130.4, 129.6, 128.6, 125.8, 80.2 (C2), 55.6 (OCH_3), 28.8, 15.5, 8.1, 4.4; IR (film) ν_{max} 1455, 1082, 750 cm^{-1}; MS, m/z (70 eV), 174 (M^+, 8), 173 (12), 158 (16), 149 (25), 143 (80), 142 (100), 141 (55), 129 (52), 128 (87), 127 (22), 116 (39), 115 (61); HRMS calcd for M^+ 174.1045, obsd 174.1046.

1,6-Methano[10]annulene (1) enriched with 9% ^{13}C at the bridging carbon (C11) was prepared from naphthalene according to the method of Vogel et al.[17] but using 9% [^{13}C]chloroform during dichlorocarbene addition to 1,4,5,8-tetrahydronaphthalene: mp 27 °C (lit.[17] mp 27 °C); ^1H NMR (400 MHz) δ 7.44 (m, 4 H), 7.1 (m, 4 H), −0.45 (t, J_{CH} = 142.3 Hz, 2 H, H11); ^{13}C NMR (100 MHz) δ 128.8, 126.2, 114.9 (C1 and 6), 34.9 (C 11, ca. 9-fold enrichment); IR (KBr) ν_{max} 1445, 1397, 1245, 756 cm^{-1}; MS, m/z (70 eV) 143 (12), 142 (M^+, 70), 141 (100), 115 (33); HRMS calcd for $^{13}C_1{}^{12}C_{10}H_{10}$ 143.0816, obsd 143.0817.

Generation and Quenching of Cations. Alcohols **4b** and **6b** (ca. 22 mg) were dissolved in either CH_2Cl_2 (ca. 0.2 mL) or SO_2ClF cooled to <0 °C, and added dropwise to a mixture of FSO_3H/SO_2ClF (1:1 v/v) cooled to <−120 °C (pentane/liquid nitrogen slush) in a 5-mm NMR tube with vortex mixing. The resulting red/brown solutions from both **4b** and **6b** gave identical ^{13}C NMR spectra of **5b**: ^{13}C NMR (100 MHz, CH_2Cl_2, −80 °C) δ 221.9 (d, J = 166 Hz, C2), 147.3 (dd, J = 164, 7 Hz, C5), 146.8 (s, C6a), 140.6 (d, J = 168 Hz, C3), 134.3 (s, C2a), 132.7 (d, J = 166 Hz, C6), 131.3 (dd, J = 168, 7 Hz, C4), 64.1 (t, J = 172 Hz, C1), 52.2 (d, J = 190 Hz, C1a), 44.1 (dd, J = 176, 7 Hz, C7a), 31.7 (t, J = 132 Hz, C7). Larger sized samples (80 mg of **4b**, **6b**) were ionized in FSO_3H/SO_2ClF (1.5 mL) by using special reaction tubes as previously described.[18] These solutions were poured slowly into sodium methoxide/methanol (2.5 M solution, 5 mL) at −80 °C with rapid stirring. The mixtures were allowed to warm to room temperature, and water was added to give a clear solution, which was extracted with pentane. The pentane extracts were dried, filtered, and concentrated under a stream of nitrogen gas to give pale yellow oils. In some cases the oils were chromatographed on silica (CH_2Cl_2 elution) to yield small amounts of purified materials. In this way, 6,7-dihydro-6-methoxy-5*H*-benzocycloheptene (**9**) (6 mg) was isolated as a colorless oil: ^1H NMR (400 MHz) δ 7.13–7.23 (complex m, 4 H), 6.50 (dt, J = 11.7, 1.7 hz, 1 H, H5), 5.86 (dt, J = 11.7, 5.1 Hz, 1 H, H6), 3.73 (m, 1 H, H1), 3.39 (s, 3 H, OCH_3), 3.02 (dd, J = 13.7, 1 Hz, 1 H), 2.92 (dd, J = 13.7, 8.3 Hz, 1 H), 2.60 (dt, J = 17.3, 5.2 Hz, 1 H), 2.37 (dddd, J = 17.3, 7.5, 4.9, 1.7 Hz, 1 H); ^{13}C NMR (100 MHz) δ 136.8, 136.3, (C3,4) 130.3, 129.89, 129.87, 127.9, 127.0, 126.4, 81.6, 56.3, 40.7, 36.4.

Similarly, the *anti*-methyl ether **8b** was recovered.

^{13}C-Labeled 1,6-methano[10]annulene, [11-^{13}C]-**1** (24 mg, 1.7 mmol), was placed in a 5-mm NMR tube together with SO_2ClF (0.1 mL) and cooled in liquid nitrogen. FSO_3H/SO_2ClF (1:1 v/v 0.5 mL) was added to the frozen mixture, and the tube warmed to −120 °C with rapid vortex mixing. A clear orange-red solution was obtained, the ^1H NMR spectrum of which was consistent with that previously reported for **2**;[1] ^1H (400 MHz, −90 °C) δ 7.82 (d, J = 6.2 Hz, 1 H), 7.38 (m, 1 H), 7.21 (d, J = 8 Hz, 1 H), 7.12 (m, 1 H), 6.93 (m, 1 H), 6.79 (m, 1 H), 6.67 (m, 1 H), 3.77 (br d, J = 24.6 Hz, 1 H, h2), 3.23 (d, J = 24.6 Hz, 1 H, H2), 1.53 (d, J = 8.8 Hz, 1 H, H11), 0.88 (d, J = 8.8 Hz, 1 H, H11); ^{13}C NMR (100 MHz, −90 °C) δ 170.9, 160.1, 150.3, 147.4, 139.0, 133.0, 131.9, 126.8, 126.1, 45.8 (relative intensity 12, C2), 39.7 (relative intensity 100, C11).

