; Tashiro, M.; Kobayashi, S. *J. Am. Chem. Soc.* **1970**, *92*, 6369−6371. (d) Olah, G. A. *Acc. Chem. Res.* **1971**, *4*, 240−248. (e) Olah, G. A.; Kobayashi, S.; Tashiro, M. *J. Am. Chem. Soc.* **1972**, *94*, 7448−7461. (f) Olah, G. A.; Olah, J. A.; Ohyama, T. *J. Am. Chem. Soc.* **1984**, *106*, 5284−5290. (g) Olah, G. A.; Lin, H. C.; Olah, J. A.; Narang, S. C. *Proc. Natl. Acad. Sci. U.S.A.* **1978**, *75*, 545−548. (h) Olah, G. A.; Yamato, T.; Hashimoto, T.; Shih, J. G.; Trivedi, N.; Singh, B. P.; Piteau, M.; Olah, J. A. *J. Am. Chem. Soc.* **1987**, *109*, 3708−3713. (i) Olah, G. A.; Farooq, O.; Farina, S. M. F.; Olah, J. A. *J. Am. Chem. Soc.* **1988**, *110*, 2560−2565. (j) Yamato, T.; Hideshma, C.; Prakash, G. K. S.; Olah, G. A. *J. Org. Chem.* **1991**, *56*, 2089−2091. (k) The natures of the σ-complexes in the two mechanisms vary. Olah claimed that the σ-complex is an aronium ion in which the electrophile is bonded to the aromatic substrate by (3c−2e) bonds.[4d,e] He viewed the σ-complex of the generally accepted mechanism[3] as preceding his aronium ion.[4d] (l) A parallel study was also reported for 3,5-dideuteriotoluene.

(5) (a) DeHaan, F. P. et al. *J. Am. Chem. Soc.* **1984**, *106*, 7038−7046. (b) DeHaan, F. P.; Covey, W. D.; Ezelle, R. L.; Margetan, J. E.; Pace, S. A.; Sollenberger, M. J.; Wolf, D. S. *J. Org. Chem.* **1984**, *49*, 3954−3958. (c) DeHaan, F. P.; Chan, W. H.; Chen, W. D.; Ferrara, D. M.; Giggy, C. L.; Pinkerton, M. J. *J. Org. Chem.* **1989**, *54*, 1206−1209. (d) DeHaan, F. P. et al. *J. Am. Chem. Soc.* **1990**, *112*, 356−363.

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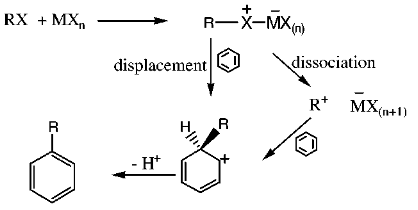
An alternative proposal[4c−e] is that the nature of the transition states leading to alkylarenes varies with the electrophilicity of the active species and with the nucleophilicity of the aromatic substrate.[4c−e] By this scheme, in reactions with relatively weak electrophiles or with weakly nucleophilic aromatics, the transition state of highest energy (σ-type) lies late on the reaction coordinate. Conversely, reactions with strongly electrophilic reagents and/or strongly nucleophilic aromatics proceed via an early (π-type) transition state of highest energy.[4c−e] The π-type transition states may or may not proceed to the σ-complex via a discrete π-complex (intermediate).[4e,k]

Benzylation of benzene−toluene mixtures has been studied particularly extensively[1b,4,5] because placing substituents on the aromatic nucleus of the benzyl moiety allows elucidation of the electronic effects operating in the reaction.[1b,4,5] The relative amounts of alkylated toluene and benzene formed (k_T/k_B) as well as the isomer distribution are typically measured. For the 4-R-benzyl cations (R = Me, H, Cl, NO_2), k_T/k_B ranges from ∼2.5 to 20 and % *meta* isomer ranges from ∼2.8 to 6.2 have been reported.[4,5]

There are several general problems associated with the standard F−C approach. These include uncertainty of the identity of the active electrophile, variable product distributions,[4,5] acid-catalyzed isomerizations[4e] and disproportionations,[4e] over-alkylation,[4b] extreme sensitivity to traces of water,[5c] rate of mixing,[4d] insolubility of the catalyst in the neat aromatic,[4,5] secondary alkylations in reactive cosolvents,[1b] etc. The identity of the actual alkylating agent has not been established in most cases or even specified; carbocations are often assumed to be the active species, but ion pairs[5a,c] and polarized alkyl halides[4a,d,g,5c] have also been invoked. Displacement reactions on the latter would then lead to the observed alkylarene (eq 1).[4a,d,g,5a]



(1)

Many standard F−C benzylations exhibit third-order kinetics:[6] first-order each in aromatic substrate, catalyst, and alkylating agent.[6] In these cases, a mechanism involving rate-determining carbocation formation followed by attack by the carbocation on the aromatic nucleus is excluded because the substrate would not appear in the rate expression. However, formation of an alkyl electrophile−Lewis acid complex followed by rate-determining reaction between the electrophile and the aromatic substrate is consistent with the observed kinetics. Presumably, as the degree of charge separation in the complex rises, the rate equation becomes zero-order in the aromatic and second-order overall. However, the latter kinetics is also consistent with slow carbocation formation and subsequent fast reaction with the aromatic substrate.

The data[7] from standard F−C runs in pure and diluted aromatic solvents show that k_T/k_B varies with the benzylating agent and with the catalyst. If the reactions were under kinetic control, then the active benzylating agent in the standard F−C approach is not a discrete carbocation because if the same species were generated in each case, the same product distributions would be expected. The active electrophile is probably a benzyl halide−Lewis acid complex. Thus, the marked (230%) rise in k_T/k_B[7] as the halide is changed from F to Br with $AlCl_3-CH_3NO_2$ as catalyst is accounted for by assuming that the k_T/k_B is inversely proportional to the extent of polarization in the complex. On the other hand, the isomer distribution, in particular the % *meta* value from the *same* experiments, remains essentially constant as the halide ion is varied.[7] This latter observation is consistent with the formation of carbocations, but this conclusion cannot be made in light of the changing k_T/k_B values. Thus the identity of the active electrophile in these benzylations is uncertain.

Standard F−C alkylations of benzene−toluene often utilize cosolvents such as acetonitrile and nitromethane to reduce complications from phase separation,[5a,b] an extreme sensitivity to traces of water,[4,5] isomerizations,[4a] and disproportionations.[4a] Such reactive solvents intercept deaminatively generated benzyl cations[1b,c,8a,9] to form less reactive, longer-lived onium ions, which cause (secondary) benzylations[1b,c,9] that are more selective than the (primary) benzylations via the first-formed benzyl cation.[1b] Thus higher values of k_T/k_B[1b] and decreased values of % *meta* are observed.[1b] A similar situation is likely to exist in the standard F−C alkylations in the presence of reactive cosolvents. Thus much, if not all, of the benzylations observed in those systems may stem from secondary electrophiles. Consequently, data obtained from these systems may not be valid for use in defining the chemistry of the F−C alkylation because the observed product distribution may not reflect (only) the first-formed electrophile.

Deaminative Approach to Friedel−Crafts Benzylation. Deamination involves the loss of N_2 (or N_2O) from an organic molecule or fragment. In these reactions, alkyl diazonium ions dediazoniate to form a highly reactive, essentially free cation (where the latter is stabilized by resonance, etc. as in the present case).[1b,8,9] The alkyl cation is believed to be the active electrophile because (1) predominant *retention* of configuration is observed in the ester from deamination of phenylethyl-*N*-nitrosonaphthamide[8b] (and its 2-butyl analog[8b]) and ^{18}O-studies of "intramolecular inversion"[8d] require the finite existence of a carbocation; (2) deamination of bridgehead amines leads to solvent-derived product (SDP),[8c,10a] which is impossible if the diazonium ion were the alkylating agent; and (3) the decomposition of *N*-methyl-*N*-nitrosotoluenesulfonamide (Diazald) in toluene does not yield the xylenes (although the sterically accessible methyl diazonium ion is believed to be the intermediate).[10b]

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[6] (a) Choi, S. U.; Brown, H. C. *J. Am. Chem. Soc.* **1963**, *85*, 2596. (b) DeHaan, F. P. et al. *J. Org. Chem.* **1986**, *51*, 1587.

