JOC The Journal of Organic Chemistry

pubs.acs.org/joc Article

Reaction Outcome Critically Dependent on the Method of Workup: An Example from the Synthesis of 1-Isoquinolones

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Cite This: J. Org. Chem. 2021, 86, 8078–8088 Read Online

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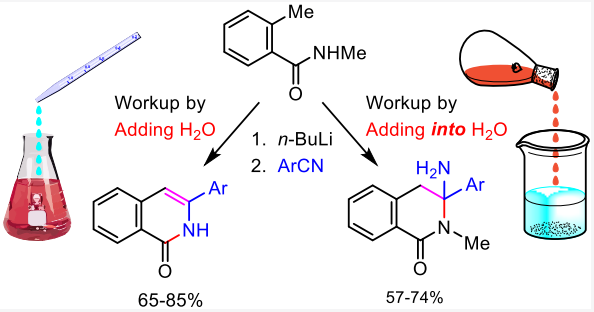
ABSTRACT: A striking dependence on the method of workup has been found for annulation of benzonitriles ArC≡N to *N*-methyl 2-toluamide (**1**), facilitated by *n*-BuLi (2 equiv): quenching the reaction by a slow addition **of** water produced the expected 1-isoquinolones **2**; by contrast, slow pouring of the reaction mixture **into** water afforded the cyclic aminals **5** (retaining the NMe group of the original toluamide). The mechanism of the two processes is discussed in terms of the actual H^+ concentration in the workup. Both **2** and **5** were then converted into the corresponding 1-chloroisoquinolines **3**, coupling of which, mediated by $(Ph_3P)_2NiCl_2/Zn$, afforded bis-isoquinolines **4**.



INTRODUCTION

There are two standard approaches to workup reaction mixtures in organic chemistry: (a) a slow addition of water or an aqueous solution of NH_4Cl to quench the reagent excess and release the final product (as with $LiAlH_4$, Grignard reagents, and RLi, etc.) followed by partition of the resulting mixture between an aqueous and organic layer and (b) pouring the mixture onto ice and water (as, e.g., in the case of acetylation of alcohols with Ac_2O/Py), followed by separation of the solid organic product and/or its extraction into an organic solvent. Herein, we describe a striking difference in the reaction outcome encountered in the annulation of benzonitriles to *N*-methyl 2-toluamide (*N*,2-dimethylbenzamide), which afforded two different products, depending on the method of the workup.

This work was aiming at the synthesis of isoquinolines and isoquinolones as potential pharmacophores and at the construction of 1,1′-bis-isoquinolines to be used as new chiral ligands and/or organocatalysts in asymmetric synthesis. To this end, we endeavored to synthesize 1-isoquinolone derivatives with various substituents at the 3-position as the key intermediates.

A number of 3-arylisoquinolines, derived from the corresponding 3-arylisoquinolones, have been developed as, e.g., antitumor agents,[1] topoisomerase I and tankyrases inhibitors,[2] and inducers of apoptosis of cervical cancer cells.[3] Some of them have been utilized as intermediates in the synthesis of benzophenathridine and protoberberine alkaloids,[4] such as oxynitidine and oxysanguinarine,[4] and related heterocyclic systems,[5] and for the development of fluorescent probes.[6]

Biaryl derivatives, such as BINOL,[7,8] NOBIN,[9] BINAP,[10] MOP,[11] MAP,[12] Segphos,[13] and their congeners,[14] have long been established as chiral ligands with many applications in asymmetric catalysis.[15] Their heterocyclic counterparts with an α,α'-bipyridine unit[16] became another popular class of complementary ligands that are capable of forming five-membered chelates with metals as an alternative to the 7-membered chelates of the former group.[16] Thus, for instance, the monoterpene-derived ligand PINDY and its analogues[17] were successfully employed in asymmetric allylic oxidation,[18] cyclopropanation,[18] Heck addition,[19] allylic substitution,[20] catalytic hydrogenation,[21] and Baeyer–Villiger oxidation[21] and for building supramolecular systems.[22] The *N*,*N*′-dioxides[23] and *N*-monooxides,[24] derived from these and other bipyridine-type derivatives found applications as organocatalysts for asymmetric allylation[24,25] and Mukaiyama aldol reactions.[25,26] Furthermore, complexes of *N*,*N*′-dioxides were also reported to catalyze asymmetric reduction of imines.[27]

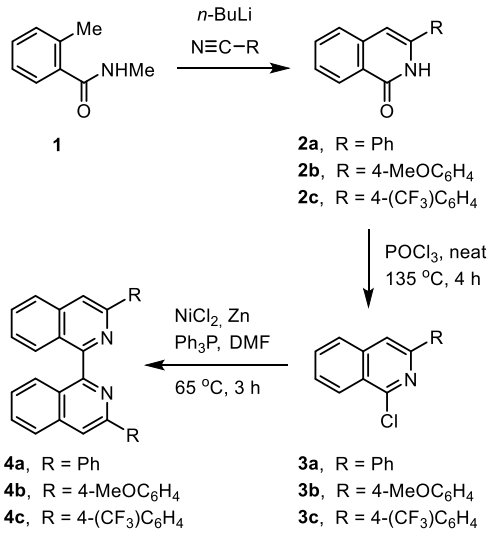
RESULTS AND DISCUSSION

Previously, we have prepared bis-isoquinoline **4a** (Scheme 1) and the corresponding *N*,*N*′-dioxide and demonstrated the catalytic activity of the latter derivative in asymmetric allylation of aldehydes with allyltrichlorosilane.[28] As an extension of the

Received: March 9, 2021
Published: May 25, 2021

https://doi.org/10.1021/acs.joc.1c00561
J. Org. Chem. 2021, 86, 8078–8088

Scheme 1. Synthesis of Bis-isoquinolines 4



portfolio of this type of catalysts, we embarked on the synthesis of analogues with substituents in the phenyl rings, such as **4b** and **4c**. Herein, we describe their synthesis, the associated problems, the mechanistic conundrums we have encountered in the preparation of the key intermediates **2**, and an improved synthetic protocol based on the mechanistic understanding, which retrospectively, may improve the synthesis of 1-isoquinolones in general.

