

# A Versatile Synthesis of Substituted Isoquinolines\*\*

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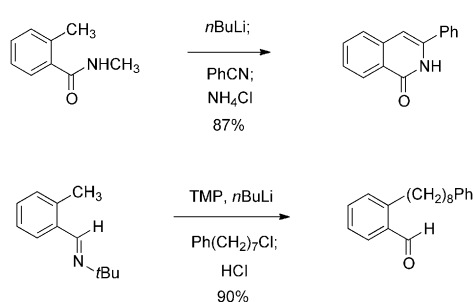
In memory of David Y. Gin

In the context of a broader program directed toward the synthesis of analogues of the isoquinoline-containing natural product cortistatin A,<sup>[1,2]</sup> we wished to prepare a diverse array of highly substituted isoquinoline coupling partners, but routes to the complex heterocyclic structures we envisioned were lengthy or impractical using classical<sup>[3]</sup> or more-modern<sup>[4–6]</sup> methods. Herein we report a method for the rapid construction of highly substituted isoquinolines of extraordinary structural versatility; this method proceeds by the convergent assembly of as few as two or as many as four components in a single operation. Further substitutional diversification can be achieved by modification of the work-up conditions and by subsequent transformations, as detailed below.

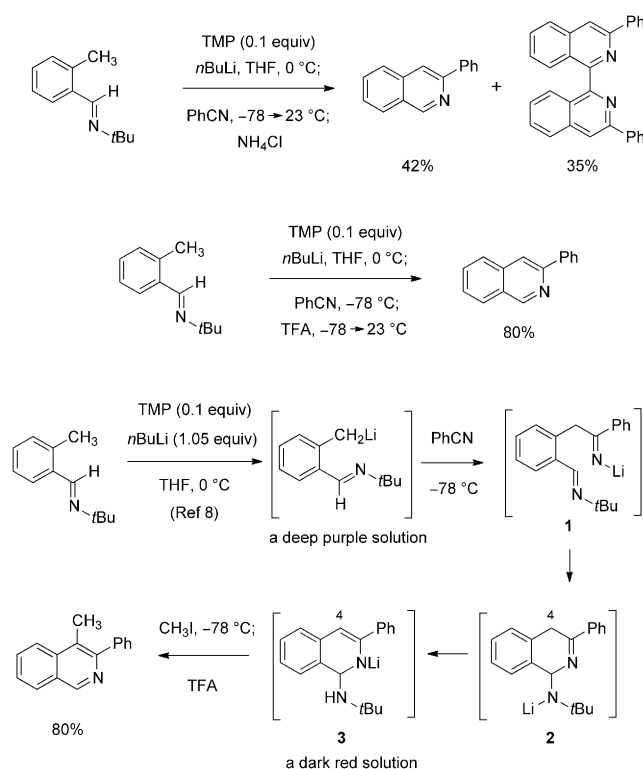
The present work was based on two important precedents. The first was the synthesis of 3-substituted isoquinolones by Poindexter; this synthesis proceeded by the addition of nitriles to *o*-tolylbenzamide dianions followed by work-up in the presence of ammonium chloride (Scheme 1).<sup>[7]</sup> The second was the method of Forth et al. for the preparation of *ortho*-substituted benzaldehyde derivatives by metalation of *o*-tolualdehyde *tert*-butylimines, followed by alkylation of the resulting anions, and then hydrolysis (Scheme 1).<sup>[8,9]</sup> We imagined and quickly brought to practice the idea that the trapping of metalated *o*-tolualdehyde *tert*-butylimines with nitriles might provide a highly direct route to 3-substituted

isoquinolines. As we will show, the chemistry proved to be much more versatile than we initially imagined; this versatility is due to the transformations that ensue subsequent to the addition of the nitrile.