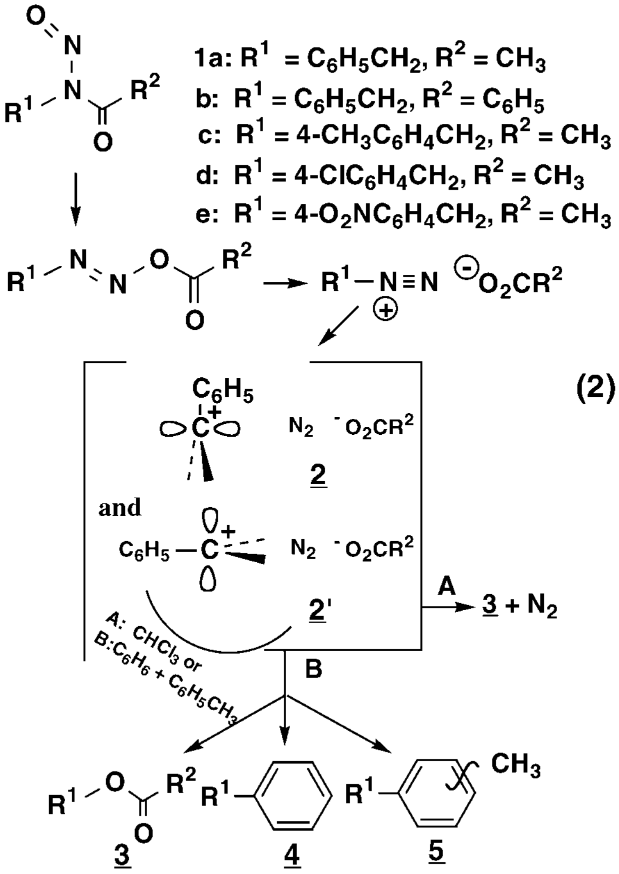
[7] Data taken from Table 11, ref 4e

[8] (a) White, E. H.; De Pinto, J. T.; Polito, A. J.; Bauer, I.; Roswell, D. F. *J. Am. Chem. Soc.* **1988**, *110*, 3708. (b) White, E. H.; Field, K. W.; Hendrickson, W. H.; Dzadzic, P.; Roswell, D. F.; Paik, S.; Muller, P. W. *J. Am. Chem. Soc.* **1992**, *114*, 8023. (c) White, E. H.; McGirk, R. H.; Aufdermarsh, C. A.; Tiwari, H. P.; Todd, M. J. *J. Am. Chem. Soc.* **1973**, *95*, 8107. (i) White, E. H.; Aufdermarsh, C. A., Jr. *J. Am. Chem. Soc.* **1961**, *83*, 1174.

[9] Darbeau, R. W.; White, E. H.; Nunez, N. P.; Coit, B.; Daigle, M. A. *J. Org. Chem.* **2000**, 1115.

[10] (a) Kirmse, W. J.; Moench, D. *Chem. Ber.* **1991**, *124*, 4, 237. (b) Brosch, D.; Kirmse, W. J. *J. Org. Chem.* **1991**, *56*, 907.

The absence of a free radical pathway is indicated by the nondetection of monodeuteriomethylbenzene or hexachloroethane from the decompositions of *N*-benzyl-*N*-nitrosobenzamide (**1b**) in 10:1 benzene/$CDCl_3$ at 80 °C. Since no D-abstraction from $CDCl_3$ occurred at a modestly high temperature in a fairly nonpolar medium, then a free radical pathway is apparently not competitive with the cationic pathway. Further, the similarity among the k_T/k_B and isomer distribution values at 80, 40, and 25 °C also indicate the absence of a competitive radical pathway.



Nitrosoamides on thermolysis produce (eq 2) a population of very short-lived, nitrogen-separated ion pairs (NSIPs) in which a fraction of the carbocations reach orientations, **2′**, such that strong π, p-electron donation from solvent molecules may occur to the electron-deficient centers.[1b,8c] Deaminatively generated carbocations exhibit high reactivities[1b,8,12] because the low activation energy required for the loss of nitrogen (or nitrous oxide) from the intermediate diazonium ion (or oxo diazonium ions) allows the cation to be formed with minimal solvent participation and maximal positive charge on the α-carbon.[8b] In addition, the first-formed (primary) carbocation is for a finite time prevented from reacting with the counterion by the physical presence of the N_2 (or N_2O) molecule, resulting in an essentially free carbocation.[1b,8b] The counterion and the aromatic substrate compete for the carbocation in irreversible reactions, and the high speed of the counterion−cation reaction to yield ester, limited by the rate of diffusion of N_2 into the medium, results in the carbocation having only a limited time to react with the aromatic compounds before being scavenged by the counterion.[1b,8b,c]

Table 1. Product Distributions in *N*-Nitrosoamide-Mediated 4-R-Benzylations of Equimolar Benzene and Toluene (ref 1d)[a−c]

nitroso-amide	R	temp (°C)	yields		k_T/k_B[e]	isomer distribution (%) (4-R-benzyltoluenes)		
			ester	SDP[d]		*ortho*	*meta*	*para*
1a	H	80	91.5	8.5	2.51	43.8	17.8	38.4
1c	Me	80	98.0	2.0	4.39	44.1	14.1	41.8
1d	Cl	80	90.7	9.3	2.41	44.0	18.3	37.7
1e	NO_2	80	73.4	26.6	1.33	45.1	26.4	28.5
1b	H	80	93.4	6.6	2.46	44.3	17.8	37.9
1b		40	89.4	10.6	2.55	46.0	19.4	34.6
1b		25	87.2	12.8	2.66	46.6	18.6	34.8

[a] Product distributions by NMR and GC (30 m SE−30, 0.25 mm i.d.; column temp, 145 °C); total yields of products, ~97%. [b] [**1**], ~0.05 M; pyridine (~0.01 M) present in all runs. [c] Maximum std deviations for k_T/k_B, 0.10; for relative yields, 0.48. [d] Solvent-derived products. [e] Values independent of solvent ratio

Large yields of SDP are effected through use of cations of high electrophilicity (e.g., 1-norbornyl[8c]), counterions of low nucleophilicity (e.g., tosylate[1b] and triflate[1b,8a]), and high mole fractions of solvents of high nucleophilicity (e.g., pyrrole[14]).

The nitrosoamide approach was employed in the present study because (1) the decompositions introduce essentially free carbocations into virtually any solvent via a unimolecular process,[1b,13] (2) the electrophile is known to be an alkyl cation, (3) minimal side reactions occur,[1b] (4) no cosolvents are necessary,[1b] and (5) no other reagents are necessary for carbocation generation.[1b] No catalysts are used in the nitrosamide approach, and the product distributions do not change during the course of the reaction or on standing; the system is under strict kinetic control. The nitrosoamide approach thus circumvents the major difficulties attending the standard F−C alkylation.

Results and Discussion

Benzylation of Benzene−Toluene. The nitrosoamides **1a−e** were decomposed in equimolar benzene−toluene. The data (Table 1) show that as the *para*-substituent on the benzyl group varies from methyl to nitro, the yields of the SDP and of the % *meta* isomer rise, while the k_T/k_B falls. This is consistent with an increase in reactivity of the substituted benzyl cation in the direction 4-Me to 4-NO_2. Additionally, an intrinsic and fundamental difference exists between the standard and the deaminative F−C benzylations. In general, the k_T/k_B values from the deaminative approach are **lower** than those from the standard approach, and the deaminative % *meta* values are **higher**. Thus the electrophiles in the standard F−C benzylations are **not** free benzyl cations.[1b]

Intra- vs Intermolecular Selectivity: The Brown Selectivity Relationship (BSR).[15] In 1953, Brown and Nelson[15a] proposed that in electrophilic substitutions of benzene−toluene mixtures the yield of the *meta* isomer

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(11) Fossey, J.; Lefort, D.; Sorba, J. *Free Radicals in Organic Chemistry;* John Wiley and Sons: New York, 1995; pp 202−203.

(12) (a) Huisgen, R.; Ruchardt, C. *Justus Liebigs Ann. Chem.* **1956**, *601*, 1. (b) White, E. H.; Dolak, L. A. *J. Am. Chem. Soc.* **1966**, *88*, 3790.

(13) (a) White, E. H.; Roswell, D. F.; Politzer, I. R.; Branchini, B. R. *J. Am. Chem. Soc.* **1975**, *97*, 2290. (b) White, E. H.; Roswell, D. F.; Politzer, I. R.; Branchini, B. R. *Methods Enzymol.* **1977**, *46*, 216. (c) White, E. H.; Jelinski, L. W.; Perks, H. M.; Burrows, E. P.; Roswell, D. F. *J. Am. Chem. Soc.* **1977**, *99*, 3171.

(14) Darbeau, R. W.; White, E. H. *J. Org. Chem.* **1997**, *62*, 8091.

"is related to the activity of the attacking species and utilize[d] the relative reactivity of toluene and benzene [k_T/k_B] in the reaction under consideration as a measure of this activity."[15a] For example, a highly active species would show little selectivity between toluene and benzene, resulting in a low k_T/k_B; it also would not distinguish electronically between the available positions on toluene resulting in a large % *meta*. To avoid complications due to steric factors at the *ortho* position, they suggested that "the polar effect of a substituent is best evaluated in terms of the *para*/*meta* (*p*/*m*) ratio rather than in terms of ratios involving the *ortho* position."[15a] They felt that the changing steric features of the attacking electrophile could affect the k_T/k_B ratio but not the *p*/*m*, and thus the ratio of the partial rate factor[15g] for *para* attack to that for *meta* attack (p_f/m_f) was used as a gauge of intramolecular selectivity. Intermolecular selectivity was measured by p_f even though this term incorporates k_T/k_B and is itself incorporated into the term for intramolecular selectivity.