After warming to −60 °C (2–3 h), the spectra of the solution prepared from ^{13}C-labeled **1** above were recorded and indicated the presence of only one cation [2,7-^{13}C]-**5b**: ^1H NMR (400 MHz, capillary, −60 °C) δ 9.54 (d, J = 7.3 Hz, 1 H) 7.37 (m, 1 H), 7.24 (d, J = 8 Hz, 1 H), 6.96 (m, 1 H), 6.90 (d, J = 7 Hz, 1 H), 3.63 (br s, 1 H) 3.19 (br m, 2 H), 3.05 (br s, 1 H), 2.83 (d m, J = 14 Hz, 1 H, H7), 1.17 (d, J = 9 Hz, H1); ^{13}C NMR (100 MHz, capillary, −60 °C δ (relative intensity, multiplicity, J, assignment) 220.4 (74, d, J = 166 Hz, C2), 146.0, (18, d, C5), 145.5 (s, C6a), 139.3 (25, d, C3), 133.0 (s, C2a), 131.33 (22, d, C6), 130.0 (25, d, C4), 62.5 (20, t, J = 170 Hz, C1), 50.7 (24, d, J = 188 Hz, C1a), 42.7 (18, dd, J = 176, 8 Hz, C7a), 30.4 (100, t, J = 132 Hz, C7).

Quenching of [2,7-^{13}C]-**5b** in NaOMe/MeOH afforded a mixture of **9** and ^{13}C-labeled **7** and **8**: ^1H NMR δ 3.3–3.6 (3 × s, 3 × OCH_3); ^{13}C NMR δ 80.3, 75.9 (2 × C2), 28.8, 29.0 (2 × C7).

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Supplementary Material Available: NMR spectra for compounds **4b**, **7b**, **8b**, **9**, **11**, **12**, and **14** (7 pages). Ordering information is given on any current masthead page.

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Benzyne Generation from Aryl Triflates

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The use of aryl triflates to form arynes as reactive intermediates is described. This allows the first general use of phenols as aryne precursors. Phenyl triflate reacts with LDA at −78 °C to form benzyne, which then reacts with diisopropylamine generating *N,N*-diisopropylaniline. Yields of diisopropylarylamines from aryne intermediates are superior to those previously reported. Regioisomeric ratios are similar to those obtained with use of other benzyne precursors.

Aryl electrophiles have become increasingly important as aryne precursors.[3,4] Classically, benzyne has been generated by the decomposition of diazocarboxylate salts,[5] by the oxidation of 1-aminobenzotriazole,[6] or by the base-catalyzed elimination of hydrogen halide from a halobenzene.[7] The ability to utilize phenols for benzyne

(1) Coe College.
(2) The University of Iowa.
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generation would greatly expand the choice of possible starting materials and accordingly would greatly enhance the synthetic utility of the benzyne intermediate. *o*-Haloaryl tosylates have proven quite useful in this respect.[8] Lithiation of the halide with concomitant elimination affords the aryne intermediate. Similarly, conversion of *o*-silylphenols into the corresponding triflates followed by treatment with fluoride generated benzynes that could be trapped in high yields.[9] This latter approach is aided by the exceptional leaving ability of the triflate anion.[10]

Fleming and Mah demonstrated that aryl benzenesulfonates generate benzyne on treatment with an excess of lithium tetramethylpiperide.[11] However, they concluded that the reaction was not useful when compared to benzyne formation from the corresponding aryl halides. Assuming that this is due, in part, to leaving group effects, it seemed that aryl triflates would offer an almost ideal system for study. Aryl triflates are readily available from the corresponding phenol on reaction with triflic anhydride in the presence of pyridine[10] and are reasonably stable. Herein, we report the first examples of the use of aryl triflates as synthetically useful benzyne precursors.[12]

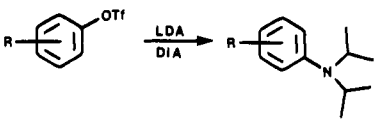
Results and Discussion

To initially test the ability to generate arynes from aryl triflates, the reaction of phenyl triflate with lithium diisopropylamide (LDA) was studied. LDA was chosen because it acts as an excellent base for aryne generation and has been shown to generate the corresponding diisopropylanilines in low to moderate yields. Because the formation of diisopropylanilines from benzyne intermediates is well precedented,[14-16] a comparison of benzyne formation from aryl triflates and aryl halides may readily be made. Treatment of aryl halides with sodium or lithium amides in the presence of alkyl- or dialkylamines has been shown to produce the corresponding anilines via an aryne intermediate.[14,15] Steric encumbrance of the amine was said to lower yields considerably.[15,16] Bunnett found that treatment of phenyl bromide with sodium amide in diisopropylamine (DIA) afforded *N,N*-diisopropylaniline (**2**) in 22% yield.[16] Biehl later showed that extension of the reaction time improved yields to 38%.[15] Caubere demonstrated that solvent effects are important to the outcome of the reaction.[14] Reaction with 2 equiv of sodium *tert*-butoxide, 4 equiv of sodium amide, and 2 equiv of DIA in THF led to a 45% yield of aniline **2**.[14] Use of 4 equiv of sodium amide and 2 equiv of DIA in 2.75:1 THF/HMPA increased the yield to 66%.[14]

We have found that aryl triflates react with LDA in the presence of excess diisopropylamine to form diisopropylanilines in good to excellent yields (Table I). Treatment of phenyl triflate (**1**) with 1.5 equiv of lithium diisopropylamide (LDA) and 10 equiv of DIA in dimethoxyethane (DME) at −78 °C rapidly caused complete consumption of the triflate and led to the formation of *N,N*-diisopropylaniline (**2**) in 67% isolated yield as the only product observed. DME and tetrahydrofuran (THF) appear to be equally suitable solvents for benzyne generation from aryl triflates, affording moderate yields of diisopropylanilines. The yield of aniline **2** under these conditions is equivalent to the highest yield yet reported for this product. Thus, aryl triflates are clearly useful aryne precursors. Yields of diisopropylanilines are improved with diisopropylamine both as an LDA precursor and as solvent (vide infra). Under these conditions 80–98% yields of aniline **2** can be obtained. As shown in the table, aryl triflates act as excellent aryne precursors whether the reaction is run in DIA (70–140 equiv of DIA based on aryl triflate) or in ethereal solvents with excess DIA.

