

InCl₃-Catalyzed Allylic Friedel–Crafts Reactions toward the Stereocontrolled Synthesis of 1,2,3,4-Tetrahydroquinolines

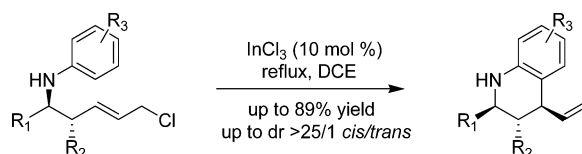
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ABSTRACT



Allyl chlorides tethered to an *N*-aryl moiety readily undergo InCl₃-catalyzed Friedel–Crafts reactions to furnish highly enantiomerically enriched 1,2,3,4-tetrahydroquinolines with good yields and excellent diastereoselectivity.

1,2,3,4-Tetrahydroquinolines are central subunits in a broad range of natural products and medicinal agents which display interesting biological and pharmacological properties.¹ Accordingly, a wealth of synthetic methods has been developed for the stereoselective synthesis of these heterocycles.² Most prominent among them are metal- and Brønsted acid-catalyzed, enantioselective hydrogenations of quinolines³ as well as enantioselective aza Diels–Alder reactions of aryl

imines and electron-rich alkenes (Povarov reaction)⁴ and those of in situ generated aza-xylylenes and electron-rich dienophiles.⁵ Other methods including ring expansion reactions,⁶ asymmetric Reissert reactions,⁷ Heck-type cyclizations,⁸ organocatalytic hydroarylations of enals,⁹ sequential aza-Michael–Mannich reaction of *ortho*-amino benzaldehydes and enals,¹⁰ Pd-catalyzed hydroaminations of anilino alkynes,¹¹ intramolecular redox reactions,¹² and the carbo-

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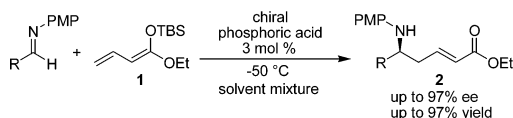
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lithiation of unsaturated *ortho*-iodo anilines¹³ have been developed additionally to access tetrahydroquinolines in optically enriched form. Recently, Lautens and co-workers reported a powerful palladium-catalyzed cyclization of allyl acetates tethered to an *N*-aryl iodide giving rise to a variety of 2,4-disubstituted tetrahydroquinolines in good yields and perfect 2,4-*trans*-diastereoselectivity, albeit as racemic mixtures.¹⁴

We report herein a straightforward and highly stereoselective approach for the synthesis of chiral, highly optically enriched 2,4-disubstituted and 2,3,4-trisubstituted tetrahydroquinolines through a metal-catalyzed, intramolecular Friedel–Crafts-type reaction of allyl chlorides tethered to an *N*-aryl moiety. Complementary to the Lautens process, this new allylic alkylation reaction proceeds in a highly *cis*-stereoselective fashion and does not require a halogen substituent on the aryl ring.

We have recently developed the Brønsted acid-catalyzed, highly enantioselective, vinylogous Mukaiyama–Mannich reaction of vinylketene silyl-*O,O*-acetals **1** furnishing δ -amino- α,β -unsaturated esters **2** with excellent enantioselectivity (Scheme 1).¹⁵ With γ -substituted dienolates a second stereogenic center was formed with good anti-diastereoselectivity. As a first synthetic application of the Mannich products obtained in this way, we recently reported a four-step synthesis of the tobacco alkaloid *S*-anabasine in optically highly enriched form.¹⁶

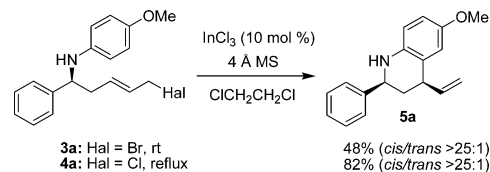
Scheme 1. Chiral Brønsted Acid-Catalyzed Vinylogous Mukaiyama–Mannich Reaction



In an effort to document further the synthesis potential of the highly functionalized Mannich products, we speculated that we could employ the *N*-aryl group not just as a nitrogen protecting group but incorporate it into the target structure through a Friedel–Crafts-type cyclization to form 1,2,3,4-tetrahydroquinolines. Specifically, we envisaged that conversion of the enoate moiety within **2** into an allylic halide

through Dibal-H reduction and halogenation would form a suitable allylic electrophile that was expected to undergo an intramolecular, metal-catalyzed allylic alkylation reaction with the electron-rich *N*-aryl group (Scheme 2).¹⁷

Scheme 2. Friedel–Crafts Reaction of Allyl Halides **3a** and **4a**



In addition to other Lewis acids commonly employed in Friedel–Crafts reactions, InCl_3 has specifically been introduced as a catalyst for the intermolecular¹⁸ and intramolecular¹⁹ reaction of arenes with allyl acetates and allyl bromides, respectively. Accordingly, we prepared both allyl bromide **3a** and allyl chloride **4a** starting from vinylogous Mannich product **2a** in good yields using standard methods (see Supporting Information) and treated them with catalytic amounts of InCl_3 and powdered 4 Å molecular sieves in 1,2-dichloroethane.