Initial experiments established the feasibility of the proposed construction in a simple system and provided insights for expansion of the method. *o*-Tolualdehyde *tert*-butylimine was metalated under the reaction conditions specified by Forth et al., using stoichiometric *n*-butyllithium and a catalytic amount of 2,2,6,6-tetramethylpiperidine in tetrahydrofuran (THF) at 0 °C for 40 minutes, thus forming the corresponding benzyl anion as a deep purple solution, as previously reported.<sup>[8]</sup> Addition of this anion to a solution of benzonitrile (1.5 equiv) in THF at –78 °C produced a dark red solution within 3 minutes.<sup>[10]</sup> Upon warming to 23 °C the reaction mixture became dark brown. Addition of saturated aqueous ammonium chloride followed by extraction and purification by flash column chromatography provided 3-



**Scheme 1.** The synthesis of isoquinolones reported by Poindexter and the method of Forth et al. for metalation/alkylation of *o*-tolualdehyde *tert*-butylimine. TMP = 2,2,6,6-tetramethylpiperidine.



**Scheme 2.** A method for the direct condensation of *o*-tolualdehyde *tert*-butylimines with nitriles to form substituted isoquinolines. The mechanistic pathway depicted accounts for the fact that addition of an alkyl halide subsequent to condensation leads to the formation of 4-alkyl substituted isoquinolines, exemplified by the formation of 4-methyl-3-phenylisoquinoline.

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phenylisoquinoline in 42% yield and, separately, 3,3'-diphenyl-1,1'-biisoquinoline, in 35% yield (Scheme 2). The latter by-product was imagined to arise by base-induced dimerization of 3-phenylisoquinoline followed by oxidation, a transformation for which there is some precedent.<sup>[11]</sup> By adopting a different quenching protocol, that is, the addition of excess trifluoroacetic acid at  $-78$  then warming to  $23$  °C, formation of 3,3'-diphenyl-1,1'-biisoquinoline was avoided and 3-phenylisoquinoline could be isolated in 80% yield. Mechanistically, we considered the imido and *tert*-butylamido anions **1** and **2**, respectively (Scheme 2), to be likely intermediates along the pathway to 3-phenylisoquinoline (although other pathways are possible), but neither species seemed likely to account for the deep red color that we observed upon addition of the *o*-tolualdehyde *tert*-butylimino anion to benzonitrile. We speculated that the *tert*-butylamido anion **2** might react further by intra- or intermolecular proton transfer to form an eneamido anion with extended conjugation (**3**), and this anion did appear to be a reasonable candidate to account for the red color we observed.<sup>[12–14]</sup> To test this hypothesis methyl iodide (2 equiv) was added to the deep red solution shortly after its formation at  $-78$  °C, and an orange solution was produced within minutes. Addition of trifluoroacetic acid after 30 minutes, also at  $-78$  °C, followed by warming to room temperature, aqueous work-up, and purification by flash column chromatography provided 4-methyl-3-phenylisoquinoline in 80% yield.

Table 1 depicts a number of examples of polysubstituted isoquinolines that were synthesized by the direct condensation of *o*-tolualdehyde *tert*-butylimino anions with different nitriles followed by electrophilic trapping at the C4-position. For the metalation of halogenated *o*-tolualdehyde *tert*-butylimino anions the protocol of Forth et al. led to decomposition, and instead metalation with lithium diisopropylamide (LDA, 1.05 equiv) was effective for these substrates (entries 2, 6 and 8). Entries 1–4 illustrate the use of aliphatic nitriles as substrates and show that a variety of alkyl halides are suitable for alkylation at the C4-

position, including ethyl iodide (entry 1), *n*-butyl iodide (entry 2), allyl bromide (entry 3), and benzyl bromide (entry 4). Although a number of potentially enolizable aliphatic nitriles were successfully employed in this formal [4+2] cycloaddition reaction, thus far acetonitrile has not proven to be a viable coupling partner, most likely because enolization is more rapid than addition to the nitrile.<sup>[15]</sup> Entries 5–9 illustrate the use of *N,N*-dialkylcyanamides as substrates; isoquinolines formed from the novel reagent *N,N*-

**Table 1:** Condensation of lithiated *o*-tolualdehyde *tert*-butylimines with nitriles followed by electrophilic trapping at the C4-position with various electrophiles provides an expedient synthetic route to multiply substituted, structurally diverse isoquinolines.<sup>[a]</sup>

