Synthetic Methods

DOI: 10.1002/ange.201104769

A Versatile Synthesis of Substituted Isoquinolines**

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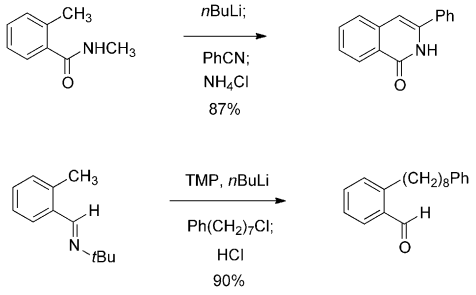
In memory of David Y. Gin

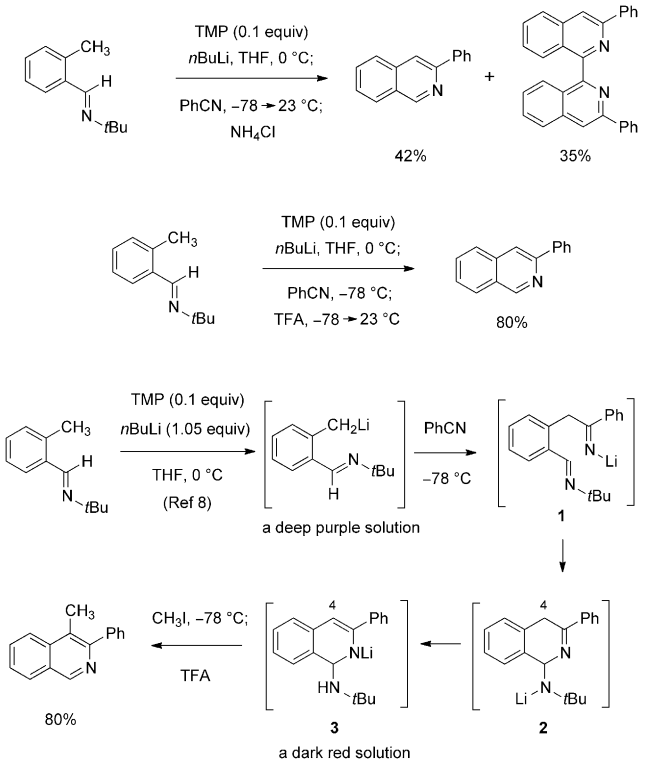
In the context of a broader program directed toward the synthesis of analogues of the isoquinoline-containing natural product cortistatin A,[1,2] we wished to prepare a diverse array of highly substituted isoquinoline coupling partners, but routes to the complex heterocyclic structures we envisioned were lengthy or impractical using classical[3] or more-modern[4–6] 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).[7] 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).[8,9] 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.



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.

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.[8] 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.[10] 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 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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[**] This research was supported by NIH grant CA-047148, stimulus grant no. CA047148-22S1, and NSF grant CHE-0749566.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201104769.

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.[11] 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*-butylimine 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.[12–14] 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*-butylimine anions with different nitriles followed by electrophilic trapping at the C4-position. For the metalation of halogenated *o*-tolualdehyde *tert*-butylimines 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.[15] 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.[a]

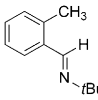
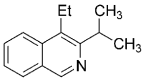
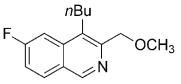
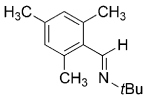
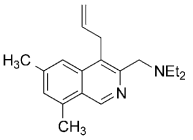
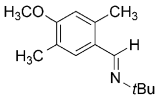
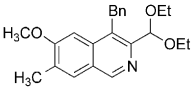
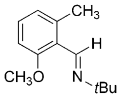
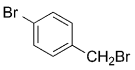
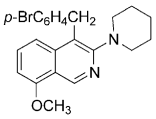
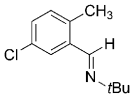
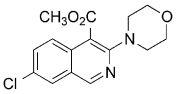
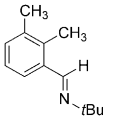
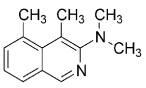
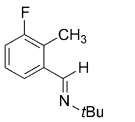
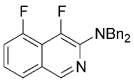
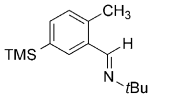
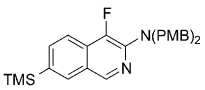
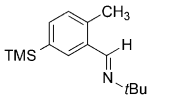
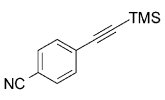
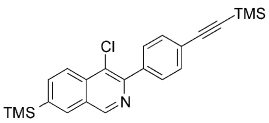
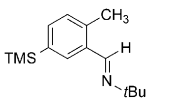
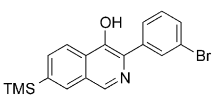
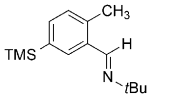
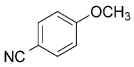
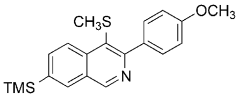
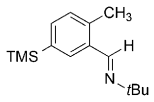
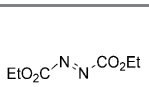
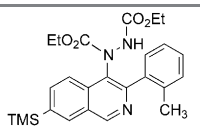
Entry	Imine	Nitrile	Electrophile	Product	Yield [%][b]
1			EtI		52
2[c]			*n*BuI		50
3[d]					60
4			BnBr		50
5[d]					52
6[c]					66
7[d]			CH_3I		54
8[c,e]			NFSI		74
9[e]			NFSI		60
10[f]			C_2Cl_6		54
11[g]			MoOPH		40
12[d]			CH_3SSCH_3		68