The existing synthetic approaches to 1-isoquinolones **2** encompass annulation of benzonitrile to *N*-methyl 2-toluamides **1**, facilitated by *n*-BuLi (2 equiv),[29] Pd-catalyzed cyclization of *o*-alkynyl Weinreb benzamide,[30] Cu-catalyzed annulation of propiolic acids $RC{\equiv}CCO_2H$ to 2-$BrC_6H_4CO_2H$,[31] Ag-catalyzed annulation of 1-alkynyl-2-triazolylbenzene derivatives,[32] Pd(II)- or Ni(II)-catalyzed addition of arylboronic acids $ArB(OH)_2$ to methyl 2-(cyanomethyl)benzoate 2-$(MeO_2C)C_6H_4CH_2CN$,[33] and other methods.[1b,34]

The synthesis of the bis-isoquinoline derivative **4a** (Scheme 1), described in our previous paper,[28] commenced with the established annulation[1,5,29a] of benzonitrile to *N*-methyl 2-toluamides (**1**), mediated by *n*-butyllithium (≥2.2 equiv) in THF. The reaction starts with generation of the red-orange dilithium dianion (−20 °C, then 0 °C for 30 min), followed by addition of PhCN (initially at −50 °C and then kept at rt for 10 min). Using this scenario, the required isoquinolone derivative **2a** was obtained in mere 36% yield after chromatographic purification, which was rather lower than that reported in the literature.[29a] Optimization of the procedure then improved the yield to 85% (vide infra). Treatment of the latter product (**2a**) with a mixture of $POCl_3$ and PCl_5 (neat) at 120 °C for 2 h[35] furnished 1-chloroisoquinoline **3a**[5] (63%). Subsequent dimerization, mediated by the in situ-generated $(Ph_3P)_2NiCl_2$ complex and zinc powder in DMF at 50 °C for 3 h,[12,17,36] provided the biaryl derivative **4a** (67%).[28,37]

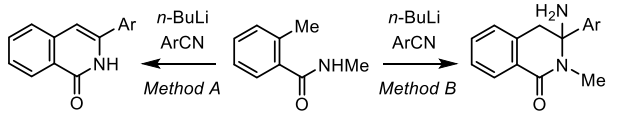
The *p*-methoxy and *p*-trifluoromethyl derivatives **2b** and **2c** were now obtained in a similar way using the appropriate benzonitriles (vide infra). Heating of **2b** with $POCl_3$ (neat) at reflux (135 °C) for 4 h gave rise to chloride **3b** (82%); subsequent nickel(0)-mediated dimerization in DMF (65 °C, 3 h) provided the bis-isoquinoline derivative **4b** (71%). Using the same protocol, **3c** was obtained from **2c** in 35% yield and then coupled to afford **4c** (68%).

Although this scheme seems to be straightforward, the initial annulation **1** → **2a** proved to be a bottleneck of the sequence, owing to rather low yields (initially 36% in our hands). Analogous annulation to provide **2b** and **2c** turned out to suffer from the same problem, which prompted us to carry out a more detailed investigation.

The transformation of toluamides **1** into isoquinolines **2** has been known for about 40 years and frequently utilized for the synthesis of pharmacologically relevant targets despite occasional reports of less than good yields.[29a] It is then rather surprising that this problem has not been addressed and apparently regarded as a phenomenon one has to live with. The issue here is obviously the mechanism, which is not fully understood.

After a modest success in the synthesis of **2a**,[28] we embarked on the preparation of the *p*-methoxy derivative **2b** (Scheme 2).

Scheme 2. Reaction Dichotomy as a Function of Workup



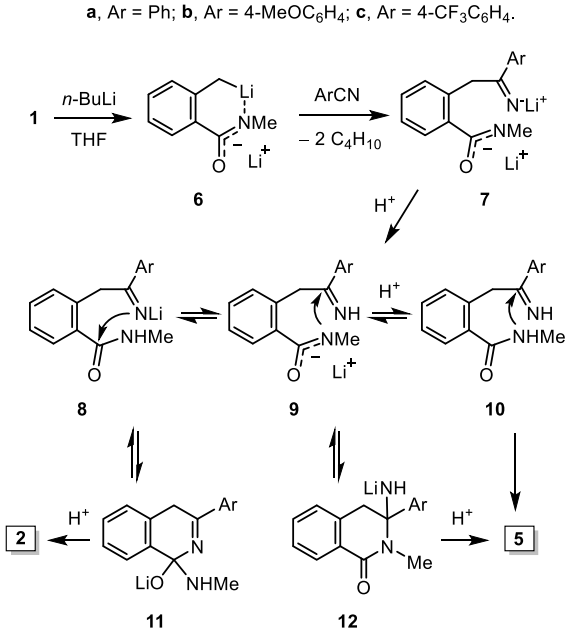
The initial experiment, carried out on a 500 mg scale was encouraging, as the expected product was obtained in 65% yield (Scheme 2). However, when the reaction was scaled up to a 20 g batch, it was found not to produce the expected isoquinolone **2b**; instead, aminal **5b** was obtained as a major product in ca. 50% yield (!) (Scheme 2). It only became obvious later that the discrepancy between the small-scale experiment and the large scale-operation resulted from a different method of workup: **2b** was obtained when the reaction was quenched by a slow addition of water (method A), whereas slow pouring of the reaction mixture into ice−water (method B) resulted in the formation of aminal **5b** as the major product. The same trend was then observed for the other two benzonitriles, producing isoquinolones **2a** and **2c** by method A and aminals **5a** and **5c** by method B.

The latter dichotomy in product formation was rather surprising and required further investigation. Since the reaction conditions were identical in all cases it was obvious that it was the method of workup that dictated the reaction outcome—a phenomenon not frequently observed or envisaged. To shed light on this issue, a series of experiments was carried out.

It can be assumed that *n*-BuLi (2.2 equiv with respect to **1**) first generates the doubly deprotonated species **6** (Scheme 3) as a result of the directing effect of the amide group.[38] The latter dilithiated species then reacts with the subsequently added nitrile $ArC{\equiv}N$ to produce the dilithiated imide **7**. It is unlikely that this formally double anion would readily undergo cyclization, as none of the two sites can be anticipated to act as an effective electrophile. Therefore, the cyclization can be assumed to proceed upon a (stepwise) protonation during the workup. The first protonation may, a priori, occur at either of the nitrogens, generating a potentially electrophilic center either at the amide moiety (**8**) or at the imine group (**9**). Full protonation would then produce the neutral species **10**. The

https://doi.org/10.1021/acs.joc.1c00561
J. Org. Chem. 2021, 86, 8078−8088

Scheme 3. Proposed Mechanism for the Formation of 2 and 5



intermediate **8** should ring close via **11** to produce isoquinolone **2**, whereas **9** should generate **12**, whose protonation would give rise to aminal **5**; the latter product could also arise from the neutral species **10**.

It can be speculated that this dichotomous cascade might be influenced by the concentration of water used in the workup. In other words, the overall outcome may depend on the way of quenching: thus, pouring the reaction mixture (a THF solution) into water (or an aqueous solution of NH_4Cl) would instantaneously generate the neutral species **10**. Since the imine moiety is prone to a nucleophilic attack (while the amide carbonyl is practically inert), the cyclization of **10** should produce aminal **5** (note that in the absence of the neighboring group it would be hydrolyzed to the corresponding ketone). By contrast, a slow addition of water into the reaction mixture may initially generate a monoprotonated species, namely **8** or **9**. Apparently, it is the former species **8** that reacts faster, so that it is siphoned off from the equilibrium, giving rise to isoquinolone **2** (via **11**), whereas the competing ring closure of **9**, leading to aminal **5** (via **12**), is apparently less favored. At this stage, it is difficult to speculate about the reasons for the reactivity preference of the monolithiated species **8**/**9** since they undoubtedly exist as complex aggregates,[39] which is likely to be reflected in their reactivity. Nevertheless, this simplistic picture can be regarded as a useful working hypothesis.