Entry	Imine	Nitrile	Electrophile	Product	Yield [%] <sup>[b]</sup>
1			EtI		52
2 <sup>[c]</sup>			<i>n</i> BuI		50
3 <sup>[d]</sup>					60
4			BnBr		50
5 <sup>[d]</sup>					52
6 <sup>[c]</sup>					66
7 <sup>[d]</sup>			CH <sub>3</sub> I		54
8 <sup>[c,e]</sup>			NFSI		74
9 <sup>[e]</sup>			NFSI		60
10 <sup>[f]</sup>			C <sub>2</sub> Cl <sub>6</sub>		54
11 <sup>[g]</sup>			MoOPH		40
12 <sup>[d]</sup>			CH <sub>3</sub> SSCH <sub>3</sub>		68

**Table 1:** (Continued)

Entry	Imine	Nitrile	Electrophile	Product	Yield [%] <sup>[b]</sup>
13 <sup>[d]</sup>					55

[a] For transformations with enolizable nitriles as substrates (entries 1–4) 1 equiv of nitrile and 1.25 equiv of *tert*-butylaldimine were used; in most other cases 1 equiv *tert*-butylaldimine and 1.25–1.5 equiv of nitrile were used. Metalation of the *tert*-butylaldimine was achieved by the method of Forth et al.<sup>[8]</sup> [b] Yields of the isolated product. [c] With the halogenated *tert*-butylaldimine substrates lithium diisopropylamide (LDA, 1.05 equiv) was used for metalation in lieu of TMP-*n*BuLi. [d] Hexamethylphosphoramide (HMPA, 2 equiv) was added prior to the addition of the electrophile. [e] 1 equiv of *N*-fluorobenzenesulfonimide (NFSI) and 1.25 equiv of *tert*-butylaldimine were used. [f] Electrophilic trapping with hexachloroethane was conducted by addition of the reaction mixture by cannula to a large excess of the electrophile (4 equiv) at  $-78^{\circ}\text{C}$ . [g] Potassium hexamethyldisilazide (KHMDS, 1 equiv) was added just prior to addition of MoOPH (1.5 equiv). Bn = benzyl, MoOPH = oxodiperoxy-molybdenum(pyridine) (hexamethylphosphoric triamide), PMB = *para*-methoxybenzyl, TMS = trimethylsilyl.

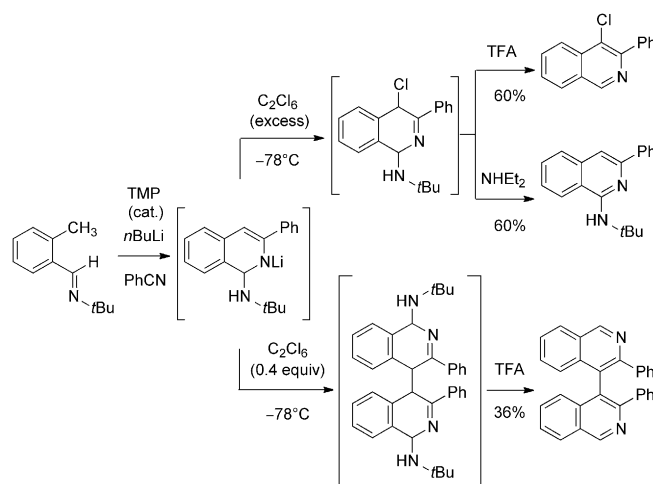
bis(*p*-methoxybenzyl)cyanamide in particular have proven to be highly versatile intermediates for further elaboration, as demonstrated below. Also, using *N,N*-dialkylcyanamides as substrates we have shown that reactions at the C4-position can be successfully achieved with Mander's reagent,<sup>[16]</sup> thus allowing introduction of a carbomethoxy group (entry 6) at the C4-position, and that fluorination of the C4 atom is possible by treatment with *N*-fluorobenzenesulfonimide (limiting reagent; entries 8 and 9). Entries 10–13 exemplify couplings with aryl nitriles as substrates as well as reactions at the C4-position to introduce other heteroatoms, including chlorine (entry 10), oxygen (entry 11),<sup>[17,18]</sup> sulfur (entry 12), and nitrogen (entry 13). In the latter two instances we found that the efficiency of the reaction at the C4-position was enhanced in the presence of the additive hexamethylphosphoramide (HMPA, 2 equiv). This additive also proved to enhance the yield of C4-alkylation products in the cases of entries 3, 5, and 7, a result which we believe is due to acceleration of an otherwise slow proton-transfer reaction that forms the eneamido anion intermediate.<sup>[21]</sup> In the absence of HMPA C4-unsubstituted isoquinolines were formed as by-products in each of these cases.