Brown defined the term log p_f/m_f as the (intramolecular) selectivity factor, S_f.[15] Thus the Brown selectivity relationship (BSR) could be written as log $p_f \alpha S_f$. A plot of log p_f vs S_f yields a straight line through the origin of slope = *b*; hence the BSR may be written as log $p_f = bS_f$ that is derivable from the Hammett equation.[15c,d] The constant, *b*, is related to the σ^+ terms for *meta* and *para* substitution by the equation $b = \sigma_p^+/(\sigma_p^+ - \sigma_m^+)$.[15f] Evaluation of the *b* value gives $b = 1.34$[16] (the value of *b* from Brown's original plot is 1.31[15c,d]). The line passes through the origin because an infinitely electrophilic species would show no selectivity and would react statistically, so $p_f = m_f = 1$ and log $p_f = S_f = 0$. The criterion for obedience to the BSR in benzene–toluene systems then are a straight line of slope = 1.31 passing through the origin. The position of the points along the line will vary with the electrophilicity of the actual benzylating agent; the most reactive species would lie closest to the origin.[15]

The BSR requires only that the intermolecular selectivity of the reaction be proportional to the intramolecular selectivity *regardless of the structure and activity of the electrophile*. Thus whether benzylations proceed via the essentially free benzyl cation of deamination, a polarized benzyl halide–Lewis acid complex, or an ion pair, all are required to fit the BSR. The validity of the BSR is supported by a considerable body of data on electrophilic aromatic substitution reactions of toluene–benzene mixtures.[15] Yet, certain characteristics of the relationship should be noted: (1) the term p_f appears in both "variables" so that the S_f term possesses an inherent dependence on the p_f term, and (2) the BSR works well only if the substituent (like methyl) has a low polarizability.[17] The quality of the "fit" may depend on the intensity of electron demand on the electrons of the substitutent group by each electrophile in the transition state.[17] Nevertheless, the BSR is an often-used yardstick against which electrophilic substitutions on aromatics are measured.

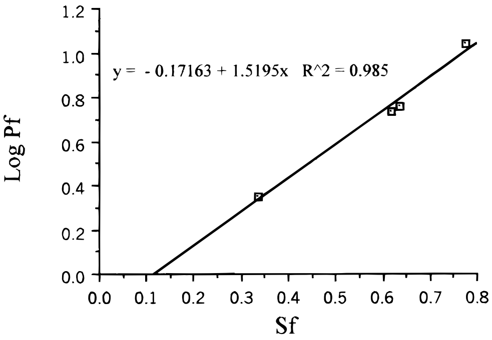

Figure 1. Plot of log p_f vs S_f for deaminative benzylation of benzene–toluene at 80 °C.

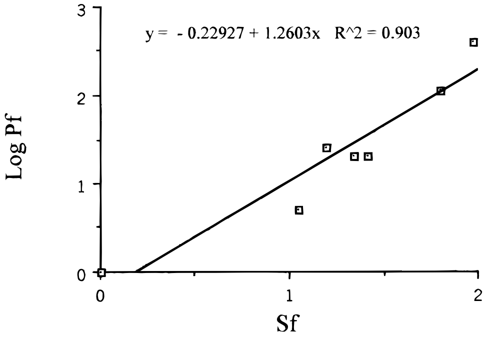

Figure 2. Plot of log p_f vs S_f for a standard Friedel–Crafts benzylation of benzene–toluene.[7]

BSR and Friedel–Crafts Alkylations. Most standard F–C alkylations, e.g., methylation, ethylation, and isopropylation, follow the BSR;[15c,d] benzylation, however, was reported to disobey the BSR[4c–e,5a] (with one exception where a *b* value of 1.4 was calculated).[5b] A plot (Figure 1) of our data (Table 1) using the BSR shows very good linearity ($R^2 = 0.985$) and a slope (1.52).[18] When $S_f = 0$, $p_f = 0.674$ (vs the expected value of unity). When log $p_f = 0$, $S_f = 0.113$, from which $m_f = 0.771$ (vs the expected value of unity).[18] These observations suggest that the deaminative benzylation of benzene–toluene does follow the BSR. The linearity also indicates that over the range of *para*-substituents used (**1a**–**e**) the mechanism of benzylation does not change and that a single type of transition state leading to the arenium ion is involved.

A BSR plot (Figure 2) of the data[7] from a standard F–C benzylation of benzene–toluene utilizing only the *para*-substituted benzyl chlorides (R = Me, H, Cl, F, and NO_2) also shows fairly good linearity ($R^2 = 0.903$) suggesting that even the standard F–C benzylations are governed by a single type of transition state. Only the *para*-substituted isomers were considered in an effort to minimize steric effects due to overalkylation. For the plot

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[15] (a) Brown, H. C.; Nelson, K. L. *J. Am. Chem. Soc.* **1953**, *75*, 6292–6299. (b) Smoot, C. R.; Brown, H. C. *J. Am.. Chem. Soc.* **1956**, *78*, 6249. (c) Stock, L. M.; Brown, H. C. *J. Am. Chem. Soc.* **1959**, *81*, 3323–3329. (d) Stock, L. M.; Brown, H. C. *Adv. Phys. Org. Chem.* **1963**, *1*, 35–154. (e) Brown, H. C.; Okamoto, Y. *J. Am. Chem. Soc.* **1958**, *80*, 4979–4987. (f) Stock, L. M. *Prog. Phys. Org. Chem.* **1976**, *12*, 21. (g) The partial rate factor, $x_f^{\,y}$, for a given electrophile in a given reaction under specified conditions is the rate at which this electrophile substitutes at the *x* position (*o*, *m*, *p*) of a mono *y*-substituted benzene relative to the rate of the same reaction at a single position in benzene under identical conditions. The partial rate factors for benzene–toluene systems are defined as: $o_f^{Me} = (k_T/k_B)(\% \textit{ortho}/100)(3)$; $m_f^{Me} = (k_T/k_B)(\% \textit{meta}/100)(3)$; $p_f^{Me} = (k_T/k_B)(\% \textit{para}/100)(6)$. Since we are dealing exclusively with benzene–toluene systems we have chosen to omit the superscript "Me" from the terms.

[16] The σ+ values were taken from Gordon, A. J.; Ford, R. A. *The Chemists Companion: A Handbook of Practical Data, Techniques and References*; Wiley- Interscience: New York, 1972; p 145.

[17] March, J. *Advanced Organic Chemistry*, 3rd ed.; John Wiley and Sons: New York., 1985; p 465.

[18] If the limiting point (0, 0) is included with the experimentally determined data points, a straight line of slope = 1.30, *y*-intercept = −0.003, and $R^2 = 0.986$ is obtained.

of the standard data, $b = 1.26$ and $S_f = 0$, $p_f = 0.590$ and at $\log p_f = 0$, $S_f = 0.182$ from which $m_f = 0.657$.[25] Here the obedience to the BSR, though fair is not as good as in the deaminative case.

Other Selectivity Plots. Apart from the BSR, other plots can be used to elucidate the relationship between inter- and intramolecular selectivities. One such plot (Figure 3) relates the statistically corrected intermolecular selectivity parameter, $6/5(k_T/k_B)$ to the Hammett $\sigma_p{}^+$ constant. Good linearity ($R^2 = 0.952$) is observed when $\log 6/5(k_T/k_B)$ is plotted against the σ^+ values for the *para*-substituents (on the electrophile). The plot predicts that a substituent with $\sigma_p{}^+ = 1.19$ will give a benzyl cation of near infinite reactivity (for which $k_T/k_B = 5/6$, ignoring steric effects). A similar plot of Brown's "best data"[15f] also gives a straight line ($R^2 = 0.990$). A plot (Figure 4) of the data (Table 1) using the relative yields of the *meta* isomer for the 4-R-substituted benzyltoluenes to that of *m*-methyldiphenylmethane (log % *m* (R)/log % *m* (H)) vs the σ^+ constants for the R groups also gives an excellent straight line ($R^2 = 0.990$).

A further advantage of the deaminative approach to the F–C benzylation is the existence of a second intermolecular selectivity term, the % SDP. A related term, % ester/% SDP, has been shown[1b] to be much more sensitive than k_T/k_B to the subtle variations that exist among the deaminative methods.[1b] As the reactivity of the carbocation rises, so does its ability to react with the medium before being scavenged by the counterion (Table 1). The yield of the SDP (relative to ester) thus rises with the reactivity of the electrophile (Table 1). An increase in carbocation reactivity is expressed intramolecularly as an increase in the % *meta* isomer. Thus a plot of log % SDP vs log % *meta* is also an inter- vs intramolecular selectivity plot.

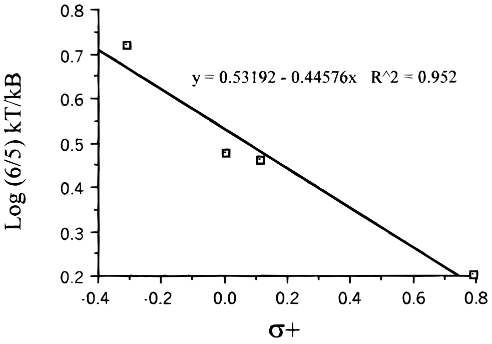

Figure 3. Plot of $\log 6/5(k_T/k_B)$ vs σ^+ for deaminative benzylation of benzene–toluene at 80 °C.

