

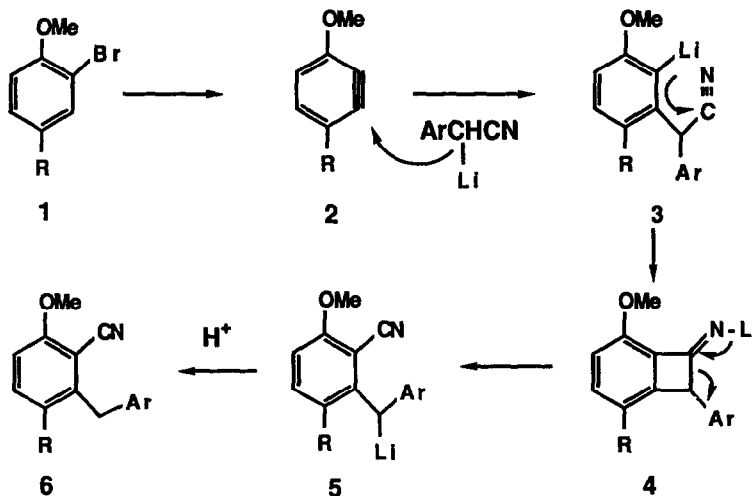
**A STEREOCONTROLLED SYNTHESIS OF
cis-3,4-DIARYLISOCHROMAN-1-ONES THROUGH DIASTEREOSELECTIVE REACTION OF
BENZALDEHYDES AND α -LITHIO-2-CYANODIARYLMETHANE INTERMEDIATES.**

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Summary. A highly diastereoselective reaction of benzaldehydes and α -lithio-2-cyanodiarylmethanes is reported. Using this approach a stereocontrolled synthesis of *cis*-3,4-diarylisochroman-1-ones is described.

Recently we observed¹ that the reaction of arynes (2) generated from 2-bromoanisoles (1) and lithium diisopropylamide with lithio aryl-nitriles led to the formation of polysubstituted benzenes (6) via tandem addition rearrangement. In the course of this work,¹ the α -lithio-2-cyanodiarylmethanes (5) obtained appeared to be valuable intermediates for electrophilic quenching. By trapping them with electrophiles, compounds could be produced possessing the ortho difunctionality.



Here we wish to report that electrophilic quenching of the α -lithio-2-cyano-diarylmethanes with benzaldehydes is highly stereocontrolled and leads to the formation of *cis*-3,4-diarylisochroman-1-ones. We examined the reaction of α -lithio-2-cyano-diarylmethanes (**5**) obtained *in situ* by the reaction of arynes generated from 2-bromoanisoles and lithio aryl-nitriles or by metallation of 2-cyano-diarylmethanes with various benzaldehydes. In a typical procedure, metallation of **7** with LDA in tetrahydrofuran (-78°C to 0°C) followed by treatment with benzaldehyde (0°C , 15 min) afforded the adduct **9a** which after neutralization gave **9b**. The reaction cited above occurred with high diastereoselectivity consistent with predictions by Cram's rule², an *anti* disposition of the diphenyl substituents about the newly formed C-C bond is highly favored. 200 MHz ^1H NMR spectra of the crude products displayed sharp doublets for the benzylic protons indicating the formation of the single isomer. ^{13}C NMR spectra also showed that a single isomer was formed in the above reaction. The stereochemistry of **9b** was established on the basis of spectroscopic (NMR) techniques. For example, on the basis of vicinal coupling constant³ $J_{1,2}$ ($J_{anti} > J_{syn}^{4,5}$). Stereochemistry of the product was further confirmed by single crystal x-ray diffractometry. The ORTEP diagram for **3** is shown in fig 2. The preference for the exclusive formation of *anti* 1,2-diphenyl alcohol (**9b**) is due to stereoelectronic and steric effects. The preferred approach of the two components is illustrated in Scheme 1 (or by the Newman projection, Figure 1)