As illustrated in Scheme 3, it proved possible to obtain 4-chloroisoquinolines, 1-*tert*-butylamino isoquinolines, and 4,4'-bisoquinolines selectively by modification of the protocol for the electrophilic trapping with hexachloroethane. Using a substoichiometric amount of the electrophile (0.4 equiv, added slowly) a 4,4'-bisoquinoline derivative was formed as the primary product, a transformation that parallels a prior observation reported by Mamane and co-workers.<sup>[12b]</sup> When instead the putative eneamido anion was quenched by addition to an excess of hexachloroethane (4 equiv) at  $-78^{\circ}\text{C}$  4,4'-bisoquinoline formation was avoided. Work-up under standard reaction conditions, with trifluoroacetic acid, led to the expected 4-chloroisoquinoline product. Importantly, using an alternative work-up procedure, that is, the addition of diethylamine rather than trifluoroacetic acid, elimination of hydrogen chloride occurred, thus forming a 1-*tert*-butylamino isoquinoline derivative, which proved valua-

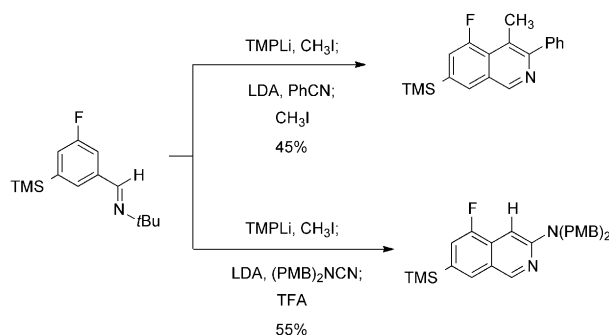
ble for subsequent diversification at the C1-position (see below).

We have also found that with *tert*-butylaldimine substrates containing a second *ortho*-directing group, such as a 3-fluoro substituent, it is possible to assemble substituted isoquinolines from as many as four components, added in sequence, in a single operation. For example, metalation of 3-fluoro-5-(trimethylsilyl)benzaldehyde *tert*-butylimine with lithium 2,2,6,6-tetramethylpiperidine (1.05 equiv) initially formed an *o*-lithio intermediate that reacted with methyl iodide (0.90 equiv; Scheme 4). Subsequent deprotonation of the methylated product in situ with lithium diisopropyl-

amide (1.05 equiv) at  $-40^{\circ}\text{C}$ , formed a dark red solution of the presumed *o*-tolyl anion, and addition of benzonitrile, followed by reaction at the C4-position with a second



**Scheme 3.** Selective preparation of 4-chloroisoquinolines, 1-*tert*-butylamino isoquinolines, or 4,4'-bisoquinolines by variation of the conditions of C4-trapping with hexachloroethane and subsequent work-up. TFA = trifluoroacetic acid.



**Scheme 4.** In substrates with an appropriate *ortho*-directing group it is possible to assemble substituted isoquinolines from as many as four components in a single operation.

equivalent of methyl iodide afforded 5-fluoro-4-methyl-3-phenyl-7-(trimethylsilyl)isoquinoline in 45% yield. A second example featuring a simpler, three-component assembly is also illustrated in Scheme 4.