To shed more light on the role of the method of workup, the following experiments were carried out. The intermediate **6a** was first generated from **1** and *n*-BuLi (2.2 equiv) in THF, and then benzonitrile (1.1 equiv) was added at −50 °C, after which the mixture was warmed up to room temperature over 10 min. The resulting solution was diluted by a large volume of another rigorously dry solvent, namely toluene, MeCN, and DMF, respectively (Table 1).[40] The reaction was then quenched by a dropwise addition of water (method A). Under these conditions, isoquinolone **2a** was obtained as a major product (70−78%). Here, very little variation of the outcome was observed as a function of the diluting solvent (Table 1, entries 1−3). Aminal **5a** was detected as a byproduct in minute quantities.

Table 1. Outcome of the Reaction of 1 with PhCN as a Function of the Workup Method (Scheme 3)

entry	added solvent	quenching medium	method[a]	product[b] **2a** (%)	product[b] **5a** (%)
1	toluene	H_2O	A	70	2
2	DMF	H_2O	A	78	5
3	MeCN	H_2O	A	76	4
4	THF	H_2O	B	12	56
5	THF	10% H_2O in THF	B	21	44
6	THF	1% H_2O in THF	B	33	37

[a]Method A: Dropwise addition of the quenching medium into the reaction mixture. Method B: dropwise addition of the reaction mixture into the quenching medium. [b]Yield.

In another set of experiments (entries 4−6), the reaction was quenched in a reversed manner, namely by adding the reaction mixture dropwise to the quenching medium, i.e., water or water in THF (10% or 1%) (method B). The product distribution, resulting from this scenario, turned out to be dramatically different, compared to method A: thus, with pure water, aminal **5a** became the major product (56%, entry 4), and its structure was proved by X-ray crystallography (see the SI). By contrast, using a 1% solution of water in THF resulted in the formation of a ∼1:1 mixture of isoquinolone **2a** and aminal **5a** (entry 6), whereas 10% water in THF gave a result that stands in between the two (entry 5).

The original literature[29] suggested quenching by a slow addition of saturated aqueous NH_4Cl rather than with pure water. In view of our findings (vide supra), we have now compared the quenching by these two media, again using method A and B, respectively (Table 2). When the reaction was quenched via a slow addition of water to the reaction mixture (method A) without a prior dilution, mainly the isoquinolone **2a** was obtained (85%, Table 2, entry 1). With the reversed order, i.e., by pouring the mixture into water (method B), aminal **5a** was obtained as the major product (57%, entry 2). The same pair of experiments was repeated with aqueous NH_4Cl: method A was found to afford **2a** in a slightly reduced yield (73%, entry 3), whereas method B increased the yield of **5a** to 65% (entry 4), demonstrating that for the formation of **2a** it is the addition of water (method A) that is favored, whereas pouring the reaction mixture into the more acidic aqueous NH_4Cl (method B) is optimal for the formation of **5a**.

Since the aromatic substituent can be assumed to influence the electrophilicity of the imine moiety (**9**/**10**) and consequently its propensity to the formation of aminal **5**, the annulation reaction was also investigated with *p*-methoxy- and *p*-(trifluoromethyl)benzonitrile **1b** and **1c** (entries 5−12). Quenching with water and/or aqueous NH_4Cl in both methods mirrored the trend observed for benzonitrile, though the yields turned out to be slightly lower in general (presumably due to the less efficient extraction). No major difference in reactivity as a function of the aromatic substituent was found. Thus, **1b** was converted into **2b** by using method A and into **5b** by method B (entries 5−8): quenching by addition of water into the reaction mixture afforded the highest yield of **2b** (65%, entry 5), whereas pouring the mixture into water produced **5b** (70%, entry 6). In a similar way, **1c** gave **2c**

https://doi.org/10.1021/acs.joc.1c00561
J. Org. Chem. 2021, 86, 8078−8088

Table 2. Products of the Reaction of 1a−c with ArCN (Ar = Ph, 4-MeOC$_6$H$_4$, and 4-CF$_3$C$_6$H$_4$) as a Function of the Way of Quenching and the Substituent (Scheme 3)

entry	substrate	Ar	quenching medium	method[a]	product[b] **2** (%)	product[b] **5** (%)
1	**1a**	Ph	H_2O	A	85	5
2	**1a**	Ph	H_2O	B	12	57
3	**1a**	Ph	NH_4Cl aq	A	73	4
4	**1a**	Ph	NH_4Cl aq	B	8	65
5	**1b**	4-MeOC$_6$H$_4$	H_2O	A	65	6
6	**1b**	4-MeOC$_6$H$_4$	H_2O	B	15	70
7	**1b**	4-MeOC$_6$H$_4$	NH_4Cl aq	A	41	1
8	**1b**	4-MeOC$_6$H$_4$	NH_4Cl aq	B	5	40
9	**1c**	4-CF$_3$C$_6$H$_4$	H_2O	A	79	5
10	**1c**	4-CF$_3$C$_6$H$_4$	H_2O	B	16	74
11	**1c**	4-CF$_3$C$_6$H$_4$	NH_4Cl aq	A	35	2
12	**1c**	4-CF$_3$C$_6$H$_4$	NH_4Cl aq	B	14	33

[a]For the method, see Table 1. [b]Yield.

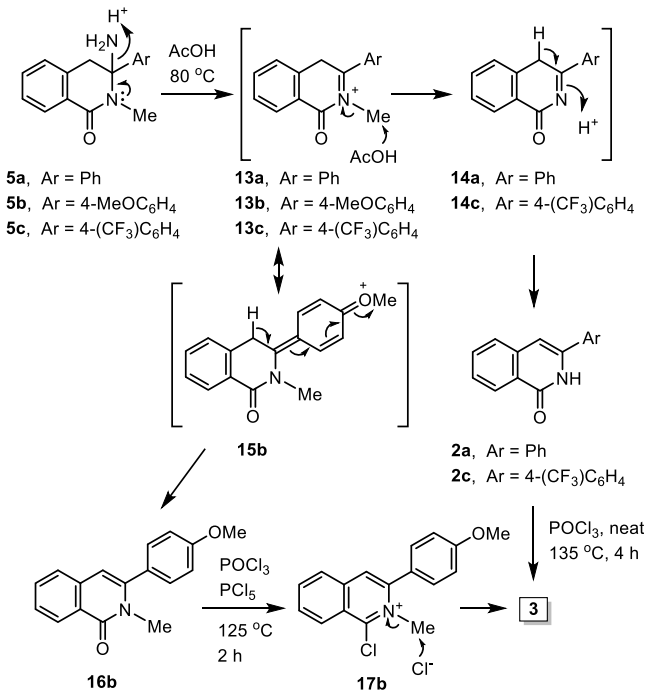
(79%, entry 9) and **5c** (74%, entry 10), respectively, when aqueous workup was employed. Quenching with aqueous NH_4Cl (entries 7, 8, 11, and 12) followed the trend observed for water but the yields turned out to be generally lower, showing that the NH_4Cl workup, suggested in the original literature,[29] is in fact contra-productive.

When excess *n*-butyllithium (>2.2 equiv) was used, as also recommended by the original literature,[29] ArCOBu was obtained as a byproduct, resulting from the reaction of the nitrile with the remaining *n*-BuLi (followed by hydrolysis in the workup). This of course required an excess of ArCN, which in light of the present study serves as a rather expensive reagent to quench the excess of *n*-BuLi. Hence, using the required 2 equiv (2.2 actually used in this study) should be sufficient.