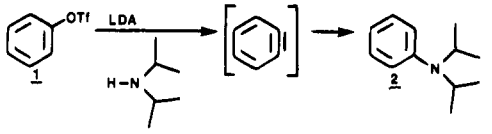
That the substitution reaction follows a benzyne mechanism is clearly indicated by the reaction of *p*-phenylphenyl triflate (**14**) with LDA (entries 13 and 14). In these cases, a mixture of *N,N*-diisopropyl-4-phenylaniline (**15**) and *N,N*-diisopropyl-3-phenylaniline (**16**) was obtained in a 1:1.3 ratio in 67–92% combined yield, depending on the solvent used. No attempt was made to separate the isomers. The yield of the mixture of anilines is improved over that previously reported for the reaction of *p*-chlorobiphenyl with LDA and diisopropylamine, though the ratio of para to meta products is roughly equivalent.[17]

Table I. Reaction of Aryl Triflates with Lithium Diisopropylamide (LDA)[a]



entry	R (aryl triflate)	init BuLi (equiv)	init DIA (equiv)[b]	product ratio ortho:meta:para	isolated yield (%)
1	H (**1**)	1.5	10		67
2		4.5	70[b]		84
3	*p*-Me (**3**)	1.5	10	0:57:43	79
4		2.0	70[b]	0:56:44	93
5	*m*-Me (**6**)	2.0	10	1:59:40	79
6		2.0	70[b]	2:56:42	80
7	*o*-Me (**8**)	2.0	10	23:77:0	79
8		3.0	70[b]	18:82:0	91[c]
9	*p*-MeO (**9**)	2.0	10	0:45:55	77
10		2.0	70[b]	0:42:58	89
11	*o*-MeO (**12**)	2.0	10	0:100:0	74
12		2.0	70[b]	0:100:0	98
13	*p*-Ph (**14**)	2.0	8	0:57:43	67
14		2.0	140[b]	0:57:43	88
15	*o*-Ph (**17**)	4.5	140[b]	7:93:0	78
16	1-naphthyl (**20**)	2.0	70[b]	8:92[d]	86
17	2-naphthyl (**23**)	2.0	70[b]	7:93[d]	86

[a] Reaction of BuLi with diisopropylamine (DIA) in either THF or DME at −78 °C followed by addition of aryl triflate. Initial BuLi and initial DIA refer to the equivalents of reagent added with respect to aryl triflate. No attempt was made to separate isomers. [b] Reaction run with aryl triflate at 0.10–0.05 M with diisopropylamine as solvent. [c] Approximately 2% *o*-methylphenol was also isolated. [d] Ratio of 1-(*N,N*-diisopropylamino)naphthalene (**21**) to 2-(*N,N*-diisopropylamino)naphthalene (**22**).



(8) For a recent example, see: Gribble, G. W.; Perni, R. B.; Onan, K. D. *J. Org. Chem.* **1985**, *50*, 2934–2939.
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Assignment of the structures of the isomers was simplified by the observation that one major product (compound **16**) was obtained from reaction of *o*-triflate **17** under similar conditions (entry 15). The low-resolution mass spectrum (LRMS) (*m/z* 253) and upfield signals in the ^{1}H NMR at δ 1.16 (d, 12 H) and 3.75 (sept, 2 H) confirmed that compound **16** was an isomer of diisopropylphenylaniline. Absorptions in the ^{1}H NMR spectrum of the product mixture at δ 6.80 (ddd, J = 8.3, 2.3, 1.0 Hz, 1 H), 6.90 (dm, J = 7.6 Hz, 1 H), 7.02 (dd, J = 2.1, 2.0 Hz, 1 H), and 7.18 (dd, J = 8.1, 7.8 Hz, 1 H) allowed assignment of the amino-substituted ring of the major product as having meta regiochemistry. Absorptions at δ 7.24 (t, 1 H), 7.34 (dd, 2 H), and 7.50 (d, 2 H) due to the para, meta, and ortho protons, respectively, of the monosubstituted phenyl ring were also observed. In addition, compound **16** displayed a ^{13}C NMR spectrum in agreement with the partial spectrum reported for *N,N*-diisopropyl-3-phenylaniline.[17] The presence of a minor amount of ortho isomer **18** was inferred from the observation of an absorption at δ 1.06 (d, J = 6.6 Hz), as well as lines in the ^{13}C NMR spectrum at δ 22.4, 50.2, 127.1, and 128.6.

In contrast, the GC–LRMS of the product mixture isolated from reaction of LDA with *p*-triflate **14** (entries 13 and 14) indicated the presence of two isomers (*m/z* 253) in a 57:43 ratio. The major isomer was found to coelute (GC) with the *m*-aniline **16** formed from *o*-triflate **17**, and the ^{1}H NMR spectrum of the product mixture contained all of the absorptions assigned to the meta product **16**. In addition, doublets at δ 6.84 (J = 8.7 Hz) and 7.36 (J = 8.8 Hz) were observed, indicating the presence of *p*-diisopropylaniline **15**. These absorptions correspond well with those previously reported for *N,N*-diisopropyl-4-phenylaniline (**15**).[17] Similarly, after absorptions due to the meta product were accounted for, the ^{13}C NMR of the minor isomer could be completely deduced and proved to agree with the partial spectrum reported for *N,N*-diisopropyl-4-phenylaniline.[17] With a similar approach, the structures of *N,N*-diisopropylmethylanilines **4**, **5**, and **7** (entries 3–8) and *N,N*-diisopropylmethoxyanilines **10** and **11** (entries 9–12) were readily assigned.