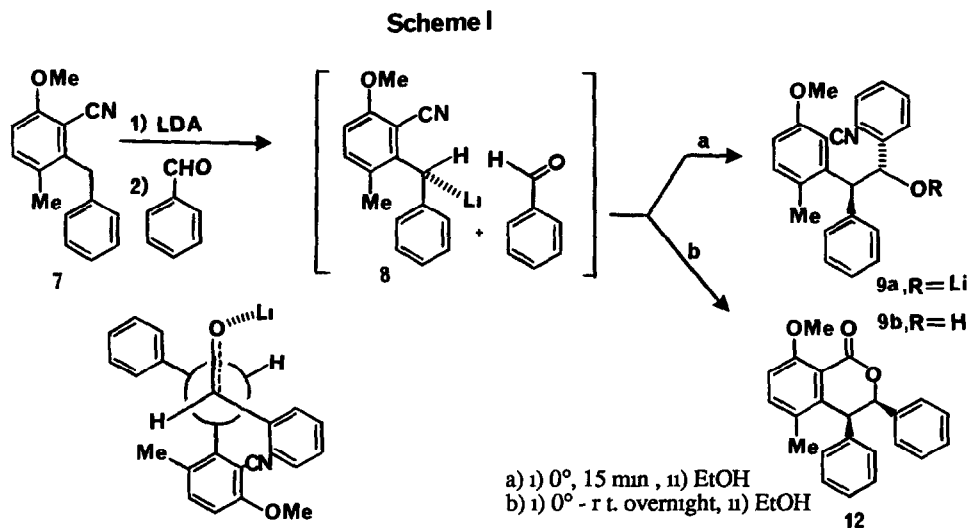
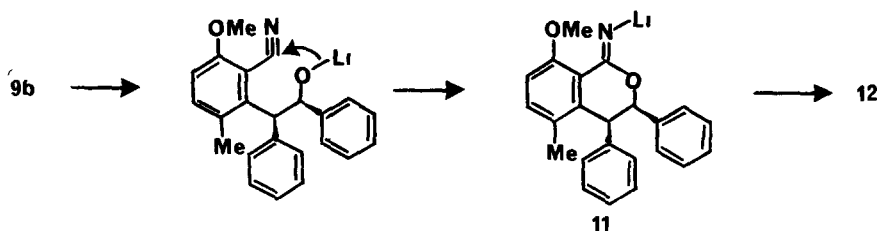


Figure 1

When the reaction mixture was stirred overnight after quenching and then neutralized, *cis*-3,4-diarylisochroman-1-one (**12**) was obtained in 70% yield. Presumably **12** is formed by the intramolecular addition of lithio-salt to nitrile to give intermediate **11**, which gives **12** upon acidic work-up.



Lithiation of alkylbenzonitriles and subsequent addition of the anions to carbonyl compounds as well as condensation with alkylbenzonitrile itself to give ketone is known in literature.⁶ The *cis*-stereochemistry was assigned to **12** on the basis of ¹H NMR data⁷ (for example *J*_{3,4} is of the order of 3–2 Hz) and was subsequently confirmed by single crystal x-ray diffractometry. The ORTEP diagram of **10** is shown in fig. 3.

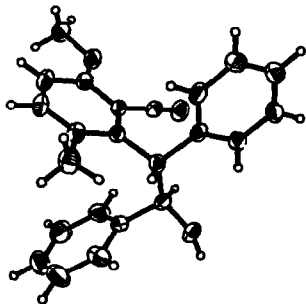


Figure 2

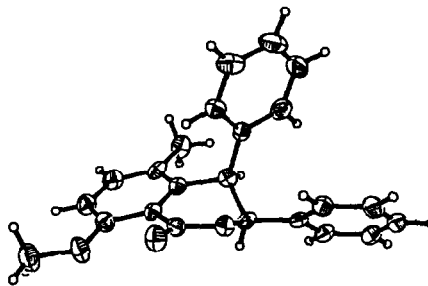


Figure 3

The stereospecific introduction of one carbon unit into substituted lithiated cyanodiarylmethanes allows chain extension at benzylic position and interesting subsequent cyclization leads to the formation of *cis*-3,4-diarylisochroman-1-one systems in one pot. 3-Arylisochroman-1-one system is present in several natural products such as hydrangenol and phylloolucin. Recently, *ortho* directed metallation of benzamides^{8,9} methodology has been used in the syntheses of these type of natural products. Reaction of aldehydes with *ortho*-toluate carbanions generated by chiral bases have been used in the syntheses of 3,4-dialkylisochroman-1-ones.¹⁰

The methodology described here can be very useful in the synthesis of isochroman-1-one class of compounds. For example, variously substituted cyano diarylmethanes can be made available through the tandem-addition rearrangement methodology¹, and the high degree of generality shown by the reaction of α -lithio-cyanodiarylmethanes and benzaldehydes (Table 1) is of real interest.

Table 1. Stereoselective reaction of 2-cyano-diarylmethanes with LDA and benzaldehydes^a

Entry	Cyanodiarylmethane	Benzaldehyde	Products	
			<i>anti</i> -1,2-diphenyl alcohol (yield %) ^b	<i>cis</i> -diaryl iso-chroman-1-one (yield %) ^b
1	13a, G=H	14a G'=3,4-Di-MeO		16a (70%)
2	13b, G=H	14b G'=3,4,5-Tri-MeO		16b (79%)
3	13c, G=H	14c G'=3-F	15c (30%) ^c	16c (35%) ^c
4	13d, G=H	14d G'=2-MeO	15d (55%)	
5	13e, G=2'-MeO	14e G'=3,4,5-Tri-MeO		16c (54%)

a) The α -lithio cyanodiaryl methanes were generated at -78°C in THF by LDA. The reaction mixture quenched with benzaldehydes and stirred for 24 h at room temperature.

b) Numbers in the parentheses are the yields based on chromatographically pure isolated products.

c) Obtained as the mixture which was separated by flash column chromatography.

We believe that the stereoselective reactions of substituted α -lithio-cyano diarylmethanes and benzaldehydes has considerable potential in polysubstituted isochroman-1-one synthesis.

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References and Notes.

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