It can also be hypothesized that the neutral imine intermediate **10** may exist in an equilibrium with the corresponding enamine[29a,41] whose electrocyclization could be conjectured to result in the formation of aminal **5** (and possibly also to produce isoquinolone **2**) as an alternative mechanism. This scenario would require a departure of one of the benzylic protons (to form the enamine), followed by an eventual reprotonation (to produce **5**). However, this mechanism can be ruled out since a control experiment, where D_2O was used for the quenching, revealed no deuterium incorporation into the product (demonstrated by mass spectrometry). Hence, the scenario portrayed in Scheme 3 and discussed above can be regarded as a plausible mechanistic hypothesis.

Regarding the original goal, i.e., to synthesize bis-isoquinolines **4a−c**, the undesired aminals **5a−c** were not wasted (especially **5b**, obtained in a relatively large quantity), as we managed, eventually, to convert them into chlorides **3a−c**, the precursors for the coupling (Scheme 4). Thus, heating of **5a** in acetic acid at 80 °C for 1 h resulted in the formation of isoquinolone **2a** (46% after crystallization), whose conversion into the 1-chloro derivative **3a** on heating with $POCl_3$ proceeded uneventfully in a 63% yield.[28] In a similar way, the (trifluoromethyl)phenyl aminal **5c** was converted into the required chloride **3c**, though in lower yield. In both cases, the reaction is presumably triggered by the neighboring group-assisted elimination of ammonia, generating the iminium ion **13a,c**. The latter intermediate apparently undergoes an S_N2 demethylation, in which AcOH serves as a nucleophile,[42,43] to give imide **14a,c**, from which isoquinolones **2a,c** are readily formed. Interestingly, the *p*-methoxyphenyl aminal **5b** was found to behave differently, as heating in AcOH was not accompanied by demethylation and *N*-methyl quinolone **16b** was obtained instead (69%). This dissent can be ascribed to the stabilization of the positive charge in **13b** by its delocalization to the *p*-methoxyphenyl group (**15b**), which in turn can be assumed to reduce the propensity of the *N*-Me group to the S_N2 displacement. As a result, competing deprotonation of the benzylic position can take place at this stage to afford the *N*-methylisoquinolone **16b** as a stable product, which was actually isolated. Only the harsh conditions of heating the latter derivative with $POCl_3$ and PCl_5 effected demethylation, presumably via the isoquinolium intermediate **17b**, to afford the desired chloride **3b** (51%).

Scheme 4. Synthesis of Isoquinolones 2a−c from Aminals 5a−c



CONCLUSIONS

We have shown that the annulation reaction of 2-toluamides (**1**) with benzonitriles ArCN, facilitated by *n*-BuLi (2 equiv), can be directed, at will, toward the formation of 1-

https://doi.org/10.1021/acs.joc.1c00561
J. Org. Chem. 2021, 86, 8078−8088

isoquinolones **2a−c** or aminals **5a−c** simply by the method of quenching the reactive dilithiated intermediate **7**. Thus, slow addition of water into the reaction mixture results in the formation of **2a−c** (85%, 65%, and 79%, respectively). On the other hand, slow pouring of the reaction mixture into ice/water gives rise to aminals **5a−c** (57%, 70%, and 74%, respectively). A similar trend was observed for the ice-cold aqueous NH_4Cl, though the yields of **5a−c** were lower, apparently due to a less efficient extraction. This easy switch that has not been described previously, apparently originates from the rate of protonation of the reactive dianion intermediate **7**, which in turn is dictated by the actual concentration of H^+ and local dilution. Aminals **5** are quite stable, so that they could be employed as an interesting new scaffold class for further derivatization toward the construction of medicinally relevant molecules and thus expand the well-established synthetic potential of isoquinolones **2**. Finally, the Ni(0)-mediated coupling of chlorides **3**, which in turn were obtained from both isoquinolones **2** or aminals **5**, gave bis-isoquinolines **4** as precursors of chiral ligands and organocatalysts for asymmetric synthesis.[28]

EXPERIMENTAL SECTION

General Information. All reagents and solvents were purchased from Sigma-Aldrich (Merck, KGaA, Darmstadt, Germany) and used without further purification. Solvents (DCM, THF) were dried prior to use (PureSolv PS-Micro, Innovative Technologies). The reactions were carried out under an argon atmosphere in oven-dried glassware using Schlenk line techniques with magnetic stirring and dried solvents. TLC analyses were performed using Merck TLC silica gel F_{254} TLC plates and visualized by UV (254 nm) in combination with staining (using the solution of $Ce(SO_4)_2{\cdot}4H_2O$ (2 g), $H_3[P(Mo_3O_{10})_4]$ (4 g), concd H_2SO_4 (10 mL), and H_2O (200 mL) with subsequent heating). Column chromatography was carried out on Merck silica gel 60 (0.040−0.063 mm). Petroleum ether (PE) refers to the fraction boiling in the range of 40−60 °C, AcOEt refers to ethyl acetate, MeOH refers to methanol, AcOH refers to acetic acid, and TsOH refers to *p*-toluenesulfonic acid. The ^1H, ^{13}C, and ^{19}F NMR spectra were recorded for DMSO-d_6 or $CDCl_3$ solutions on a Varian VNMR S500 instrument. The chemical shifts were recorded as δ values in parts per million (ppm) reported relative to TMS and referenced to the residual solvent peaks; the chemical shifts in ^{19}F spectra were indirectly referenced to trifluoroacetic acid as an external standard (−76.87 ppm). Coupling constants (J) are given in hertz. IR spectra were recorded on a Nicolet 6700 FT-IR equipped with an ATR device. LR-MS data were obtained on Expression^L CMS in connection with Plate Express, Advion, Inc. (USA) instrument. HR-MS data were recorded on a QTOF mass spectrometer using the electrospray ionization or microTOFq spectrometer using chemical ionization. Melting points were determined on a Stuart SMP30 apparatus or on a Kofler block and are uncorrected. Yields are given for isolated products[44] showing one spot on a TLC plate and no impurities detectable in the NMR spectrum. The identity of the products prepared by different methods was checked by comparison of their NMR, IR, and MS data and by the TLC behavior. Heating of reaction mixtures was provided by an oil bath, unless stated otherwise. Cooling to subzero temperatures was provided by Julabo FT902 FT Immersion Cooler combined with an ethanol bath.

Annulation of *N*-Methyl-*o*-toluamine with Benzonitriles. Method A. A 10 M solution of *n*-BuLi in hexanes (0.44 mL 4.4 mmol) was added dropwise over a period of 5 min to a solution of *N*-methyl-*o*-toluamide **1**[45] (298 mg; 2 mmol) in dry THF (5 mL) in an oven-dried flask under Ar at −20 °C (cryocooler). The mixture was stirred for 30 min at −20 °C, and then it was allowed to warm to 0 °C and stirred for another 30 min. The resulting orange-red solution was cooled to −50 °C (cryocooler), and a solution of the nitrile (2.2 mmol) in dry THF (5 mL) was added in one portion. The resulting mixture was warmed up rapidly to room temperature during a period of 10 min. Water (5 mL) was added slowly and dropwise at room temperature (the reaction is exothermic). The resulting suspension was diluted with CH_2Cl_2 (40 mL) after 15 min, and the organic phase was separated. Solid NaOH (0.4 g) was added to the aqueous phase, and the aqueous phase was extracted with CH_2Cl_2 (40 mL). Combined organic phases were washed with water (1 × 40 mL) and brine (1 × 40 mL) and dried ($MgSO_4$). The drying agent was filtered off, and the solvent was evaporated in vacuo. The resulting solid was purified by chromatography on a column of silica gel (15 g) using a mixture of petroleum ether and ethyl acetate (7:1 to 1:1) as an eluent.