In addition to aniline formation, reaction of LDA and DIA with triflate **14** in DME (entry 13) afforded a small amount of biphenyl (**19**). There has been some controversy about the mechanism of the reduction of aryl halides in the presence of metal amides. The hydridic nature of LDA, while somewhat rare, has been observed previously.[18] Transfer of an α-hydride from LDA either to the aryl triflate in an S_NAr reaction[19] or, more probably, to the aryne intermediate[20] would afford the products of reduction. Alternatively, Ohashi and co-workers have proposed that reduction occurs through an electron-transfer pathway leading to an aryl radical that is subsequently quenched by the solvent.[17]

Reduction of the benzyne intermediate can be minimized by use of a sufficient excess of diisopropylamine as a trapping agent. As the ratio of DIA to *n*-butyllithium (used to form LDA) is increased, the isolated yield of anilines **15** and **16** increases and the isolated yield of biphenyl decreases (Figure 1). It would appear that while LDA causes formation of benzyne and is also responsible for the reduction of the benzyne, it is diisopropylamine that reacts

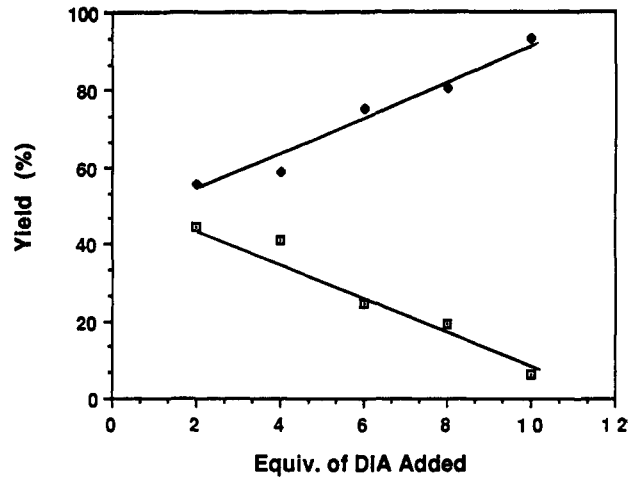
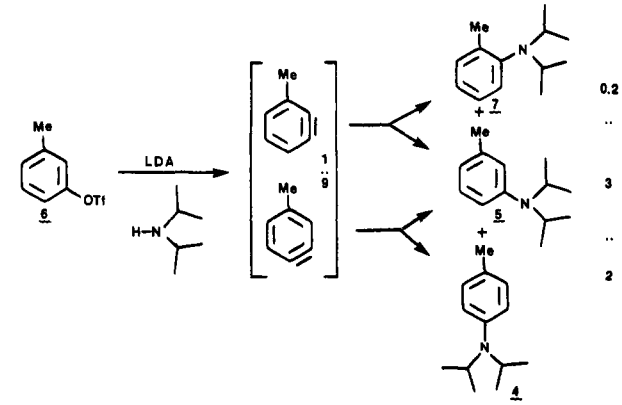


Figure 1. Normalized yields of biphenyl (□) and total diisopropylanilines (♦) with respect to the amount of diisopropylamine (DIA) added for the reaction of *p*-phenylphenyl triflate with 2.0 equiv of BuLi and excess DIA in THF at −78 °C.

with benzyne to form the aniline. Most examples of benzyne formation reported in the table were run with 1.5–2 equiv of *n*-butyllithium and either 10 equiv of diisopropylamine in ethereal solvent or neat diisopropylamine.

In contrast to most benzyne reactions, the choice of base used to convert aryl triflates into the benzyne is critical. Due to the steric constraints of the reagent, LDA has little tendency to react with most aryl triflates at sulfur. Stronger nucleophiles, however, cause displacement at sulfur, generating the corresponding phenoxide anion. For example, treatment of triflate **14** with *n*-butyllithium, $NaNH_2$, sodium acetylide, or 2-lithiofuran followed by an acidic quench returned *p*-phenylphenol in nearly quantitative yield.

Benzyne formation from *m*-methylphenyl triflate (**6**) could in theory proceed by preliminary abstraction of the proton ortho or that para to the methyl group. The ratio of ortho to meta to para products was readily determined by relative areas of the isopropyl methyl doublets (ortho, 0.96; meta, 1.19; para, 1.13), aryl methyl singlets (ortho, 2.31; meta, 2.30; para, 2.27) and isopropyl methine septets (ortho, 3.47; meta, 3.76; para, 3.67) in the ^{1}H NMR. Comparison of the product ratios obtained from reaction of triflate **6** in DIA with those obtained from the ortho and para analogues (entries 4, 6, and 8) suggests that approximately 10% of the deprotonation occurs at the ortho position and 90% occurs at the para position.