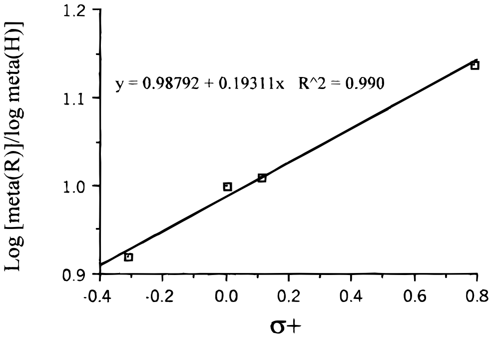

Figure 4. Plot of log % *meta*(R)/log % *meta*(H) vs σ^+ for deaminative benzylation of benzene–toluene at 80 °C.

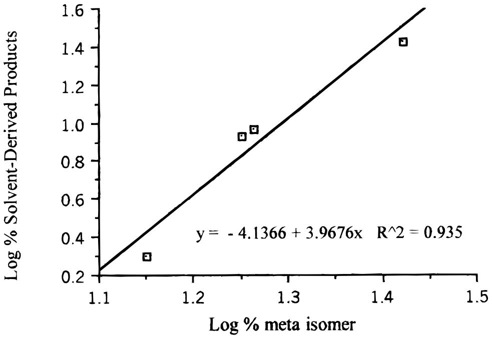

Figure 5. Plot of log % solvent-derived products vs log % *meta* isomer for deaminative benzylation of benzene–toluene at 80 °C.

Such a plot (Figure 5) of our data (Table 1) gives a straight line ($R^2 = 0.935$) (a non-log plot of the data gives $R^2 = 0.998$), demonstrating again the existence of a direct proportionality between inter- and intramolecular selectivities for benzylation in agreement with the conclusions made from the selectivity plots in Figures 1 and 3. Interestingly, if the cation is assumed to be infinitely reactive so that it is captured exclusively by the solvent during its brief insulation from the counterion, then % SDP = 100 and log % SDP = 2, from which, by interpola-

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(21) Johnson, C. D.; Schofield, K. *J. Am. Chem. Soc.* **1973**, *95*, 270.

(22) Hammond, G. S. *J. Am. Chem. Soc.* **1979**, *101*, 1337.

(23) Ingold, C. K. *Structure and Mechanism in Organic Chemistry*, 2nd ed.; Cornell University Press: Ithaca, NY, 1969; p 290.

(24) (a) University of Illinois Mass Spectrometry Laboratory. (b) **Determination of the Number of Deuterium Atoms per Molecule of the 4-Nitrobenzyltoluenes using 2,4,6-Trideuteriotoluene.** 1.^{1}H NMR data: extent of D incorporation in 2,4,6-trideuteriotoluene (TDT) = 95.9%. 2. GC–MS data:

	peak intensity				
isomer	M − 2	M − 1	M	M + 1	M + 2
meta	1.96	13.44	100.00	19.41	2.18
ortho		6.05	100.00	18.93	2.23
para	1.62	7.85	100.00	20.52	2.68

3. Sample calculation for the *para* isomer: (A) statistical distribution: number of D atoms per molecule of TDT = 0.959 × 3 = 2.877, ∴ number of residual (*o*, *p*) H atoms per molecule = 3 − 2.877 = 0.123. Let the ratio of D/H = α, then α = 2.877/0.123 = 23.39. The statistical distribution of D's in TDT is thus given by Pascal's triangle as $H_3 = 1$, $H_2D = 3\alpha$, $HD_2 = 3\alpha^2$, and $D_3 = \alpha^3$, from which % H_3 = 0, % H_2D = 0.5, % HD_2 = 11.3 and % D_3 = 88.2. (B) M + 1 correction: each peak possesses a M + 1 contribution from its M − 1 neighbor. The average intensity of the M + 1 peak from multiple analyses (not shown) = 19.58%. If x is the % of the observed M + 1 peak due to the true M peak, and y is the M + 1 contribution to the M peak by the M − 1 peak, then $19.58 = x(100 - y)$ and $y = x(7.85)$. Solving the simultaneous equations gives $x = 0.199$ and $y = 1.56$. Applying these corrections gives M = 98.44, M − 1 = 7.85, and M + 1 = 19.59. The residual M + 1 = 20.52 − 19.59 = 0.93 (which probably represents a D_3 species). (C) correction for % D_3 incorporation: the "new" M is thus 98.44 × 94.9/88.2 = 107.03, ∴ difference in M = 107.03 − 98.44 = 8.59. Corrected value for M − 1 = 8.59, but observed M − 1 = 7.85, ∴ amount of D_1 (i.e., H_2D) = 7.85 − 8.59 = −0.74. This is an "overcompensation" which implies that no D_1 species are present in the sample of TDT. Consequently, since the intensity of the D_2 species = 107.03 and that of the D_3 species = 0.93, then % D_2 = 99.1 and % D_3 = 0.9. Thus the *para* isomer contains the amount of D's expected for direct attack at that position, indicating the absence of rearrangements in the arenium ion.

(25) Abstract of ref 4f; also addressed in ref 14(b) and in refs 4a,b,d,e,h,i.

tion, % *meta* = 35.2. If instead, we assume that an infinitely reactive cation yields 40% *meta* isomer, then from Figure 5, the % SDP = 166%. This extrapolation suggests that an infinitely reactive carbocation in a NSIP generated in benzene−toluene will capture *exclusively* the solvent even in the presence of the negatively charged counterion. Such a prediction is interesting in the context that the 1-norbornyl cation yields ~60% of the alkyl chloride in methylene chloride[8c] and that the benzyl cation in pyrrole generates ~80% of benzyl pyrroles,[14] both reactions occurring in the presence of a carboxylate ion.

Friedel−Crafts Benzylations and the BSR. It is apparent that in deaminative benzylations the inter- and intramolecular selectivities are proportional. Furthermore, data[7] from a representative standard F−C benzylation also show fair proportionality when complicating variables are eliminated. This observed proportionality is not consistent with claims[4c−e,5a] that F−C benzylations do not fit the BSR.

In the deaminative benzylations, the observed ranges for the k_T/k_B and % *meta* values are 1.33−4.39 and 26.4−14.1, respectively, for 4-R = NO_2 *to* Me (Table 1). In these cases an essentially free 4-R-benzyl cation is believed to be involved (vide supra). In a representative standard F−C benzylation,[7] where a less reactive benzyl electrophile is generated, the k_T/k_B and % *meta* values over the same range of *para* substituents are 2.5−29.0 and 6.2−2.1, respectively.[7] These latter values move in the right direction for less reactive electrophiles, in accordance with the tenets of the BSR, and yet the data do not fit the BSR, suggesting that although the "gross" changes in k_T/k_B and % *meta* are correct, the "fine" values are not correct. If it were assumed that benzylations should obey the BSR (as do other alkylations[15c,d]), then it would appear that in the standard F−C runs, for a given % *meta* value, the k_T/k_B value is too large, or for a given k_T/k_B value, the % *meta* value is too small.

If the k_T/k_B value is arbitrarily raised while the isomer distribution is held constant, the plot moves closer to the origin, the quality of the line (R^2) increases, but the *b* value falls. If the % *meta* isomer is raised at constant % *ortho* or constant % *para* and the k_T/k_B is kept constant, the R^2 and *b* values rise and the line drifts closer to the origin. Consequently, the standard F−C reactions would be more obedient to the BSR if they yielded either larger k_T/k_B values for their observed isomer distributions or larger % *meta* values for their observed k_T/k_B values. The fit is even better if both the k_T/k_B and % *meta* values were higher than observed. If it is assumed that a nonisomerizing, homogeneous standard F−C system existed (i.e., one which approached the deaminative conditions) and that in such a system the BSR is obeyed (as it is in the deaminative case), then we must conclude that in the standard systems that have been studied, factors are in operation that serve to lower the k_T/k_B and % *meta* values so that the observed data poorly fit the BSR.

Given that the toluene-derived products are more nucleophilic than the benzene-derived ones and are also more soluble in the catalyst layer where the catalyst-mediated reactions actually occur,[19] it is likely that they suffer overalkylation[4b] (kinetic yields of the *meta* isomer can be depleted preferentially by overalkylations, which are fastest for this isomer) and disproportionation[4,5] to a greater extent than the benzene-derived products. Such secondary reactions would effect a lowering of the k_T/k_B. Additionally, DeHaan[5b] has observed that the product yields in the standard F−C reactions are very sensitive to the amount of moisture present; when moisture is minimized by use of vacuum line techniques "the data are in good agreement with the BSR".[5b] It would thus appear that the standard F−C benzylations may produce data that fit the BSR if postreaction isomerizations and moisture can be eliminated. The use of a mild Lewis acid such as Ag^+,[4a] at moderate temperatures in dry, basic conditions, would appear to present the best circumstances for this to be achieved.