Method B. A 10 M solution of *n*-BuLi in hexanes (0.40 mL 4.0 mmol) was added dropwise over a period of 5 min to a solution of *N*-methyl-*o*-toluamide **1**[45] (297 mg; 2 mmol) in dry THF (5 mL) in an oven-dried flask under Ar at −20 °C (cryocooler). The resulting orange-red solution turned red after addition of half of the *n*-BuLi solution. The mixture was stirred at −20 °C for 30 min, allowed to warm to 0 °C, and stirred for another 30 min. The mixture was cooled to −50 °C (cryocooler), and a solution of the corresponding nitrile (2.2 mmol) in dry THF (5 mL) was added in one portion. The mixture was warmed rapidly to room temperature during a period of 10 min and then added dropwise to water or to a saturated aqueous solution of NH_4Cl or to a mixture of water and THF (40 mL). The resulting suspension was diluted with CH_2Cl_2 (40 mL), and the organic phase was separated. Solid NaOH (0.4 g) was added to the aqueous phase, and the aqueous phase was extracted again with CH_2Cl_2 (2 × 40 mL). Combined organic phases were washed with water (1 × 40 mL) and brine (1 × 40 mL) and dried ($MgSO_4$). The drying agent was filtered off, and the solvent was evaporated in vacuo. The resulting solid was purified by chromatography on a column of silica gel (15 g) using a mixture of petroleum ether and ethyl acetate (7:1 to 1:1) as an eluent.

3-Phenylisoquinolin-1(2*H*)-one (2a). Compound **2a** was synthesized from **1** and benzonitrile according to method A and was further purified by crystallization from AcOEt to afford **2a** as white crystals (619 mg, 85%): mp 203−205 °C [lit.[46] mp 205 °C]; R_f = 0.57 (petroleum ether−AcOEt 1:1, visualized by UV); ^1H NMR (500 MHz, DMSO-d_6) δ 11.52 (s, 1H), 8.21 (dd, J = 8.0 Hz, J = 1.1 Hz, 1H), 7.76−7.82 (m, 2H), 7.67−7.75 (m, 2H), 7.42−7.53 (m, 4H), 6.91 (s, 1H); $^{13}C\{^1H\}$ NMR (125.7 MHz, DMSO-d_6) 162.9 (CO), 140.2 (C), 138.1 (C), 134.1 (C), 132.8 (CH), 129.4 (CH), 128.9 (CH), 126.9 (CH), 126.84 (CH), 126.80 (CH), 126.6 (CH), 125.0 (C), 103.4 (CH) in accordance with the literature data;[45] MS (APCI) m/z 443.2 $[2M + H]^+$ (20), 222.2 $[M + H]^+$ (100).

From Aminal ***5a***. A solution of 3-amino-2-methyl-3-phenyl-3,4-dihydroisoquinolin-1(2*H*)-one(**5a**) (300 mg, 1.2 mmol) in glacial acetic acid (10 mL) was stirred at 80 °C (oil bath) for 1 h. The reaction mixture was allowed to cool to room temperature, and the acetic acid was evaporated *in vacuo*. The solid was dissolved in diethyl ether (10 mL), washed with brine (1 × 15 mL) and water (1 × 15 mL), and dried (Na_2SO_4). The drying agent was filtered off, and the solvent was evaporated *in vacuo*. The crude product was purified by crystallization from AcOEt to afford **2a** as yellowish crystals (122 mg, 46%), identical with an authentic sample prepared from **2a**: ^1H NMR (500 MHz, DMSO-d_6) δ 11.54 (s, 1H), 8.21 (d, J = 8.0 Hz, 1H), 7.76−7.82 (m, 2H), 7.70 (d, J = 4.0 Hz, 2H), 7.42−7.52 (m, 4H), 6.91 (s, 1H); $^{13}C\{^1H\}$ NMR (125.7 MHz, DMSO-d_6) δ 163.0, 140.2, 138.1, 134.1, 132.8, 129.4, 129.0, 126.89, 126.85, 126.82, 126.6, 125.1, 103.4; HRMS (TOF-ESI$^+$) m/z $[M + H]^+$ Calcd for $C_{15}H_{12}NO$ 222.0913; Found 222.0918.

3-(4′-Methoxyphenyl)isoquinolin-1(2*H*)-one (2b). was synthesized from **1** and 4-methoxybenzonitrile according to method A and was further purified by crystallization from AcOEt to afford **2b** as white crystals (1.10 g, 65%): mp 238−241 °C [lit.[45] mp 242 °C]; R_f = 0.5 (petroleum ether−AcOEt 1:1, visualized by UV). ^1H NMR (500 MHz, DMSO-d_6) δ 11.43 (s, 1H), 8.18 (dd, J = 8.0, 1.3 Hz, 1H), 7.78−7.72 (m, AA′ BB′, 2H), 7.71−7.64 (m, 2H), 7.46−7.42 (m, 1H), 7.07−7.01 (m, AA′ BB′, 2H), 6.83 (s, 1H), 3.81 (s, 3H), consistent with the literature data;[45] $^{13}C\{^1H\}$ NMR (125.7 MHz,

https://doi.org/10.1021/acs.joc.1c00561
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DMSO-d_6) δ 163.0 (CO), 160.3 (C), 140.0 (C), 138.3 (C), 132.7 (CH), 128.2 (CH), 126.8 (CH), 126.7 (CH), 126.3 (C), 126.2 (CH), 124.7 (C), 114.4 (CH), 102.2 (CH), 55.5 (CH_3); MS (APCI) m/z 252.0 $[M + H]^+$ (100), 149.0 (25); HRMS (CI, isobutane) m/z $[M + H]^+$ Calcd for $C_{16}H_{14}NO_2$ 252.1019; Found 252.1023.

