

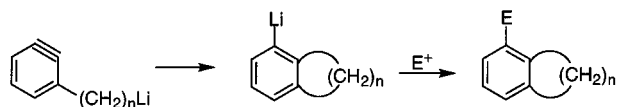
Generation and Cyclization of a Benzyne-Tethered Alkylolithium: Preparation of 4-Substituted Indans

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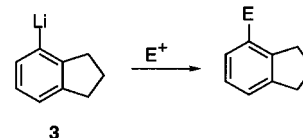
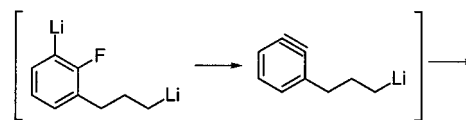
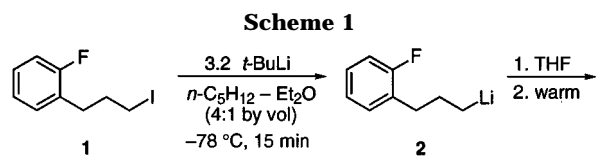
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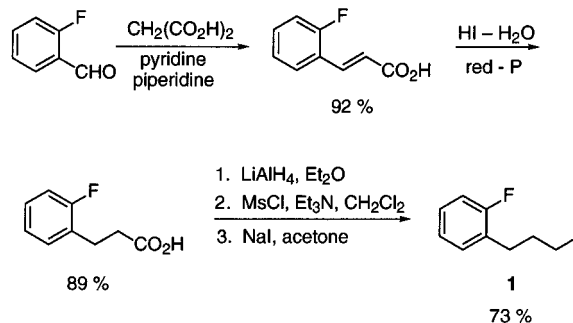
The intramolecular addition of an organolithium to a tethered benzyne intermediate, illustrated below, offers a conceptually simple route to functionalized benzo-fused carbocycles. Although intermolecular addition of an organolithium to a benzyne is a well characterized process,¹ and while intramolecular trapping of benzyne intermediates by tethered heteroatomic nucleophiles or a stabilized carbanions, first demonstrated by Bunnett² and Huisgen,³ has been widely used for the construction of a variety of systems,⁴ the possibility of effecting carbon–carbon bond formation by cyclization of a benzyne-tethered organolithium appears not to have been explored. In light of the facile 5-exo-dig cyclization of simple acetylenic alkylolithiums,⁵ we were prompted to investigate the 5-exo cyclization of a benzyne-tethered alkylolithium. Herein we report that this methodology may be used to advantage for the preparation of 4-substituted indans via cyclization of the benzyne-tethered propylolithium generated from readily available 2-fluoro-1-(3-iodopropyl)benzene (**1**). The novel five-step, one-pot synthetic sequence, summarized in Scheme 1, delivers synthetically pure indans in 60–70% yield.



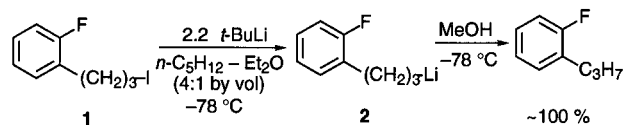
The preparation of 2-fluoro-1-(3-iodopropyl)benzene (**1**) was accomplished in straightforward fashion using classical chemistry as illustrated in Scheme 2. At the inception of this study it was realized that conversion of **1** to a benzyne-tethered propylolithium would involve three discrete steps, each of which finds ample literature precedent: (i) lithium–iodine exchange to give 3-(2-fluorophenyl)propylolithium (**2**),⁶ regioselective abstraction of the proton ortho to the fluorine substituent⁷ in **2** to generate a dilithio species, and (iii) rapid



Scheme 2



loss of LiF to deliver the 1,2-dehydrobenzene intermediate.¹ The first of these steps, the exchange reaction, was easily accomplished following our general protocol.⁶ Thus, treatment of an approximately 0.1 M solution of **1** in dry *n*-pentane–diethyl ether (4:1 by vol) at –78 °C with 2.2 molar equiv of *tert*-butyllithium (*t*-BuLi) cleanly generates the corresponding alkylolithium **2** as demonstrated by the fact that quench of such a reaction mixture with MeOH at –78 °C affords 2-fluoro-1-propylbenzene in essentially quantitative yield.⁸ Ortho lithiation of **2** to produce the dilithio precursor of the benzyne intermediate proved more problematic.