Table 2. Product Distribution from Silver Ion-Promoted Benzylation of Benzene−Toluene[a−d]

		temp	equiv of			isomer distribution		
precursor	run	(°C)	base[e]	Ag^+	k_T/k_B[f]	*ortho*	*meta*	*para*
			$PhCH_2Cl$					
series A[g]								
	1	25	*h*	*h*	2.95	39.5	3.1	57.4
series B								
5 min	1	25	1.5	0.5	6.30	29.5	3.7	66.8
1 h	1				6.32	29.9	3.9	66.2
1min	2[i]	0	1.5	0.5	10.35	31.1	4.3	64.6
5 min	2[i]				10.31	31.5	4.0	64.5
1 h	2[i]				10.30	32.0	3.9	64.1
5 min	2[j]	0	1.5	0.5	8.48	26.1	2.1	71.7
10 min	2[j]				8.52	26.2	2.1	71.7
			$PhCH_2O_2CCl$					
series C	1	25	1.5	0.5	3.02	35.6	5.2	59.2

[a] Data measured by GC. [b] $AgBF_4$ was used in series A, and $AgSbF_6$ was used in series B and C. [c] Benzyl chloride (series A and B) and benzyl chloroformate (series C) were used as benzylating agents. [d] Equimolar benzene−toluene was used in all runs. [e] 2,6-Di-*tert*-butyl-4-methylpyridine was used in series B and C. [f] Relative rate of benzylation of toluene and benzene. [g] From Table 3, ref 3a. [h] Unknown. [i] $AgSbF_6$ was pumped to constant weight at oil pump pressure prior to use; the solvents and benzyl chloride were dried over $MgSO_4$. [j] $AgSbF_6$ was pumped at oil pump pressure for 1 day prior to use; the solvents were predried over $MgSO_4$ and then over sodium and were then distilled from lithium aluminum hydride; the hindered pyridine was sublimed at oil pump pressure and the freshly distilled benzyl chloride was dried over $MgSO_4$.

Silver Ion-Assisted Friedel−Crafts Benzylation of Benzene/Toluene. Silver hexafluoroantimonate (0.5 equiv) was employed to effect F−C benzylation of benzene−toluene mixtures using benzyl chloride and benzyl chloroformate as substrates. The reactions were vigorously stirred in the dark in the presence of 1.5 equiv of base. The data (Table 2) show that the product distributions do not change with time and that as moisture is removed from the system, the calculated *b* value rises from 0.90 through 1.08 to 1.17, approaching the theoretical (BSR) value of 1.31. This result appears to substantiate our belief that standard F−C benzylations give faulty data because of problems with moisture and acid-catalyzed secondary reactions.

Silver ion-assisted decarboxylation of benzyl chloroformate in benzene−toluene results in a lower k_T/k_B and a larger yield of the *meta* isomer than from the corresponding ionization of benzyl chloride (Table 2). This observation is consistent with the formation of a molecule of CO_2 between the incipient benzyl cation and the silver chloride, similar to the N_2 (or N_2O) separated ion pairs generated via deamination. The deaminative approach appears to be superior to the decarboxylative one with respect to the reactivity of the electrophile generated, as evidenced by the lower k_T/k_B values and higher yields of the *meta* isomer in the former approach.

Influence of Trace Moisture on the Friedel−Crafts Reactions. We have shown (Table 2) that in the standard F−C benzylations performed under basic conditions in the presence of a mild Lewis acid, the k_T/k_B value *generally* increases as the moisture content of the system decreases. It is known that the standard F−C reactions in excess aromatic solvents are "difficult to run in an homogenous, reproducible fashion".[5a] Phase separation involving precipitations was reported for $TiCl_4$-catalyzed benzylations performed in excess benzene and excess toluene.[5] The results were found to depend "strongly upon the amount of moisture present",[4a] so much so that k_T/k_B values of 20 ± 12 were obtained using vacuum-line techniques.[5b] The large standard deviation was attributed to the difficulty in "controlling the moisture problem".[5b] Interestingly, the amount of moisture does not seem to affect the isomer distribution as much as it does the k_T/k_B ratio, as is evidenced by the smaller standard deviations for the isomer distributions in the same run: % *ortho* = 41 ± 3, % *meta* = 6 ± 2, % *para* = 53 ± 3.[5b] In the presence of the cosolvent nitromethane, the sensitivity of the system to moisture is diminished.[4,5a,b]

No explanations have been offered for the effect of moisture on the F−C reaction *only* in an excess of the aromatic solvent. Water is not soluble in the aromatic solvent, so trace moisture may exist as polar microcapsules (especially when they react with catalyst to form HCl). A significant fraction of the F−C reaction may then occur in these microcapsules, the kinetics of which may differ markedly from those reactions that are "extracapsular". As the amount of water is varied it would be expected that the observed kinetics would vary markedly. In nitromethane, where the medium is, ostensibly, completely homogeneous, these "hot spots" or microcapsules would be absent and all of the reaction would occur in a monophasic system even as the amount of moisture varies (within limits). Water reacts with the F−C catalyst and may generate *n* molecules of HCl per molecule of catalyst (MX_n). HCl is soluble in the aromatic solvent and may catalyze secondary reactions of the kinetic products. This enhanced formation of acid in the presence of water may also contribute to the sensitivity of the system to trace moisture. In the presence of the mildly basic nitromethane or acetonitrile, the generation of HCl may be effectively buffered and the system would ostensibly be less sensitive to trace moisture.

Conversely, the product distribution from the decomposition of *N*-nitrosoamides in benzene−toluene is identical in 75% $CDCl_3$/benzene−toluene and in 75% cyclohexane/benzene−toluene.[1b] This indicates that the yields are independent of the (polarity of the) solvent. Additionally, the addition of 0.1% (molar) of water to the deamination in benzene−toluene of the nitrosoamide **1b**, yields data (k_T/k_B = 2.40, *ortho* = 44.5%, *meta* = 17.7%, *para* = 37.8%)[1b] that are statistically indistinguishable from the data obtained from the runs performed in its absence (Table 1). Further, the product distribution from decompositions performed in the presence of 2 equiv of pyridine are identical to that in its absence.[1b]

Ages of Complexes and Selectivity in S_EAr Reactions. There is a considerable body of evidence suggesting that the BSR fails for benzylations.[4g,20] To explain these observations, the rate-determining formation of a π-complex has been postulated.[4c−e] In this model, the position of attack is not determined in this rate-limiting step but in a later step leading to the arenium ion, so inter- and intramolecular selectivities are not determined by the same process and are unrelated.[4] The BSR would not apply in this postulate.[4c−e]

Johnson and Schofield[21] have pointed out the inherent danger of using ρ values to substantiate reactivity−selectivity relationships in accordance with the Hammond postulate.[22] For electrophiles whose strengths can be varied by substitution, they argued that if the low intermolecular selectivity of powerful electrophiles arises because they traverse an early transition state, then in such cases there is little development of positive charge on the aromatic nucleus so ρ is small and negative. For weak electrophiles (high selectivity) that are assumed to proceed via late transition states, ρ will be large and negative. However, a point arises where weak electrophiles react faster than powerful ones. Such a reversal of reactivities does not appear to be reasonable. Thus the hypothesis of separate early (π-type) and late (σ-type) transition states for very reactive and weakly reactive electrophiles, respectively, must be eliminated from contention. Explanations other than the position of the highest transition states along the reaction coordinate must be sought.

With powerful electrophiles the accuracy of competitive experiments is often in doubt because of the likelihood of incomplete mixing before fast reactions.[23] Relative rates from noncompetitive studies have reported to be in good agreement with competitive data for weaker electrophiles, such as those derived from *para*-substituted benzyl halides;[4e,5b] it is unknown whether the same is true of more powerful electrophiles because of the difficulty of measuring absolute rates in these cases.[4d,15] Rapid secondary reactions prior to or after product formation[4,5] may also play a role, as can the preferential solubility of the products in the catalyst layer.[19]

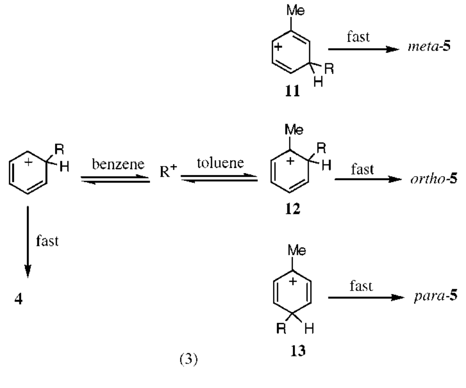
It must be reiterated that the deaminative approach to the F−C problem circumvents these problems because of the noncatalytic, unimolecular[12] delivery of the cation into a homogeneous medium in which both the precursors and the products are soluble. Additionally, the requirement of independent transition states to account for apparently independent selectivities appears to be a problem unique to such powerful electrophiles as NO_2^+.[3d,15] If the unstabilized alkyl (e.g., Me, Et, ^{i}Pr) electrophiles generated by the standard F−C approach are insufficiently active to require these independent transition states (because the BSR applies in those cases),[15c,d] then the stabilized benzyl electrophile in the standard F−C approach certainly should not. It is thus reasonable to expect the standard F−C benzylation to fit the BSR. We have shown that this is true of deaminative benzylations where the more electrophilic benzyl cation is involved; therefore, it must also hold true for the standard case if the reaction conditions could be engineered to eliminate unwanted side reactions.

Yield of the *Ortho* Isomer. As the 4-substituent is varied from methyl to nitro in the deaminative benzylations, the yield of the *meta* isomer rises from 14.1% to 26.6% and that of the *para* isomer falls from 41.8% to 28.5% (Table 1). In contrast, the yield of the *ortho* isomer is virtually constant at 44.2 ± 0.6% (Table 1). Interestingly, in a representative standard F−C benzylation[7] over the same range of substituents, the % *ortho* almost doubles from 31.4% to 59.4%. The constancy of the yield of the *ortho* isomer in the deaminative benzylations suggests that under these ideal F−C conditions a near statistical yield of *ortho* isomer is obtained and that the observed increase in the *meta* isomer comes at the expense of the *para* isomer.