3-(4′-(Trifluoromethyl)phenyl)isoquinolin-1(2*H*)-one (2c). Compound **2c** was synthesized from **1** and 4-trifluoromethylbenzonitrile according to method A and further purified by crystallization from AcOEt to afford **2c** as white crystals (980 mg, 79%): mp >250 °C (dec) [lit.[33] mp 279−280 °C]; R_f = 0.64 (petroleum ether−AcOEt 1:1, visualized by UV); ^{1}H NMR (500 MHz DMSO-d_6) δ 11.39 (s, 1H), 8.24 (d, J = 8.0 Hz, 1H), 8.03−7.94 (m, AA′ BB′, 2H), 7.87−7.77 (m, AA′ BB′, 2H), 7.73−7.72 (m, 2H), 7.58−7.45 (m, 1H), 6.98 (s, 1H); ^{13}C{^{1}H} NMR (125.7. MHz, DMSO-d_6) δ 162.4 (CO, C1), 138.4 (C, C3), 137.7 (C, C1′), 137.4 (C, C4a), 132.4 (CH, C6), 129.2 (q, J = 31.6 Hz, C, C4′), 127.3 (CH, C2′, C6′), 126.7 (CH, C5), 126.7 (CH, C7), 126.5 (CH, C8), 125.2 (C, C8a), 125.3 (q, J = 4.0 Hz, CH, C3′, C5′), 123.9 (q, J = 271.6 Hz, CF_3), 104.4 (CH, C4); ^{19}F NMR (470 MHz, DMSO-d_6) δ −61.6; IR ν 3169, 1638, 1620, 1325, 1112, 1072, 821 cm^{-1}; MS (APCI) m/z 290.0 $[M + H]^+$ (100), 157 (10); HRMS (CI, isobutane) m/z $[M + H]^+$ Calcd for $C_{16}H_{11}F_3NO$ 290.0787; Found 290.0795.

From Aminal ***5c***. A solution of 3-amino-2-methyl-3-(4′-(trifluoromethyl)phenyl)-3,4-dihydroisoquinolin-1(2*H*)-one (**5c**) (150 mg, 0.468 mmol) in glacial acetic acid (5 mL) was stirred at 80 °C (oil bath) for 1 h. The reaction mixture was allowed to cool to room temperature, and the acetic acid was evaporated *in vacuo*. The solid was dissolved in diethyl ether (10 mL), washed with brine (1 × 15 mL) and water (1 × 15 mL), and dried (Na_2SO_4). The drying agent was filtered off, and the solvent was evaporated *in vacuo*. The crude product was purified by crystallization from AcOEt to afford **2c** as white crystals (116 mg, 82%).

1-Chloro-3-(4′-methoxyphenyl)isoquinoline (3b). A solution of isoquinolone **2b** (6.00 g, 23.8 mmol) in $POCl_3$ (50 mL) was heated to reflux using an oil bath (135 °C) for 4 h. Then the mixture was allowed to cool to room temperature and poured slowly and portionwise into a large excess of ice. The resulting mixture was allowed to warm to room temperature, and the solid product was filtered off and washed with plenty of water (until neutral reaction to litmus). The crude product was dried in the air and was further purified by crystallization from hexane to give pure chloride **3b** (5.25 g, 82%) as white crystals. For the characterization data, see below.

From ***16b***. A solution of **16b** (11.8 g, 41.5 mmol) in $POCl_3$ (100 mL) was heated to reflux using an oil bath (135 °C) for 4 h to afford **3b** as white crystals (6.10 g, 51%): mp 84−87 °C [lit.[47] gives 88 °C]; R_f = 0.50 (petroleum ether−AcOEt 7:1, visualized by UV); ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.38 (s, 1H), 8.23 (d, J = 8.0 Hz, 1H), 8.13−8.09 (m, AA′ BB′, 2H), 8.06 (d, J = 8.0 Hz, 1H), 7.86 (t, J = 8.0 Hz, 1H), 7.74 (t, J = 8.0 Hz, 1H), 7.12−7.05 (m, AA′ BB′, 2H), 3.83 (s, 3H) in accordance with the literature;[48] ^{13}C{^{1}H} NMR (125.7 MHz, DMSO-d_6) δ 160.4 (C), 150.0 (C), 149.1 (C), 138.8 (C), 132.0 (CH), 129.8 (C), 128.9 (CH), 128.0 (CH), 127.8 (CH), 125.8 (CH), 124.9 (C), 115.5 (CH), 114.5 (CH), 55.5 (CH_3); IR ν 2936, 2836, 1606, 1560, 1516, 1249, 1173, 976, 824, 745 cm^{-1}; MS (APCI) m/z 270.0 $[M + H]^+$ (100), 149.0 (15); HRMS (CI, isobutane) m/z $[M + H]^+$ Calcd for $C_{16}H_{13}{}^{35}ClNO$ 270.0680; Found 270.0688; Calcd for $C_{16}H_{13}{}^{37}ClNO$ 272.0651; Found 272.0658.

1-Chloro-3-[4′-(trifluoromethyl)phenyl]isoquinoline (3c). A solution of isoquinolone **2c** (215 mg, 0,743 mmol) in $POCl_3$ (5 mL) was heated to reflux using an oil bath (135 °C) for 4 h. Then the mixture was allowed to cool to room temperature and poured slowly and portionwise into a large excess of ice and water. The resulting mixture was allowed to warm to room temperature and then diluted with CH_2Cl_2 (15 mL). The organic phase was separated, and the aqueous phase was extracted with CH_2Cl_2 (15 mL). The combined organic phases were washed with brine (1 × 20 mL) and dried (Na_2SO_4). The drying agent was filtered off, and the solvent was evaporated. The crude product was purified by chromatography on a column of silica gel (10 g), using a mixture of petroleum ether and ethyl-acetate (8:2) as an eluent. The resulting solid was further purified by crystallization from hexane to give chloride **3c** (80 mg, 35%) as white crystals:[49] mp 63−65 °C; R_f = 0.76 (petroleum ether−AcOEt 7:3, visualized by UV; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.59 (s, 1H), 8.36−8.31 (m, AA′ BB′, 2H), 8.28−8.21 (m, 1H), 8.16−8.05 (m, 1H), 7.93−7.88 (m, 1H), 7.88−7.83 (m, AA′ BB′, 2H), 7.83−7.76 (m, 1H); ^{13}C{^{1}H} NMR (125.7 MHz, DMSO-d_6) δ 150.4 (C, C1), 147.2 (C, C3), 141.1 (C, C1′), 138.4 (C, C4a), 132.3 (CH, C6), 129.9 (CH, C7), 129.3 (q, J = 31.9 Hz, C, C4′), 128.3 (CH, C5), 127.2 (CH, C2′, C6′), 125.9 (q, J = 3.8 Hz, CH, C3′, C5′), 125.8 (CH, C8), 125.7 (C, C8a), 124.4 (q, J = 272.1 Hz, CF_3), 118.1 (CH, C4); ^{19}F NMR (470 MHz, DMSO-d_6) δ −61.5; IR ν 1620, 1593, 1564, 1488, 1425, 1321, 1314, 1263, 1168, 1153, 1102, 1068 cm^{-1}; MS (APCI) m/z 308.1 $[M + H]^+$ (100), 149.0 (10); HRMS (TOF-ESI$^+$) m/z $[M + H]^+$ Calcd for $C_{16}H_{10}ClF_3$ N 308.0448; Found 308.0455.