Although fluorobenzene may be regioselectively lithiated at the ortho position by treatment with an alkylolithium,⁷ the fact that **2** is itself an alkylolithium presents an obvious dilemma; the molecule is capable of acting as the base for the ortho-lithiation. As illustrated below, such self-lithiation by intermolecular proton transfer between two molecules of **2**, which occurs when a solution of **2** is warmed, potentially halves the yield of the benzyne intermediate. Fortunately, this difficulty may be circumvented by judicious choice of

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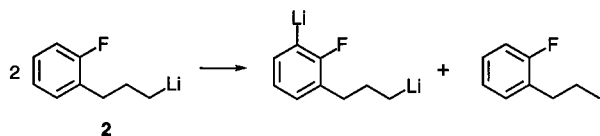
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(8) It might be noted that the second equivalent of *t*-BuLi used for the exchange is not available for ortho-lithiation of **2** since it is rapidly consumed by reaction with the cogenerated *t*-BuI to give isobutane, isobutylene, and lithium iodide.⁹

the alkyllithium and solvent system used for the ortho-lithiation of **2**.



Extensive exploratory studies revealed that regioselective deprotonation may be effected by treatment of **2** with 1 equiv of *t*-BuLi in a solution containing a quantity of THF sufficient to render the *t*-BuLi monomeric.⁹ Apparently, monomeric *t*-BuLi is a much more effective reagent for ortho-lithiation than is **2**, or other primary alkyllithiums.⁷ It should be noted, however, that since ether-solvated, dimeric *t*-BuLi [viz. (*t*-BuLi·2 Et₂O)₂]¹⁰ is apparently required for efficient lithium–iodine exchange,⁶ it is imperative that the initial conversion of **1** → **2** be conducted in the absence of THF.

Given the preliminaries outlined above, optimal conditions for generation and cyclization of the benzyne-tethered alkyllithium were readily established (Scheme 1). Thus, **2** was generated at –78 °C by addition of 3.2 molar equiv of *t*-BuLi to a 0.1 M solution of **1** in *n*-pentane–diethyl ether (4:1 by vol). The reaction mixture was stirred for 15 min at –78 °C to complete the exchange prior to addition of enough dry, deoxygenated THF (ca. 0.5 mL/mmol of substrate) to render the residual equivalent of *t*-BuLi monomeric. The cooling bath was then removed, and the mixture was allowed to warm for 30 min to effect the cascade illustrated in Scheme 1; namely, ortho-lithiation of **2**, loss of LiF to generate the benzyne-tethered propyllithium intermediate, and 5-exo cyclization to deliver 4-indanyllithium (**3**). As demonstrated by the results presented in Table 1, **3** may be trapped by addition of any of a variety of electrophiles to give isomerically pure 4-substituted indans in 60–70% isolated yield.¹¹

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Table 1. Preparation of 4-Substituted Indans^a

entry	E ⁺	E	yield, ^b %
1	H ₂ O	H	77
2	CH ₃ OD	D	79 ^c
3	Br(CH ₂) ₂ Br	Br	62
4	ClCO ₂ C ₂ H ₅	CO ₂ C ₂ H ₅	66
5	(CH ₃) ₂ NCHO	CHO	60
6	PhCHO	PhCH(OH)	62

^a 3-(2-Fluorophenyl)propyllithium (**2**) was generated at –78 °C by addition of 3.2 equiv of *t*-BuLi to a solution of **1** in *n*-pentane–diethyl ether (4:1 by vol). Deoxygenated THF was then added at –78 °C, the cooling bath was removed, and the mixture was allowed to warm for 30 min before the addition of an excess of the electrophile. ^b Isolated yield of chromatographically pure product. ^c Determined by GC/MS analysis of the product.

The chemistry described above, and summarized in Scheme 1, provides a novel and convenient route to 4-substituted indans, a class of compounds that are difficult to prepare in isomerically pure form using classical techniques.¹² More generally, the demonstration that a benzyne-tethered organolithium may be efficiently generated and subsequently trapped via intramolecular cyclization suggests that this methodology may prove useful for the preparation of other benzo-fused systems. We are in the process of exploring the scope and limitations of this chemistry.

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Supporting Information Available: Detailed experimental procedures for the preparation of **1** (Scheme 2) and 4-substituted indans (Table 1) are available (7 pages).

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(11) All of the indans prepared in this study (Table 1) are known compounds whose physical and spectroscopic properties are fully in accord with those reported in the literature. Details may be found in the Supporting Information that accompanies this article.

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