On a purely statistical basis, toluene is expected to yield 40% *ortho* by examination of the available positions in the ground-state molecule. In accordance with the Hammond postulate,[22] however, the arenium ion is a better model for the (σ-type) transition state than is toluene. The charge distribution in the benzenium ion generated by the protonation of benzene possesses about 25% of the total positive charge at each *ortho* position.[4d] If the benzenium ion is accepted as a model for arenium ions in general, and by extension for the σ-type transition states preceding them, then a methyl group *ortho* to the entering electrophile is less efficient than a *para* methyl group at stabilizing the arenium ion. Consequently, the yield of *ortho* isomer should be somewhat less than 40%, the same conclusion could be made from steric factors.

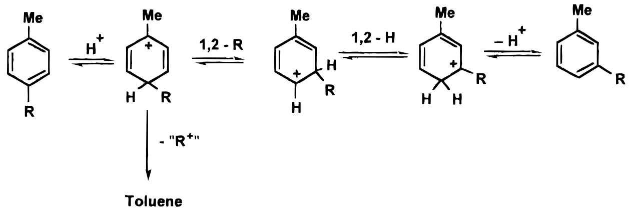
It is not clear why the % *ortho* is constant in the deaminative benzylations; however, the 4-methylbenzyl cation and the 4-nitrobenzyl cation yield 44.1% and 45.1% of the *ortho* isomer, respectively, so a near constancy of % *ortho* may be expected. It is not clear why the yield of the *ortho* isomer is >40%, although an argument can be made in terms of the existence of the largest electron density at the *ortho* position of toluene as a result of the electronic effect of the methyl group.

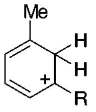
Arenium Ion Intermediates and the Source of the *Meta* Isomer.[1d] The decomposition of the nitrosoamide **1e** in 2,4,6-trideuteriotoluene was examined in an effort to detect hydrogen rearrangements (and linked alkyl rearrangements) that might be occurring during the lifetime of the arenium ion intermediates (**13**, e.g.).[4f] The nitrosoamide **1e** was chosen because (1) the yield of SDP was large, ∼27%; (2) the yield of the (analytically most important) *meta* isomer was large, ∼26%; (3) the 4-nitrobenzyltoluenes on electron impact give localized ionizations with low (∼4%) % M-1 signals and very low (∼0.3%) M-2 signals; and (4) the known absence of product isomerizations.[1b] Analysis of the nitrobenzyltoluenes formed (Table 1) by GC−MS[24a] showed that within experimental error (∼2%), the *ortho* and *para* isomers contained the number of deuterium atoms expected for direct reaction of the 4-nitrobenzyl cation at those positions: 2.00 and 2.00 D/mol, respectively.[24b] The value for the *meta* isomer was 2.93 D/mol, indicating that >90% of this isomer is formed with hydrogen loss occurring directly from the site of substitution. In this case, then, <10% of the molecules are derived via D-loss (probably via **11** to **14** to *meta*-**5**).[1d] Thus, the benzyl carbocation reacts with toluene to produce three distinct arenium ions (eq 3), that undergo subsequent deprotonation, with little rearrangements of deuterium and, by inference, alkyl groups.



(3)

Scheme 1. Olah's Proposed Mechanism for Arenium Ion Rearrangement





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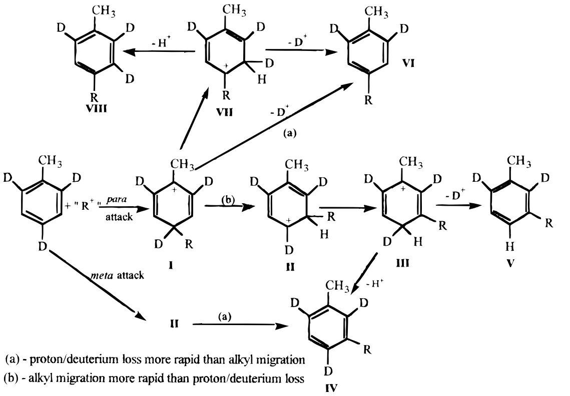
The migratory aptitude of the 4-nitrobenzyl group is likely to be lower than that of the parent benzyl group, so the extent of migration in the former case is likely to be lower than in the parent case. However, the fairly large yield of the hydrocarbons and the high yield of the *meta* isomer in the former case increase the likelihood that significant migrations would be detected. The deaminations of nitrosocarboxamides generate the carboxylate anion, which is more basic than the usual counterions encountered in the standard F−C alkylations. Its tendency to decrease the potential for migratory events due to rapid proton abstraction from the arenium ions is not likely to be significant, however. Thus, in this regard, the deaminative system is very similar to the standard F−C system. That alkyl migrations were not observed in the present work indicates that such migrations/rearrangements are also absent in the standard F−C alkylations. Thus each isomer originates *exclusively* from its own corresponding arenium ion intermediate (eq 3) in agreement with the generally accepted mechanism for the F−C alkylation.[3]

The present results, however, are not consistent with a proposal[25] that in F−C alkylations the *meta* isomer stems to an indeterminate degree, from rearrangements occurring during the lifetimes of the *para* and *ortho* arenium ion intermediates. Olah et al. have proposed that "alkylated product formation in case of toluene...is proceeded (sic) by intramolecular, 1,2-alkyl, and hydrogen...shifting resulting...in an increased *meta* substitution" (Scheme 1).[25] Support for the rearrangements [**I** to **II** (Scheme 2) or **11**,**12** to **13** (eq 3)] was adduced from deuterium scrambling results[4f] and NMR studies. They methylated 2,4,6-trideuteriotoluene[4l] using methyl bromide and $AlCl_3$ and claimed that "with respect to the isomer distribution of the products...in the case of 2,4,6-trideuteriotoluene the deuterium content (analyzed by NMR spectroscopy and GC-mass spectrometry)...exceeded by about 24% that expected assuming that no intramolecular methyl and hydrogen−deuterium shifts took place prior to product formation."[4f] It is not clear how these conclusions were reached because no details of the isotope analyses were provided. Both toluene and the xylenes produce large M-1 (∼50%) and M-2 (∼14%)

Scheme 2. Expanded Version of Olah's Proposed Mechanism for Arenium Ion Rearrangement



peaks,[26a] so MS determination of deuterium loss (if any) is nearly impossible[26b] because the M-2 peak due to any "real" D-loss is significantly enriched by M-1 contribution from the M-1 peak.

The rearranged arenium ion, **III**, (Scheme 2, an extended version of Scheme 1) could lose either H^+ or D^+ to form **IV** or **V**, respectively. The relative yields of **IV** and **V** depend on the isotope effect (k_H/k_D values of 1.5−1.6 have been reported for hydrogen loss α to a carbocation).[27] Additionally, migration of the D-atom from the *ipso* position of **I** should predominate over alkyl migration. A pathway *involving hydrogen migration* was proposed,[4f] and attempts were made to detect deuterium migration and, by inference, alkyl migrations. Such an inference is dubious because hydrogens and deuteriums undergo equilibration in the parent ion generated on electron impact during MS analyses.[26] Thus, it may not be possible to conclude whether H/D scrambling occurred during the actual F−C experiment or during the subsequent MS analyses. Also "the F-C reaction conditions which were used do not allow quantitative evaluation of the data as some acid-catalyzed intermolecular hydrogen-deuterium exchange can take place".[4f] Schemes 1 and 2 predict a lower deuterium content, rather than an excess, for direct alkylation at C-3 for the *meta* isomer; thus, it would not appear that the *excess* deuterium detected bears any direct relationship to *alkyl* rearrangements.[28]

Ortho and *para* arenium ions do rearrange in HF−SbF_5 into the *meta* isomer,[29a] but (1) the lifetimes of arenium ions are much longer in strongly acidic media than in the standard F−C alkylations, where the more basic counterions could abstract protons before rearrangements could occur, (2) the order (methyl ≈ ethyl > benzyl) cited[4h] is inconsistent with the aptitudes for migration of alkyl groups to electron-deficient centers,[30] and (3) hydrogen shifts can occur independently of alkyl shifts, so H-isotope scrambling cannot be linked directly with alkyl shifts or *meta* substitution. Moreover, even small errors in the (low) yield of the *meta* isomer (∼2.8−6.2%)[4,5] may compromoise the observed data.