3,3′-Bis(4′-Methoxyphenyl)-1,1′-bisisoquinoline (4b). Zinc dust (855 mg, 13.1 mmol) and $NiCl_2{\cdot}6H_2O$ (3.11 g, 13.1 mmol) were added to a solution of triphenylphosphine (13.65 g, 52.1 mmol) in DMF (45 mL), and the mixture was left in an ultrasound bath for 30 min, while a steady stream of argon was bubbled through the suspension. The suspension was then heated at 65 °C (oil bath) while stirring under argon for 1 h, during which period it changed color from green to orange. A solution of chloride **3b** (2.35 g, 8.70 mmol) in DMF (10 mL) was then added in one portion, and the mixture was stirred at 65 °C for 3 h and then allowed to cool to room temperature. A 30% aqueous solution of ammonia (300 mL) was then added, and the mixture was allowed to stand in a refrigerator overnight, while yellow crystals of product **4b** were formed and isolated by filtration (1.44 g, 71%): mp 242−245 °C; R_f = 0.59 (petroleum ether−AcOEt 1:1, visualized by UV); ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.55 (s, 2H), 8.18−8.14 (m, 6H), 7.80 (dd, J = 8.3 Hz, J = 6.8 Hz, 2H), 7.72 (d, J = 8.3 Hz, 2H), 7.51 (dd, J = 8.3 Hz, J = 6.8 Hz, 2H), 7.10−7.03 (m, AA′ BB′, 4H), 3.81 (s, 6H); ^{13}C{^{1}H} NMR (125.7 MHz, DMSO-d_6) δ 160.2 (C, C4′), 157.4 (C, C1), 148.7 (CH, C3′), 137.8 (C, C4a), 131.3 (C, C1′), 130.9 (CH, C6), 128.2 (CH, C2′, C6′), 127.7 (CH, C5), 127.6 (CH, C7), 126.8 (CH, C8), 126.2 (C, C8a), 115.6 (CH, C4), 114.4 (CH, C3′, C5′), 55.4 (CH_3, OCH_3); IR ν 3052, 2830, 1607, 1514, 1244, 1175, 1028, 835, 750 cm^{-1}; MS (APCI) m/z 469.2 $[M + H]^+$ (35), 279.0 (70), 149.0 (100); HRMS (FAB, NOBA) m/z $[M + H]^+$ Calcd for $C_{32}H_{25}N_2O_2$ 469.1911; Found 469.1919.

3,3′-Bis[4′-(trifluoromethyl)phenyl]-1,1′-bisisoquinoline (4c). Zinc dust (21 mg, 0,321 mmol) and $NiCl_2{\cdot}6H_2O$ (76 mg, 0,321 mmol) were added to a solution of triphenylphospine (377 mg, 1,28 mmol) in DMF (5 mL), and the mixture was left in an ultrasound bath for 30 min, while a steady stream of argon was bubbled through the suspension. The suspension was then heated to 65 °C (oil bath) while stirring under argon for 1 h, during which period it changed color from green to orange. A solution of chloride **3c** (66 mg, 0,214 mmol) in DMF (5 mL) was then added in one portion, and the mixture was stirred at 65 °C (oil bath) for 3 h and then allowed to cool to room temperature. A 30% aqueous solution of ammonia (20 mL) was then added, and the mixture was allowed to stand in a refrigerator overnight. The resulting suspension was extracted with CH_2Cl_2 (2 × 20 mL), and the combined organic phases were washed with brine (1 × 20 mL) and dried (Na_2SO_4). The drying agent was filtered off, and the solvent was evaporated *in vacuo*. The crude product was purified by chromatography on a column of silica gel (30 g) using a mixture of petroleum ether and ethyl acetate (99:1 to 95:5) as an eluent to afford **4c** as a white solid (40 mg, 68%): mp 269−271 °C (hexane); R_f = 0.74 (petroleum ether−AcOEt, visualized by UV); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.37−8.29 (m, 6H), 8.06 (d, J = 8.5 Hz, 2H), 7.98 (d, J = 8.5 Hz, 2H), 7.83−7.72 (m, 6H), 7.57−7.50 (m, 2H); ^{13}C{^{1}H} NMR (125.7 MHz, $CDCl_3$) δ 158.0 (C, C1), 148.3 (C, C3), 142.7 (C, C1′), 137.8 (C, C4a), 130.7 (CH, C6), 130.4 (q, J = 32.3 Hz, C, C4′), 127.9 (CH, C7), 127.6 (CH, C5), 127.5 (C, C8a), 127.4 (CH, C8), 127.3 (CH, C2′, C6′), 125.7 (q, J = 3.8 Hz, CH, C3′, C5′), 124.3 (q, J = 273.4 Hz, CF_3), 117.7 (CH, C4); ^{19}F NMR (470 MHz, $CDCl_3$) δ −63.48; IR (ATR) ν 2963, 1619, 1561, 1493, 1444, 1418, 1326, 1264, 1168, 1151, 1099, 1070, 1014 cm^{-1}; MS

https://doi.org/10.1021/acs.joc.1c00561
J. Org. Chem. 2021, 86, 8078−8088

(APCI) m/z 545.2 $[M + H]^+$ (100), 359.4 (70), 331.3 (100); HRMS (TOF-ESI$^+$) m/z $[M + H]^+$ Calcd for $C_{32}H_{19}F_6N_2$ 545.1447; Found 545.1449.

3-Amino-2-methyl-3-phenyl-3,4-dihydroisoquinolin-1(2*H*)-one (5a). Compound **5a** was synthesized from **1** and benzonitrile according to method B and further purified by crystallization from EtOH to afford **5a** in the form of white crystals (423 mg, 57%): mp 166−168 °C; R_f = 0.20 (petroleum ether−AcOEt 1:1, visualized by UV); ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.89−7.85 (m, 1H), 7.35−7.30 (m, 1H), 7.30−7.26 (m, 1H), 7.26−7.22 (m, 4H), 7.20−7.15 (m, 1H), 7.09−7.04 (m, 1H), 3.37 (d, J = 16.0 Hz, 1H), 3.26 (d, J = 16.0 Hz, 1H), 2.98 (s, 2H), 2.96 (s, 3H); ^{13}C{^{1}H} NMR (125.7 MHz, DMSO-d_6) δ 164.6 (CO, C1), 143.6 (C, C1′), 135.4 (C, C4a), 131.8 (CH, C6), 128.9 (C, C8a), 128.3 (CH, C3′, C5′), 127.53 (CH, C5), 127.51 (CH, C4′), 127.3 (CH, C8), 126.9 (CH, C7), 126.3 (CH, C2′, C6′), 76.0 (C, C3), 44.7 (CH_2, C4), 28.0 (CH_3, NCH_3); IR ν 3395, 3316, 1636, 1491, 1443, 1375, 1325, 737 cm^{-1}; MS (APCI) m/z 254.0 $[M + H]^+$ (40), 236.1 $[M - NH_3+H]^+$ (30), 222.0 $[M - NH_3 - CH_3 + H]^+$ (100); HRMS (CI, isobutane) m/z $[M + H]^+$ Calcd for $C_{16}H_{17}N_2O$ 253.1335; Found 253.1345.