Table 1: (Continued)

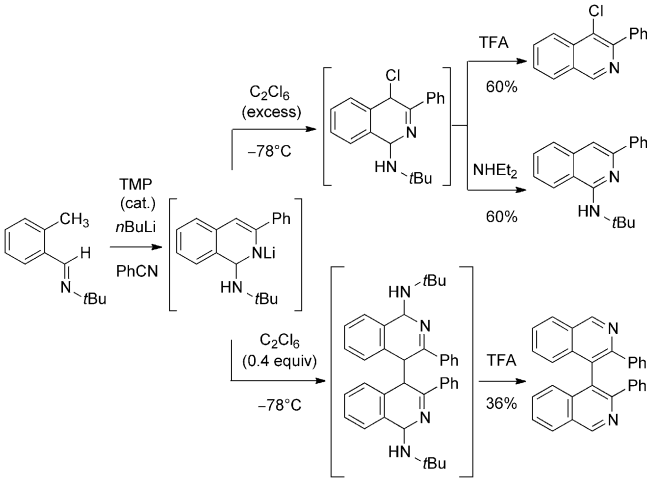
Entry	Imine	Nitrile	Electrophile	Product	Yield [%][b]
13[d]					55

[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.[8] [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 °C. [g] Potassium hexamethyldisilazide (KHMDS, 1 equiv) was added just prior to addition of MoOPH (1.5 equiv). Bn = benzyl, MoOPH = oxodiperoxymolybdenum(pyridine)(hexamethylphosphoric triamide), PMB = *para*-methoxybenzyl, TMS = trimethylsilyl.

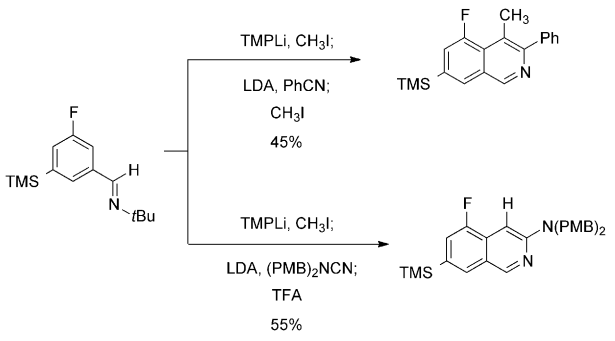
bis(*p*-methoxybenzyl)cyanamide in particular have proven to be highly versatile intermediates for further elaboration, as demonstrated below. Also, using *N*,*N*-dialkylcyanamides as substrates we have shown that reactions at the C4-position can be successfully achieved with Mander's reagent,[16] thus 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 arylnitriles as substrates as well as reactions at the C4-position to introduce other heteroatoms, including chlorine (entry 10), oxygen (entry 11),[17,18] 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.[21] 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′-biisoquinolines 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′-biisoquinoline derivative was formed as the primary product, a transformation that parallels a prior observation reported by Mamane and co-workers.[12b] When instead the putative eneamido anion was quenched by addition to an excess of hexachloroethane (4 equiv) at −78 °C 4,4′-biisoquinoline 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 valuable 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-tetramethylpiperidide (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 diisopropylamide (1.05 equiv) at −40 °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′-biisoquinolines by variation of the conditions of C4-trapping with hexachloroethane and subsequent work-up. TFA = trifluoroacetic acid.

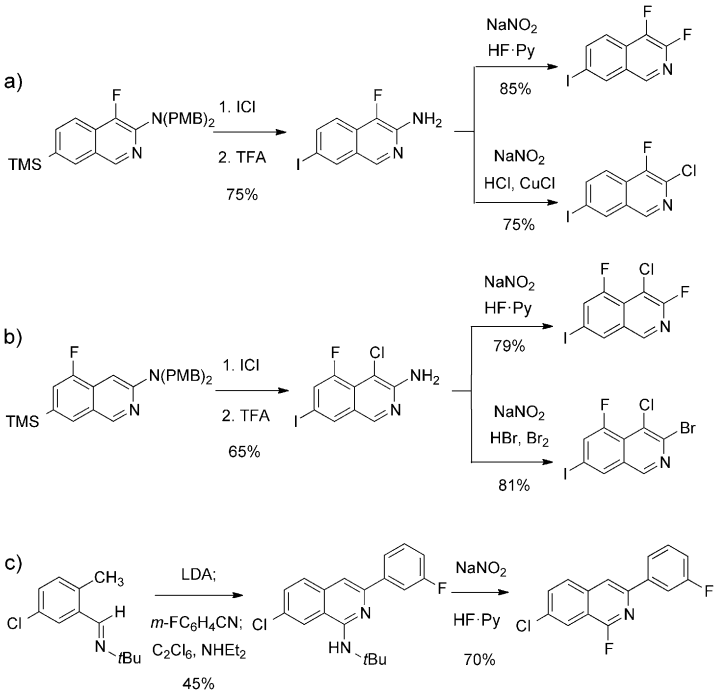


Scheme 4. In substrates with an appropriate *ortho*-directing group it is possible to assemble substituted isoquinolines from as many as four components in a single operation.

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[22] 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;[23] 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),[24] should allow for further diversification at the C1-position by standard nucleophilic aromatic substitution reactions.

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



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

Received: July 8, 2011
Published online: September 9, 2011

Keywords: cyclization · nitriles · nitrogen heterocycles · *o*-tolualdehyde *tert*-butylimines · synthetic methods

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