1-Naphthyl triflate (**20**) can only form one aryne, which ultimately leads to the formation either 1- or 2-(diisopropylamino)naphthalene (**21** or **22**). Reaction of triflate **20** with 2.0 equiv of LDA in diisopropylamine afforded two

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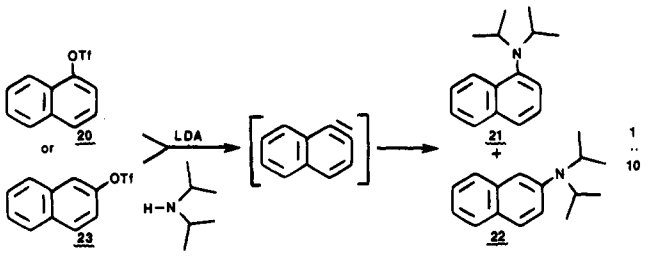

isomeric naphthylamines in a 92:8 ratio (86%) along with a small amount of naphthalene (7–8%). No attempt was made to separate the isomers. Use of ^{13}C NMR to determine the regiochemistry of the major isomer proved to be ambiguous.[21] The structure of the major product could be assigned as amine **22** based on the observation of a broad doublet at δ 7.06 (J = 1.0 Hz) in the ^1H NMR, which may be assigned to the C-1 proton. In addition, doublets at δ 7.55, 7.56, and 7.59 correlate well with absorptions assigned[22] to C-8 (δ 7.51), C-4 (δ 7.54), and C-5 (δ 7.54) for 2-(*N,N*-dimethylamino)naphthalene. Further support for this assignment was obtained from the observation of strong bands in the IR at 820, 805, and 735 cm^{-1}.[23]

In contrast, the minor product showed discernible absorptions in the ^1H NMR at δ 8.55, 7.70, and 7.35. These data along with the observation of a downfield shift for the minor methine carbon (δ 50.1 vs δ 47.8)[21] and an upfield shift for the minor methine proton (δ 3.58 vs δ 3.79) supported the assignment of the minor isomer as amine **21**. The product mixture is of the same regiochemistry as that reported by Gilman and by Huisgen for the conversion of 1-halonaphthalenes into aminonaphthalenes with lithium dialkylamides.[24] Nucleophilic addition to 1-naphthyne occurs largely at the β-position.[24]

2-Naphthyl triflate (**23**) can generate two arynes and, to the degree that 2-naphthyne is formed, should lead to a lower ratio of amine **21** to **22**. Submission of triflate **23** to the reaction conditions afforded a reaction mixture indistinguishable from that obtained from 1-naphthyl triflate. Thus, 2-naphthyl triflate is deprotonated at the C-1, and essentially no 2-naphthyne is formed during the reaction. Exclusive metalation of 2-halonaphthalenes at C-1 has been reported previously.[25]

Conclusions

In conclusion, it has been shown that aryl triflates offer a facile entry into benzyne-mediated reactions. Use of 2–3 equiv of LDA and 7–8 equiv of diisopropylamine in ethereal solvents leads to good yields of diisopropylanilines along with a small amount of the corresponding arene. If diisopropylamine is used as solvent, the yield of aniline is increased by up to 25%. The reaction allows the use of phenols as aryne precursors and thus should be of use in any synthetic schemes involving benzyne. The finding that aryl triflates undergo benzyne formation on treatment with bases should also serve as a warning about possible side effects that might occur during reaction with higher order cuprates.[26] Further studies on the scope and limitations of aniline formation, as well as the extension of the nucleophiles capable of participation in the reaction, and the development of the methodology for the formation of Diels–Alder and dimerization adducts of the benzyne intermediate are currently under way and will be reported in due course.

Experimental Section

^1H and ^{13}C NMR spectra were obtained in $CDCl_3$. Low-resolution GC–mass spectra were obtained at an ionization potential of 70 eV. Capillary gas chromatographic analyses were run on a chromatograph equipped with a 0.53 mm × 5 m methyl silicone column and a flame ionization detector or with a 0.25 mm × 25 m OV-17 column and a flame ionization detector. High-pressure liquid chromatographic analyses were run on a dual-pump chromatograph equipped with a 4.6 mm × 250 mm 5-μm C_{18} column (Alltech Econosphere), eluting with 80% CH_3CN/20% H_2O and monitoring at 254 nm. Thin-layer chromatography plates (EM silica gel 60F-254) were stored under an atmosphere of triethylamine for at least 24 h prior to use. Radial chromatography was performed on a Harrison Research Chromatotron. No attempt was made to separate isomeric anilines. Combustion analyses were performed by Desert Analytics, Tucson, AZ. Attempts to obtain satisfactory combustion analyses for compounds **4**, **5**, **7**, **10**, and **11** were unsuccessful (C <2.5% less than theoretical and N <±0.7% of theoretical). All mixtures of diisopropylanilines were >95% pure as determined by GC, HPLC, TLC, ^1H NMR, and ^{13}C NMR analyses. Absorptions in the ^{13}C NMR are somewhat concentration dependent. All spectral information reported is for the mixture of isomers described in the table.

Phenyl triflate,[27] *p*-methylphenyl triflate,[28] *m*-methylphenyl triflate,[29] *o*-methylphenyl triflate,[29] *p*-methoxyphenyl triflate,[30] *o*-methoxyphenyl triflate,[27] *p*-phenylphenyl triflate,[31] *o*-phenylphenyl triflate,[31] 1-naphthyl triflate,[30] and 2-naphthyl triflate[28] were prepared according to literature methods.[10,32] Tetrahydrofuran (THF) and 1,2-dimethoxyethane (DME) were doubly distilled from potassium. Diisopropylamine (DIA) was freshly distilled from CaH_2. All reactions were performed under positive argon or nitrogen pressure.