3-Amino-3-(4′-methoxyphenyl)-2-methyl-3,4-dihydroisoquinolin-1(2*H*)-one (5b). Compound **5b** was synthesized from **1** and 4-methoxybenzonitrile according to method B and was further purified by crystallization from EtOH to afford **5b** as white crystals (865 mg, 70%): mp 141−143 °C; R_f = 0.21 (petroleum ether−AcOEt 1:1, visualized by UV); ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.87 (dd, J = 7.5 Hz, J = 1.5 Hz, 1H), 7.33 (td, J = 7.5 Hz, J = 1.5 Hz Hz, J = 1H), 7.30−7.24 (m, 1H), 7.17−7.11 (m, AA′ BB′, 2H), 7.09−7.04 (m, 1H), 6.82−6.75 (m, AA′ BB′, 2H), 3.66 (s, 3H), 3.34 (d, J = 16.0 Hz, 1H), 3.21 (d, J = 16.0 Hz, 1H), 2.94 (s, 3H), 2.93 (bs, 2H); ^{13}C{^{1}H} NMR (125.7 MHz, DMSO-d_6) δ 164.6 (CO, C1), 158.6 (C, C4′), 135.6 (C, C4a), 135.4 (C, C1′), 131.8 (CH, C6), 128.9 (C, C8a), 127.6 (CH, C5), 127.5 (CH, C2′, C6′), 127.3 (CH, C8), 126.8 (CH, C7), 113.6 (CH, C3′, C5′), 75.7 (C, C3), 55.2 (CH_3, OCH_3), 44.7 (CH_2, C4), 27.8 (CH_3, NCH_3); IR ν 3397, 3298, 2967, 1634, 1605, 1578, 1383, 1242, 1030, 833, 733 cm^{-1}; MS (APCI) m/z 283.1 $[M + H]^+$ (85), 266.0 $[M-NH_3+H]^+$ (100), 252.0 $[M-NH_3-CH_3+H]^+$ (60); HRMS (EI) m/z $[M]^+$ Calcd for $C_{17}H_{18}N_2O_2$ 282.1368; Found 282.1364.

3-Amino-2-methyl-3-(4′-(trifluoromethyl)phenyl)-3,4-dihydroisoquinolin-1(2*H*)-one (5c). Compound **5c** was synthesized from **1** and 4-trifluoromethylbenzonitrile according to method B and further purified by crystallization from EtOH to afford orange crystals of **5c** (456 mg, 74%): mp 142−145 °C; R_f = 0.23 (petroleum ether−AcOEt 1:1, visualized by UV); ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.88 (dd, J = 7.6 Hz, J = 1.5 Hz, 1H), 7.66−7.60 (m, AA′ BB′, 2H), 7.49−7.44 (m, AA′ BB′, 2H), 7.34 (td, J = 7.4 Hz, J = 1.6 Hz, 1H), 7.29 (ddd, J = 8.3 Hz, J = 7.5 Hz, J = 1.2 Hz, 1H), 7.08 (d, J = 7.3 Hz, 1H), 3.42 (d, J = 16.1 Hz, 1H), 3.34 (s, 3H), 3.28 (d, J = 16.1 Hz, 1H), 3.13 (s, 2H), 2.97 (s, 3H); ^{13}C{^{1}H} NMR (125.7 MHz, DMSO-d_6) δ 164.8 (CO, C1), 148.8 (C, C1′), 135.3 (C, C4a), 132.2 (CH, C6), 129.0 (C, C8a), 128.5 (q, J = 31.9 Hz, C, C4′), 127.8 (CH, C5), 127.66 (CH, C8), 127.65 (CH, C2′, C6′), 127.3 (CH, C7), 125.6 (q, J = 3.8 Hz, CH, C3′, C5′), 124.6 (q, J = 272.2 Hz, CF_3), 76.2 (C, C3), 44.6 (CH_2, C4), 28.3 (CH_3, NCH_3); ^{19}F NMR (470 MHz, DMSO-d_6) δ −61.4; IR ν 3387, 3281, 1640, 1325, 1159, 1111, 1067, 839, 739 cm^{-1}; MS (APCI) m/z 290.0 $[M - NH_3 - CH_3 + H]^+$ (100), 240 (15); HRMS (CI, isobutane) m/z $[M + H]^+$ Calcd for $C_{17}H_{16}F_3N_2O$ 321.1209; Found 321.1217.

3-(4′-Methoxyphenyl)-2-methylisoquinolin-1(2*H*)-one (16b). A solution of 3-amino-3-(4-methoxyphenyl)-2-methyl-3,4-dihydroisoquinolin-1(2*H*)-one (**5b**) (18.3 g, 64.8 mmol) in glacial acetic acid (100 mL) was stirred at 80 °C (oil bath) for 8 h. The mixture was allowed to cool to room temperature, and the acetic acid was evaporated *in vacuo*. The crude product was purified by crystallization from AcOEt to afford **16b** as yellow crystals (11.8 g, 69%): mp 133−135 °C [lit.[34c] mp 136 °C]; R_f = 0.5 (petroleum ether−AcOEt 1:1, visualized by UV); ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.23 (dd, J = 8.0 Hz, J = 1.4 Hz, 1H), 7.69 (dd, J = 8.2 Hz, J = 7.0 Hz, 1H), 7.64 (d, J = 8.1 Hz, 1H), 7.52−7.43 (m, 3H), 7.09−7.03 (m, AA′ BB′, 2H), 6.54 (s, 1H), 3.82 (s, 3H), 3.31 (s, 3H) in accordance with the literature;[50] ^{13}C{^{1}H} NMR (125.7 MHz, DMSO-d_6) δ 164.8 (CO, C1), 148.8 (C, C1′), 135.3 (C, C4a), 132.2 (CH, C6), 129.0 (C, C8a), 128.5 (q, J = 31.9 Hz, C, C4′), 127.8 (CH, C5), 127.66 (CH, C8), 127.65 (CH, C2′, C6′), 127.3 (CH, C7), 125.6 (q, J = 3.8 Hz, CH, C3′, C5′), 124.6 (q, J = 272.2 Hz, CF_3), 76.2 (C, C3), 44.6 (CH_2, C4), 28.3 (CH_3, NCH_3); IR ν 2999, 2967, 2936, 1637, 1609, 1510, 1246, 1179, 1032, 822, 758 cm^{-1}; MS (APCI) m/z 266.1 $[M + H]^+$ (100), 149 (20); HRMS (CI, isobutane) m/z $[M + H]^+$ Calcd for $C_{17}H_{16}NO_2$ 266.1176; Found 266.1183.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.1c00561.

^{1}H, ^{13}C, and ^{19}F NMR spectra; cystallographic data; experimental details (PDF)

Accession Codes

CCDC 2065025 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This paper is dedicated to Dr. Ivo Starý on the occasion of his 60th birthday. This work was supported by the Czech Science Foundation (Project No. 18-17868S) and by the project EFSA-CDN (No. CZ.02.1.01/0.0/0.0/16_019/0000841) co-funded by ERDF. Graduate studentships (P.M. and O.K.) were provided by Charles University (projects No. 262416 and SVV 260 547) and the University of Glasgow. We thank the COST office for support via the ORCA action CM905, the Erasmus exchange program for supporting the stay of M.M., and the late Dr. Alfred Bader for additional funding. M.M. acknowledges support from the European Union's Horizon 2020 research and innovation program (Marie Skłodowska-Curie Grant Agreement No. 892479). P.K. acknowledges support from the Wenner-Gren Foundation. Institutional support from Charles University (project No. Q42) and the Institute of Organic Chemistry and Biochemistry of the Czech Academy of Sciences are also gratefully acknowledged.

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