Reaction Mechanism.[1d] No hydrogen isotope effect was detected ($k_T/k_B = 2.34 \pm 0.08$) in fully deuterated solvents, in $C_6H_6 + C_7D_8$, and in $C_6D_6 + C_7H_8$, so proton-loss in the deaminative benzylations is not a significant part of the rate-determining step.[31] The data in Table 1 show that the term $[6/5(k_T/k_B)/2/3(o + p)/m]$ is nearly constant at unity. This suggests that the methyl group of toluene exerts a similar effect on both inter- and intramolecular selectivity. It would appear that the same transition states that determine the intramolecular selectivity [those leading to **12** and **13** in conjunction with the transition state leading to **11** (a benzene-like transition state)] also determine the intermolecular selectivity in conjunction with the transition state for the alkylation of benzene;[1d] the activation barrier differences (presumably with respect to σ-complex intermediates)[3c] for reaction with benzene and with toluene at the *o, m, p* positions would thus determine both types of selectivity (eq 3). This interpretation provides a conceptual basis for the BSR, and it may be applicable to other electrophilic substitutions that follow that relationship.[1d]

Thus the mechanism for the F−C benzylation reaction involves a rate-determining reaction between the electrophile and the aromatic substrate that proceeds via a single σ-type transition state to the σ-complex or arenium ion (**11**−**13**). The activation energy barrier differences in the transition states for the formation of these σ-complexes determine both types of selectivity. The complexes rearomatize by rapid proton loss to form the substituted aromatics **4**, **5** (eq 3) (isomerizations of the complexes do not occur).[1d]

Deaminative Benzylation of Benzene−Anisole. The decomposition of the nitrosoamide **1b** in mixtures of benzene−anisole at 80 °C has been previously reported.[1b] The data[1b] show that (1) the product distribution is independent of the relative amount of the aromatic substrates and the presence of base, (2) as with the benzene−toluene system, the relative rate k_A/k_B (5.23 ± 0.11) is significantly lower than the values (∼14−18) obtained from the standard F−C approach,[4f] and (3) the yield of the *meta* isomer via deamination (2.1%) is larger than that reported for the standard F−C approach (<0.3%).[4f] These observations are consistent with the earlier conclusions that the less selective benzyl cations are involved in the deaminative but not in the standard F−C benzylations.[1b]

It is not possible to apply the BSR to reactions in which the substituent that is varied (in the present case ,Me to MeO) is on the nucleophile since two different slopes (1.31 and 0.94,[32] respectively) are involved. Selectivity plots, e.g., log $6/5(k_X/k_B)$ vs log % *meta* also yield poor linearity when both sets of data are plotted together. In contrast, if the two families of data are co-plotted using log(6/5)-k_X/k_B vs log % *para* − log[1/3(100 − % *ortho*)], a good straight line ($R^2 = 0.912$) is obtained (Figure 6). At infinite reactivity, log(6/5)$k_X/k_B = 0$ and from Figure 6, log % *para* − log[1/3(100 − % *ortho*)] = 0.095 (the limiting

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[26] (a) Baldwin, M. A.; McLafferty, F. W.; Jerina, D. M. *J. Am. Chem. Soc.* **1975**, *97*, 6169−6174. (b) Biemann, K. *Mass Spectrometry: Organic Chemical Applications*; McGraw-Hill Book Company, Inc.: New York, 1962; p 209.

[27] Silver, M. S. *J. Am. Chem. Soc.* **1965**, *83*, 3487.

[28] If arenium ion rearrangements of the type postulated by Olah[4f] had occurred, then the *meta* isomer would possess much less than 3 atoms D per molecule, especially in light of the sizable k_H/k_D value (1.5−1.6)[27] that implies that ∼60% of the deprotonations of **III** would result in residual D-incorporation. Conversely, both the *ortho* and *para* isomers would contain more than 2 atoms D per molecule.

[29] Koptyug, V. A. *Contemporary Problems in Carbonium ion Chemistry III: Arenium Ions-Structure and Reactivity*; Springer-Verlag: New York, 1984; (a) p 164; (b) p 159.

[30] Hedaya, A. E.; Winstein, S. *J. Am. Chem. Soc.* **1967**, *89*, 1661−1672.

[31] An H/D isotope effect of 1.13 has been reported for standard F−C benzylations.[4a]

[32] From the σ^+ constants,[16] the theoretical *b* value for the benzene−anisole system is 0.94.

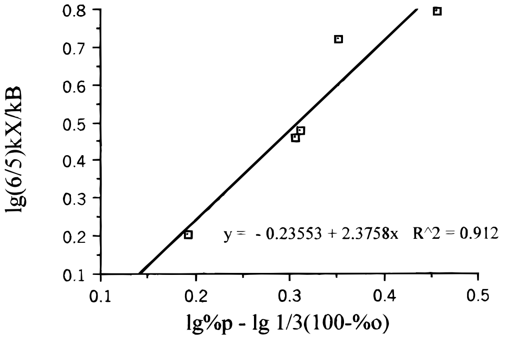

Figure 6. Double log plot of the statistically corrected k_X/k_H (relative rate ratio) vs log % p − log 1/2(100 − % o).

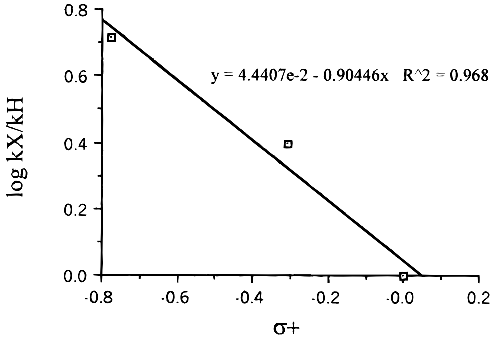

Figure 7. Plot of log k_X/k_H vs σ^+ for deaminative benzylation of benzene/cosolvent (toluene, anisole) at 80 °C.

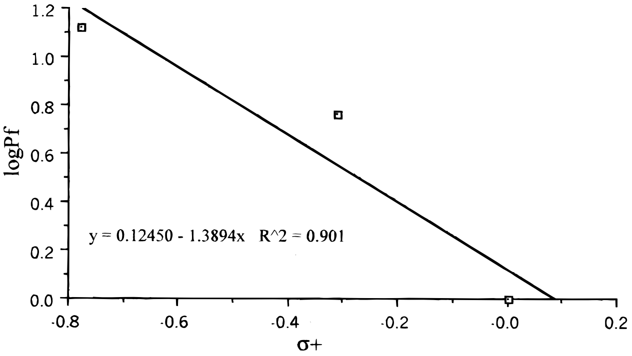

Figure 8. Plot of log p_f vs σ^+ for deaminative benzylation of anisole, toluene, and benzene using *N*-benzyl-*N*-nitrosobenzamide at 80 °C. The p_f is defined as $p_f = 6\ (k_X/k_H)(\%\ para/100)$; X = OMe, Me, H.[21]

value = 0). [A similar plot (not shown) of the data from the benzene−toluene system is also linear ($R^2 = 0.915$) with intercepts at (0, −0.40) and (0.13, 0)]. A Hammett-type plot (Figure 7) of log k_X/k_H vs σ^+ for X = MeO, Me, H also yields a very good straight line ($R^2 = 0.968$) of slope $\rho = -0.90$. The modestly large negative value is consistent with the rate-determining formation of an arenium ion in the F−C reaction. A related plot (Figure 8) of log p_f [= log(k_X/k_H) (% *para*/100) (6)] vs σ^+ is also linear ($R^2 = 0.901$).

Deaminative *vs* Standard Friedel−Crafts Benzylation. The deaminative F−C benzylation reaction via *N*-nitrosoamides is superior to the standard route because in the former approach (1) the identity of the electrophile is known; (2) the electrophile is a reactive benzyl cation; (3) the reaction is under kinetic control, i.e., no isomerizations, disproportionations, or overalkylations occur; (4) no catalysts are required and the reactions are unimolecular and homogeneous; and (5) the chemistry is simple and produces minimal side reactions. These properties make the deaminative approach an ideal one for synthetic and mechanistic studies of the F−C reaction.

Experimental Section

General Methods and Materials. Spectra were recorded on 300 MHz FT-NMR, FT-IR, and UV−Vis spectrometers. The gas chromatography data were obtained using a flame ionization detector. A 30 m SE−30 column with i.d. 0.25 mm and film thickness 0.25 μm was used for GC analyses. Helium was used as the carrier gas. GC data for the 4-R-substituted diphenylmethanes and methydiphenylmethanes were obtained at 145 °C/13 psi (for R = H, Me, Cl) and at 160 °C/10 psi (for R = NO_2). All relative response factor data were obtained using the method of Rosie and Grob[33] under conditions identical to those used for the respective analyses. All syntheses and reactions of the *N*-nitrosoamides were performed in the dark; in many instances, reactions were performed in evacuated sealed NMR tubes. TLC analyses were performed on UV-fluorescent silica gel plates unless otherwise stated. Commercial reagents were used without further purification unless otherwise stated.

Stability of the Precursors. Handling and Storage. *N*-Nitrosoamides in addition to being thermolabile are labile in the presence of acids, bases, and moisture. As a result, the dry, neutral oils were stored at −25 °C in desiccators. The compounds used in this study could be stored in this fashion for at least 1 month before detectable decomposition into ester occurred. The half-lives of these compounds vary from ∼5 h (for **1e**) to ∼40 days (for **1a**) at 25 °C in benzene−toluene. All compounds were handled in the dark. **Caution!** Nitrosoamides should be handled with extreme care because of their possible mutagenicity[34a] and carcinogenicity (local and systemic).[34b] Efficient fume hoods and appropriate personal protection (chemical-resistant gloves, safety glasses, lab coat, etc.) are recommended when handling these compounds.