General Procedure. *N,N*-Diisopropylaniline (2; Entry 1). To a solution of diisopropylamine (2.8 mL, 20.0 mmol, 10 equiv) in DME (20 mL) at −78 °C was added *n*-BuLi (1.13 mL, 2.66 M in hexanes, 3.0 mmol, 1.5 equiv). This mixture was allowed to stir at −78 °C for 15 min, and then a solution of phenyl triflate (0.45 g, 2.0 mmol) in DME (5 mL) was slowly added. The deep red mixture was allowed to stir at −78 °C for 1.5 h after which GC analysis indicated the complete consumption of starting material. Separation between water and 1:1 ether/hexanes, followed by washing of the organic phase with water and a saturated NaCl solution, drying (Na_2SO_4), and concentration afforded an orange-brown oil. Bulb-to-bulb distillation at 60–70 °C (0.4 mmHg) gave **2** (0.24 g, 67% yield) as a colorless oil [lit.[14] bp 95–96 °C (11 mmHg)]: TLC (hexanes) R_f 0.75; IR (neat) 3080, 3040, 1580, 1475, 730, 680 cm^{-1}; ^1H NMR (360 MHz) δ 1.19 (d, 12 H, J = 6.8 Hz), 3.76 (sept, 2 H, J = 6.7 Hz), 6.76 (t, 1 H, J = 7.3 Hz), 7.16 (d, 2 H, J = 8.4 Hz), 7.18 (dd, 2 H, J = 8.5, 7.3 Hz); ^{13}C NMR

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(91 MHz) δ 21.3 (4 C), 47.6 (2 C), 118.3, 119.5 (2 C), 128.4 (2 C), 148.0; LRMS *m/z* (relative abundance) 177 (14%).

Reactions run in ethereal solvents often afforded minor amounts of reduced starting material. When not volatile, these were readily removed by chromatography (Chromatotron; hexane, 1% triethylamine/hexane, 2% triethylamine/hexane). Reactions run with DIA as solvent did not contain these impurities, and the products could be purified by bulb-to-bulb distillation at the specified oven temperature.

***N,N*-Diisopropyl-4-methylaniline and *N,N*-diisopropyl-3-methylaniline (4 and 5; entries 3 and 4)**: oven temperature 70–75 °C (0.3 mmHg) [lit.[33] bp 110 °C (14 mmHg)]; TLC (hexane) R_f 0.75; IR (neat) 3045, 1585, 1555, 1495, 1475, 1440, 780, 740, 720, 690, 675 cm^{-1}.

Para isomer (4): ^{1}H NMR (300 MHz) δ 1.13 (d, *J* = 6.7 Hz, 12 H), 2.27 (s, 3 H), 3.67 (sept, *J* = 6.6 Hz, 2 H), 6.85 (d, *J* = 8.5 Hz, 2 H), 7.00 (d, *J* = 8.6 Hz, 2 H); ^{13}C NMR (75 MHz) δ 20.5, 21.3 (4 C), 47.8 (2 C), 115.2, 122.0 (2 C), 128.9 (2 C), 145.2; LRMS *m/z* (relative abundance) 191 (23%); HRMS for $C_{13}H_{21}N$, calcd 191.1674, found 191.1679.

Meta isomer (5): ^{1}H NMR (300 MHz) δ 1.19 (d, *J* = 6.6 Hz, 12 H), 2.30 (s, 3 H), 3.76 (sept, *J* = 6.8 Hz, 2 H), 6.59 (br d, *J* = 7.2 Hz, 1 H), 6.70–6.75 (m, 2 H), 7.08 (dd, *J* = 9.0, 7.4, 1 H); ^{13}C NMR (75 MHz) δ 21.3 (4 C), 21.9, 47.6 (2 C), 116.6, 119.2, 120.1, 128.2, 138.0, 148.0; LRMS *m/z* (relative abundance) 191 (32%); HRMS for $C_{13}H_{21}N$, calcd 191.1674, found 191.1669.

No attempt was made to separate the isomeric anilines. The ratio of products was determined by relative areas of the doublets at δ 1.1–1.2, singlets at δ 2.2–2.3, septets at δ 3.6–3.7, and aryl peaks at δ 6.7 (meta) and δ 7.0 (para). Anilines 4 and 5 could not be separated by GC.

The spectral properties of the product mixture obtained from *m*-methylphenyl triflate (entries 5 and 6) were similar to those obtained from *p*-methylphenyl triflate. The identification and quantification of the ortho isomer (7) was accomplished as described for entries 7 and 8. GC analyses of the product mixtures obtained from these reactions indicated <5% ortho product.

***N,N*-Diisopropyl-3-methylaniline and *N,N*-diisopropyl-2-methylaniline (5 and 7; entries 7 and 8)**: oven temperature 65–73 °C (0.4 mmHg); TLC (hexane) R_f 0.82, 0.94; IR (neat) 3080, 3040, 3020, 1580, 1555, 1475, 1450, 1430, 740, 690, 675 cm^{-1}.

Ortho isomer (7): ^{1}H NMR (300 MHz) δ 0.96 (d, *J* = 6.5 Hz, 12 H), 2.31 (s, 3 H), 3.47 (sept, *J* = 6.4 Hz, 2 H), 7.02–7.21 (m, 4 H); ^{13}C NMR (75 MHz) δ 19.0, 21.0 (4 C), 49.7 (2 C), 124.7, 125.2, 129.3, 130.2, 140.2, 146.7; LRMS *m/z* (relative abundance) 191 (25%); HRMS for $C_{13}H_{21}N$, calcd 191.1674, found 191.1676.

The ^{1}H NMR and ^{13}C NMR spectra and LRMS and HRMS for meta isomer 5 are identical with those reported for entries 3 and 4. No attempt was made to separate the isomeric anilines. The ratio of products was determined by relative areas of the doublets at δ 0.9–1.2, singlets at δ 2.2–2.3, and septets septets at δ 3.4–3.7. GC analyses were consistent with the ratios determined by NMR spectroscopy.

***N,N*-Diisopropyl-4-methoxyaniline and *N,N*-diisopropyl-3-methoxyaniline (10 and 11; entries 9 and 10)**: oven temperature 85–88 °C (0.25 mmHg) [lit.[34] bp 110–113 °C (4 mmHg)]; TLC (hexane) R_f 0.57, 0.65; IR (neat) 3090, 3000, 1585, 1500, 1485, 1440, 1200, 1150, 1120, 820, 790, 760, 720, 660 cm^{-1}.