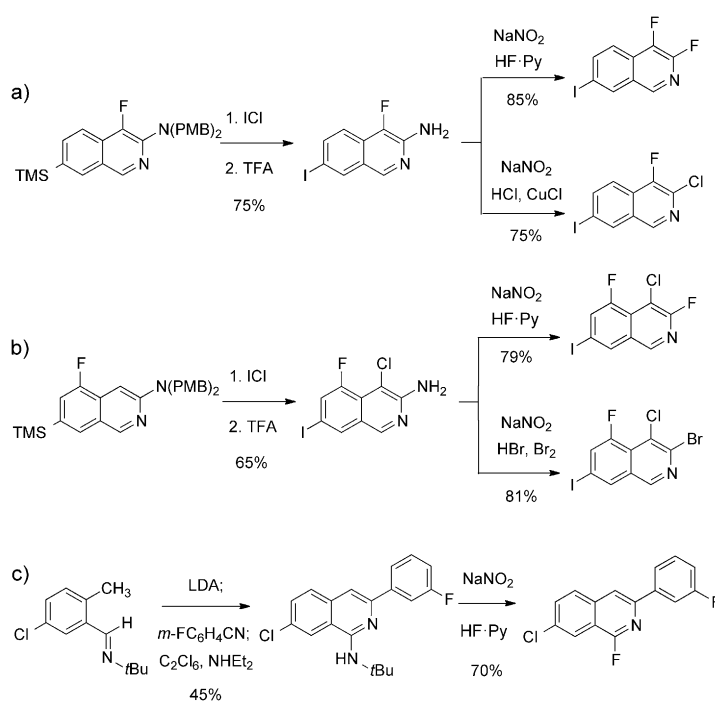
1-*tert*-Butylaminoisoquinoline (Scheme 3) and 3-*N,N*-bis(*p*-methoxybenzyl)aminoisoquinoline derivatives (Table 1, entry 9 and Scheme 4, bottom) were found to be especially valuable intermediates for further diversification, as were 7-trimethylsilylisoquinolines (Table 1, entries 9–13). For example, treatment of 4-fluoro-3-*N,N*-bis(*p*-methoxybenzyl)amino-7-(trimethylsilyl)isoquinoline with iodine monochloride in dichloromethane at 0°C afforded the product of 7-iododesilylation, and<sup>[22]</sup> subsequent addition of trifluoroacetic acid (neat) led to cleavage of the *p*-methoxybenzyl groups to provide 3-amino-4-fluoro-7-iodoisoquinoline in 75% yield (Scheme 5a). Diazotization of the latter product in the presence of fluoride and chloride sources gave rise to the corresponding 3-haloisoquinoline derivatives in good yield (Scheme 5a). Application of the same reaction sequence to 5-fluoro-3-*N,N*-bis(*p*-methoxybenzyl)amino-7-(trimethylsilyl)isoquinoline proceeded with chlorination at the C4-position followed by a slower 7-iododesilylation reaction during the initial treatment with iodine monochloride;<sup>[23]</sup> subsequent transformations proceeded as expected to provide polyhalogenated isoquinolines, including the novel product 3-bromo-4-chloro-5-fluoro-7-iodoisoquinoline (Scheme 5b). Lastly, we observed that 1-*tert*-butylaminoisoquinoline derivatives, prepared by condensation then chlorination with modified work-up (see above and Scheme 3), are transformed directly into 1-haloisoquinolines by dealkylative diazotization in the presence of halide ions. We anticipate the synthesis of a 1-fluoroisoquinoline (Scheme 5c),<sup>[24]</sup> should allow for further diversification at the C1-position by standard nucleophilic aromatic substitution reactions.

The direct assembly of substituted isoquinolines and bisisoquinolines described herein provides a highly versatile and uniquely enabling methodology for the construction of these important heterocycles.<sup>[25]</sup>

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**Scheme 5.** Preparation of halogenated isoquinolines from 1- and 3-aminoisoquinolines obtained by the formal [4+2] cycloaddition of *o*-tolualdehyde *tert*-butylimine with nitriles.

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