2-, 3-, and 4-Methyldiphenylmethanes. General method and ^{1}H NMR data previously reported in ref 1a.

Other 4-Substituted Diphenylmethanes (substituent = Me, Cl) and Isomeric 4-Substituted Phenylmethyl Toluenes (substituent = Me, Cl, NO_2). General method and GC data previously reported in ref 1a.

4-Nitrodiphenylmethane. General method and ^{1}H NMR data previously reported in ref 1a.

2-Methoxy- and 4-Methoxydiphenylmethanes. General method and ^{1}H NMR data previously reported in ref 1a.

Relative Response Factor Analyses. Data previously reported in ref 1a.

2,4,6-Trideuteriotoluene. This compound was prepared from *m*-toluidine (1.07 g, 0.01 mol) by exchanging the hydrochloride with D_2O [^{1}H NMR (D_2O) δ 3.86 (s, 3H), 8.75, (m, 2H), 8.84 (s, 2H), 8.91 (m, 1H)] in an evacuated, sealed tube.[35] Two "pre-exchanges" (N−H to N−D) were performed, each with fresh D_2O (2.2 cm^3, 0.12 mol) at 25 °C until the N−H signal at δ 6.42 was absent in the ^{1}H NMR spectrum. Two C−H to C−D exchanges were performed next with fresh D_2O (2.2 cm^3, 0.12 mol) at 100 °C. The resulting *N*,*N*,*N*-trideuterio-2,4,6-trideuterio-3-toluidinium hydrochloride [^{1}H NMR (D_2O) δ 3.86 (s, 3H), 8.90 (s, 1H)] was then "post-exchanged" twice, with fresh H_2O (2.2 cm^3, 0.12 mol) [^{1}H NMR (D_2O) δ 3.86 (s, 3H), 6.42 (s, 1H), 8.75 (m, 2H), 8.84 (s, 2H), 8.91 (m, 1H)]. It was then deaminated with hypophosphorus acid.[36] The reaction mixture was extracted twice with pentane (15 cm^3) and dried over Na_2SO_4, and the dry solution was fractionally distilled (109−112 °C) to yield ∼40% of product. ^{1}H NMR ($CDCl_3$) δ

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7.25 (s, 2H), 2.35 (s, 3H); the % exchange was 96 ± 0.35. We were unable to obtain complete exchange in the *ortho* and *para* positions of the product toluene. However, ^{1}H NMR analyses of the antecedent *N*,*N*,*N*,-trideuterio-2,4,6-trideuteriotoluene in D_2O showed no residual *o*, *p* protons.

***N*-Alkylacetamides, *N*-alkylbenzamides, and *N*-Alkyl-*N*-nitrosoamides (1a−f).** General methods and physical data previously reported in ref 1a.

***p*-Dibenzylbenzene.** A solution of *p*-dichloromethylbenzene (200 mg, 1.14 mmol) in benzene (4 cm^3, 44.8 mmol) was added dropwise with stirring to a solution of $TiCl_4$ (0.25 cm^3, 2.28 mmol) in benzene (4 cm^3, 44.8 mmol) at −10 °C. After complete addition the solution was incubated at −10 °C for 6 h. It was then quenched with ice-cold saturated NaCl (5 cm^3), and the organic phase was washed in turn with saturated solutions of $NaHCO_3$ and NaCl. It was then dried over $MgSO_4$, and the dry solution was evaporated in vacuo to yield a colorless (lilac fluorescent) viscous oil that solidified on standing. Recrystallization from acetone yielded white crystals (0.25 g, 85%): mp 85−87 °C (lit.[37] 86−88 °C); IR ($CHCl_3$) 3085, 3050, 3014, 2906, 2950, 1596, 1508, 1480, 1452, 1426 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.94 (s, 4H), 6.91−7.45 (m, 14H); t_R(145 °C/13 psi) min.

Decompositions of *N*-Alkyl-*N*-nitroso in Benzene−Toluene. In a typical run ~5 mg of nitrosoamide and 2 equiv of pyridine were dissolved in 500 μL of solvent (usually equimolar benzene−toluene or a mixture containing it) in an NMR tube, which was then attached to a vacuum line. Prior to evacuation, the solution was frozen in liquid N_2 and then degassed, and finally the NMR tube was evacuated again and flame-sealed while still under vacuum. The sealed tube was then incubated at the necessary temperature until decomposition was complete (as verified by the absence of starting material by NMR).

Silver Hexafluoroantimonate Promoted F−C benzylation. Method 1. (Series A, Table 2) In a typical run 0.5 equiv of the silver salt was added to a solution of 1.5 equiv of 2,6-di-*tert*-butyl-4-methylpyridine in 75 equiv of equimolar benzene−toluene in a round-bottom flask. The benzylating agent in solution in 25 equiv of equimolar benzene−toluene was then added to the stirred solution. Aliquots were removed and quenched in a solution of NaOH (pH ≈ 10) and NaCl in water, and extraction with ether and drying over $MgSO_4$ followed. All manipulations of the reaction mixture were performed in the dark, under dry nitrogen gas. **Method 2. Vacuum Line Technique.** (Series B, Table 3) The silver salt (15 mg, 43.3 μmol) was dried for 2 days at the oil pump, and it was then cooled with liquid nitrogen while still under vacuum. Equimolar benzene−toluene (500 μL) (predried over Na) was distilled from lithium aluminum hydride under vacuum into the cooled receptacle containing the silver salt. Benzyl chloride (10 μL, 86.9 μmol) (freshly distilled and stored over $MgSO_4$) and 4-methyl-2,6-di-*tert*-butylpyridine (35.7 mg, 174 μmol) (freshly sublimed at oil pump vacuum) were also distilled under vacuum into the cooled benzene−toluene/silver salt suspension. The total distillation time was kept below 2 min; the sublimation of the hindered pyridine was assisted by a hot air gun. The suspension was warmed to 0 °C and stirred at that temperature, dry air was readmitted into the system,and aliquots were withdrawn under nitrogen and quenched in ice-cold saturated solutions of NaCl and $NaHCO_3$. The organic phase was extracted with ether and dried over Na_2SO_4.

Demonstration of Kinetic Control. Experiment 1. Part A. *N*-Benzyl-*N*-nitrosobenzamide (**1b**) was decomposed in equimolar benzene−toluene at 40 °C. The run was quenched after 30% completion (determined by NMR) by reducing active nitrosoamide **1b** with 5 equiv of lithium aluminum hydride[38] at 25 °C for 1 day (see **Parts B** and **C**). The resulting suspension was filtered, and the filtrate was washed with water, dried, and analyzed. No nitrosoamide **1b** was present; benzyl alcohol and benzylamine from the reduction of the nitrosoamide **1b** were present. Analysis of the products gave results ($k_T/k_B = 2.52$, % *ortho* = 45.6, % *meta* = 19.6, % *para* = 34.8) that are statistically indistinguishable from those obtained (Table 1) after 100% decomposition. **Part B.** A known mixture of the isomeric methyldiphenylmethanes (MeDPMs) and diphenylmethane (DPM) (ratio of MeDPMs/DPM = 3.00, % *ortho* = 50.0, % *meta* = 22.5, % *para* = 27.5) in equimolar benzene−toluene was treated with an excess of $LiAlH_4$ at 25 °C for 5 days. The resulting suspension was worked up as in **Part A**. Reanalyzis of the solution gave results that were identical to those obtained prior to incubation with $LiAlH_4$. **Part C.** A solution of the nitrosoamide **1b** in toluene was treated with 5 equiv of lithium aluminum hydride as in part A; the subsequent workup was also the same. The resulting solution was analyzed by GC; benzyl alcohol and benzylamine were present. No methyldiphenylmethanes were observed. **Experiment 2.** The product mixture (% ester = 91.5, % hydrocarbon = 8.5, $k_T/k_B = 2.51$, % *ortho* = 43.8, % *meta* = 17.8, % *para* = 38.4) from a fully decomposed sample of *N*-benzyl-*N*-nitrosoacetamide (**1a**) in equimolar benzene−toluene at 80 °C was heated for an additional 2 days at 100 °C. The product distribution (% ester = 91.5, % hydrocarbon = 8.5, $k_T/k_B = 2.50$, % *ortho* = 43.8, % *meta* = 17.7, % *para* 38.5) was essentially unchanged.

Demonstration of the Absence of a Radical Pathway. *N*-Benzyl-*N*-nitrosoacetamide (**1a**) was decomposed at 80 °C in $CDCl_3$, equimolar $CDCl_3$−benzene, and 10:1 (mol/mol) benzene−$CDCl_3$. No monodeuteriomethylbenzene ($PhCH_2D$) was observed[11] [absence of a doublet at δ 2.35 in $CDCl_3$ (^{1}H NMR) and absence of a signal at $t_R = 7.2$ min at 100 °C /5 psi (GC)].

Demonstration of Lack of Overalkylation. Benzylation of benzene yields diphenylmethane; overbenzylation of benzene would be expected to yield the isomeric dibenzylbenzenes with a preponderance of the *para* isomer. *p*-Dibenzylbenzene was not observed from the deaminative benzylation of benzene−toluene (absence of signal at t_R = min (145 °C/13 psi) and absence of a singlet at δ 3.72 in the ^{1}H NMR spectrum.

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