Para isomer (10): ^{1}H NMR (300 MHz) δ 1.03 (d, *J* = 6.4 Hz, 12 H), 3.77 (sept, *J* = 6.9 Hz, 2 H), 3.78 (s, 3 H), 6.79 (d, *J* = 8.9 Hz, 2 H), 6.97 (d, *J* = 8.9 Hz, 2 H); ^{13}C NMR (75 MHz) δ 21.3 (4 C), 48.6 (2 C), 55.3, 113.3 (3 C), 127.4 (2 C), 155.4; LRMS *m/z* (relative abundance) 207 (30%); HRMS for $C_{13}H_{21}NO$, calcd 207.1623, found 207.1628.

The ^{1}H NMR and ^{13}C NMR spectra, as well as LRMS and HRMS for meta isomer 11 were identical with those reported for entries 11 and 12. No attempt was made to separate the isomeric anilines. The ratio of products was determined by relative areas of the doublets at δ 1.0–1.2, septets at δ 3.5–3.7, and aryl multuplets at δ 6.3–7.1. GC analyses were consistent with the ratios determined by NMR spectroscopy.

***N,N*-Diisopropyl-3-methoxyaniline (11; entries 11 and 12)**: oven temperature 85–90 °C (0.4 mmHg) [lit.[34] bp 110–113 °C (4 mmHg)]; TLC (hexane) R_f 0.65; IR (neat) 3060, 3020, 1590, 1550, 1470, 1440, 1200, 1120, 800, 720, 660 cm^{-1}; ^{1}H NMR (300 MHz) δ 1.27 (d, *J* = 7.1 Hz, 12 H), 3.54 (sept, *J* = 6.8 Hz, 2 H), 6.32 (ddd, *J* = 8.4, 2.4, 1.0 Hz, 1 H), 6.43 (dd, *J* = 2.4, 2.4 Hz, 1 H), 6.50 (ddd, *J* = 8.3, 2.4, 1.0 Hz, 1 H), 7.09 (dd, *J* = 8.2, 8.2 Hz, 1 H); ^{13}C NMR (75 MHz) δ 21.2 (4 C), 47.4 (2 C), 54.9, 102.3, 104.9, 111.5, 128.8, 149.3, 160.0; LRMS *m/z* (relative abundance) 207 (27%); HRMS for $C_{13}H_{21}NO$, calcd 207.1623, found 207.1620.

***N,N*-Diisopropyl-4-phenylaniline and *N,N*-diisopropyl-3-phenylaniline (15 and 16; entries 13 and 14)**: oven temperature 190 °C (1.2 mmHg) [lit.[17] 170–185 °C (0.5 mmHg)]; TLC (hexane) R_f 0.66; IR (neat) 3080, 3050, 3010, 1580, 1480, 1220, 850, 760 (sh), 730, 680 cm^{-1}.

Para isomer (15): ^{1}H NMR (300 MHz) δ 1.17 (d, *J* = 6.8 Hz, 12 H), 3.75 (sept, *J* = 6.8 Hz, 2 H), 6.84 (d, *J* = 8.8 Hz, 2 H), 7.10–7.30 (m, 3 H), 7.36 (d, *J* = 8.7 Hz, 2 H), 7.48 (dd, *J* = 7.5 Hz, 2 H); ^{13}C NMR (75 MHz) δ 21.3 (4 C), 47.5 (2 C), 118.2 (2 C), 126.0, 126.2 (2 C), 127.2 (2 C), 128.6 (2 C), 130.0, 141.2, 147.5; LRMS *m/z* (relative abundance) 253 (22%).

Meta isomer (16): ^{1}H NMR (300 MHz) δ 1.16 (d, *J* = 6.7 Hz, 12 H), 3.75 (sept, *J* = 6.8 Hz, 2 H), 6.80 (ddd, *J* = 8.3, 2.3, 1.0 Hz, 1 H), 6.90 (dm, *J* = 7.6 Hz, 1 H), 7.02 (dd, *J* = 2.1, 2.0 Hz, 1 H), 7.18 (dd, *J* = 8.1, 7.8 Hz, 1 H), 7.24 (t, *J* = 7.2 Hz, 1 H), 7.34 (dd, *J* = 7.2, 7.2 Hz, 2 H), 7.50 (d, *J* = 7.4 Hz, 2 H); ^{13}C NMR (75 MHz) δ 21.4 (4 C), 47.6 (2 C), 117.2, 118.0, 118.1, 126.9, 127.1 (2 C), 128.6 (2 C), 128.8, 141.6, 142.2, 148.4; LRMS *m/z* (relative abundance) 253 (32%).

The ^{1}H NMR and ^{13}C NMR spectra of 15 and 16 are in agreement with the partial data previously reported.[17] No attempt was made to separate the isomeric anilines. The ratio of products was determined by GC analysis assuming equal FID response factors for 15 and 16.

***N,N*-Diisopropyl-3-phenylaniline and *N,N*-diisopropyl-2-phenylaniline (16 and 18; entry 15)**: oven temperature 82 °C (0.15 mmHg); TLC (hexane) R_f 0.66; IR (neat) 3070, 3040, 1595, 1515, 1480, 750, 690 cm^{-1}.

The ^{1}H NMR and ^{13}C NMR spectra and the LRMS for meta isomer 16 were identical with those reported for entries 13 and 14. No attempt was made to separate the isomeric anilines. The ortho and meta isomers could not be separated by gas chromatography. The presence of the ortho isomer (18) was inferred by the observation of an absorption at δ 1.06 (d, *J* = 6.6 Hz) in the ^{1}H NMR, as well as lines in the ^{13}C NMR at δ 22.4, 50.2, 127.1, and 128.6. The ratio of products was determined by relative areas of the doublets at δ 1.06 and 1.16.

1-(*N,N*-Diisopropylamino)naphthalene and 2-(*N,N*-diisopropylamino)naphthalene (21 and 22; entry 16): oven temperature 105–110 °C (0.2 mmHg) [lit.[24b] bp 95–110 °C (0.01 mmHg)]; TLC (hexane) R_f 0.66; IR (neat) 3060, 1620, 1590, 1500, 1470, 820, 805 (sh), 735 cm^{-1}. Anal. Calcd for $C_{16}H_{21}N$: C, 84.53; H, 9.31; N, 6.16. Found: C, 84.26; H, 9.31, N, 6.08.

2-Isomer (22): ^{1}H NMR (300 MHz) δ 1.18 (d, *J* = 6.8 Hz, 12 H), 3.79 (sept, *J* = 6.7 Hz, 2 H), 7.06 (br d, *J* = 1.0 Hz, 1 H), 7.10–7.17 (m, 2 H), 7.26 (ddd, *J* = 7.0, 6.8, 1.1 Hz, 1 H), 7.55 (d, *J* = 6.6 Hz, 1 H), 7.56 (d, *J* = 9.2 Hz, 1 H), 7.59 (d, *J* = 8.2 Hz, 1 H); ^{13}C NMR (75 MHz) δ 21.6 (4 C), 47.8 (2 C), 113.4, 122.0, 122.5, 125.8, 126.4, 127.3, 127.5, 127.7, 134.8, 146.2; LRMS *m/z* (relative abundance) 227 (43%); HRMS for $C_{10}H_{21}N$, calcd 227.1674, found 227.1673.

No attempt was made to separate the isomeric anilines. The presence of the α-isomer was inferred by the observation of absorptions at δ 1.14 (d, *J* = 6.4 Hz), 3.58 (sept, *J* = 6.4 Hz), 7.3–7.4 (m), 7.6–7.7 (m), and 8.5–8.6 (m) in the ^{1}H NMR, as well as lines in the ^{13}C NMR at δ 50.1, 125.2, and 125.6 and a peak in the GC–LRMS with *m/z* (relative abundance) 227 (26%) (HRMS for $C_{10}H_{21}N$, calcd 227.1674, found 227.1673). The ratio of products was determined by relative areas of the septets at δ 3.5–3.8. GC and GC–MS and HPLC analyses were consistent with the ratios determined by NMR spectroscopy. The spectral properties of the product mixture obtained from 2-naphthyl triflate (entry 17) were identical with those obtained from 1-naphthyl triflate.

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Supplementary Material Available: ^1H and ^{13}C NMR spectra for the diisopropylaniline mixtures isolated from reactions described in entries 2, 4, 6, 8, 10, 12, and 14–16 of Table I (18 pages). Ordering information is given on any current masthead page.

Optically Active Building Blocks from the SPAC Reaction: A Completely Asymmetric Synthesis of (4*S*-*cis*)-5-(Cyclohexylmethyl)-4-hydroxy-2-pyrrolidinone, a Statine Analogue

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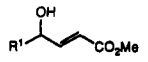
Factors that govern chemical and optical yields of methyl γ-hydroxy-α,β-unsaturated esters 1 formed in reactions of optically active sulfinylacetates 2 with aldehydes (the "SPAC" reaction) are defined. Racemic samples of these chirons (1) can be resolved via acylations mediated by crude preparations of the lipase *Pseudomonas* K-10 in organic solvents. Combinations of asymmetric SPAC reactions with these biocatalytic resolutions provide routes to highly optically active esters 1 in good yields. This methodology is applied in a completely asymmetric synthesis of (4*S*-*cis*)-5-(cyclohexylmethyl)-4-hydroxy-2-pyrrolidinone (15), a cyclic derivative of (3*S*,4*S*)-4-amino-5-cyclohexyl-3-hydroxypentanoic acid (ACHPA).

γ-Hydroxy-α,β-unsaturated esters 1 are versatile synthons.[2-9] The hydroxyl group of these compounds can be transformed into a leaving group and displaced with inversion of configuration via S_N2 processes, or with net retention via transient formation of π-allyl complexes.[10,11] Anti S_N2' displacement of the leaving group from such substrates is also well documented and provides access to α-substituted-β,γ-unsaturated esters.[12,13] Furthermore, the chiral hydroxymethine fragment can exert a powerful stereodirecting influence and this has been used in conjugate additions and similar reactions to produce β-functionalized derivatives.[14-22]



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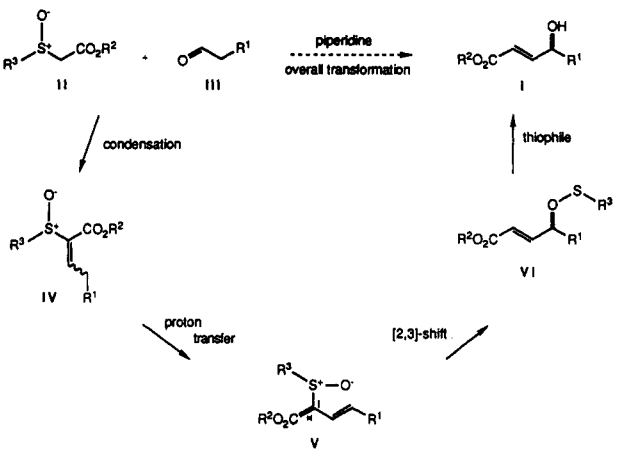
Scheme I. SPAC Reaction. Intermediate V Preferentially Adopts the Conformation Shown Due to 1,3-Allylic Strain



In view of this potential it is unfortunate that substances 1 in a high state of enantiomeric purity have been relatively inaccessible. Optically active samples are not, for instance, easily obtained via Sharpless' kinetic resolution/epoxidation[23] due to the deactivating influence of the ester substituent. The most practical approach to these chirons has been to react optically active α-hydroxy aldehyde

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