Friedel–Crafts cyclization of **3a** was very rapid even at ambient temperature and furnished tetrahydroquinoline **5a** in moderate yield (*cis/trans* > 25:1) along with some unidentified byproducts (Scheme 2). In fact, **3a** proved to be so reactive that it partially cyclized during its preparation. On the other hand, Friedel–Crafts reaction of allyl chloride **4a** was a much cleaner process and delivered **5a** in 82% isolated yield as a single diastereomer (*cis/trans* > 25:1) with 95% ee after refluxing a solution of **4a** for 18 h in 1,2-dichloroethane. We assume that the catalytic activity of InCl_3 in this reaction rests on its halophilic nature activating the allyl system via chloride abstraction.²⁰ Only trace amounts of **5a** were obtained in the absence of InCl_3 .

With optimal conditions for the cyclization in hand, a series of vinylogous Mannich products **2b–n**, which were prepared in optically highly enriched form using our Brønsted acid-catalyzed process, was converted into allyl chlorides **4b–n** via the above-mentioned reduction–halogenation sequence. Subsequently, they were cyclized with InCl_3 as catalyst (10 mol %) in the presence of 4 Å molecular sieves to furnish 1,2,3,4-tetrahydroquinolines **5b–n** in typically good yields and up to >25:1 diastereoselectivity in favor of

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Table 1. Intramolecular InCl₃-Catalyzed Friedel–Crafts Reaction^a

entry	product ^b	entry	product ^b	entry	product ^b
1	 5a , 18 h, 82% yield, 95% ee, >25/1 dr	6	 5g , 15 h, 88% yield, 77% ee, >25/1 dr	10 ^c	 5k , 71 h, 81% yield, 91% ee, 12/1 dr
2 ^c	 5b , 46 h, 77% yield, 97% ee, 19/1 dr	7 ^c	 5h , 62 h, 74% yield, 95% ee, 13/1 dr	11 ^c	 5l , 64 h, 67% yield, 93% ee, 12/1 dr
3	 5c , 20 h, 73% yield, 91% ee, >25/1 dr	8 ^{c,d}	 5i , 96 h, 70% yield, 98% ee, 10/1 dr	12 ^{c,e}	 5m , 93 h, 58% yield, 95% ee, 4/1 dr
4	 5d , 14 h, 89% yield, 87% ee, >25/1 dr	9 ^c	 5j , 88 h, 71% yield, 94% ee, 15/1 dr	13	 5n , 15 h, 81% yield, 95% ee, 15/1 dr
5	 5e , 16 h, 64% yield, 89% ee, 14/1 dr		 5f , 16 h, 11% yield, 89% ee, >25/1 dr		

^a Reactions were performed with allyl chloride **4** (0.30 mmol, 1.00 equiv), InCl₃ (0.03 mmol, 0.10 equiv), and 4 Å molecular sieves under reflux in anhydrous 1,2-dichloroethane (2.0 mL). ^b Yields refer to chromatographically purified material. Enantiomeric excesses were determined by chiral HPLC and were identical for vinylogous Mannich products **2** and tetrahydroquinolines **5** (see Supporting Information); diastereomeric ratios were determined by ¹H NMR spectroscopy or HPLC. ^c K₂CO₃ (3.0 equiv) was added. ^d 20 mol % of InCl₃ was used. ^e 25 mol % of InCl₃ was used.

the 2,4-cis-diastereomer (Table 1). The configurational assignment was based upon the characteristic coupling constants in the ¹H NMR spectrum. The exceptionally high diastereoselectivity in favor of the 2,4-cis-isomer is believed to originate from the favorable pseudoequatorial positions of the substituents in the transition state of the cyclization.

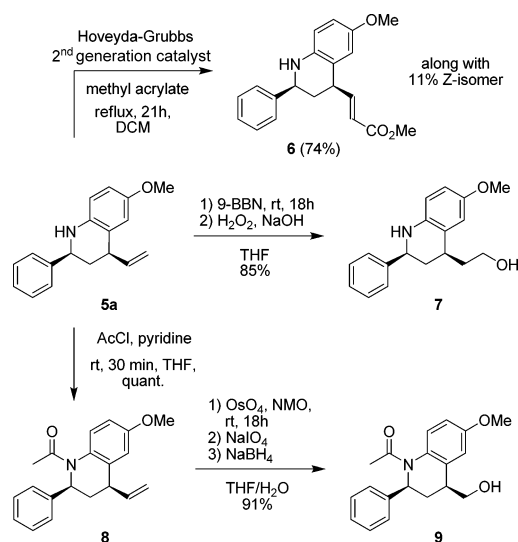
Whereas substrates with alkoxy-substituted *N*-aryl groups reacted rather quickly, those with *N*-aryl groups lacking any further electron donation or carrying electron-withdrawing substituents required extended reaction times at elevated temperatures and occasionally increased catalyst loadings (entries 8 and 12). Also, the addition of 3 equiv of K₂CO₃ to the reaction mixture was beneficial in those cases to neutralize the in situ generated HCl, which slowly led to decomposition of the starting materials (entries 7–12).

Furthermore, the reaction could be successfully extended to the preparation of the 2,3,4-trisubstituted tetrahydroquinoline **5n**, which was obtained in 81% yield and 15:1 cis/trans-diastereoselectivity (entry 13).

It is important to note that due to the modular-type three-component vinylogous Mannich reaction a variety of tetrahydroquinolines with different substituents both in the aromatic portion of the heterocycle as well as in the 2- and 3-positions are accessible in highly enantiomerically enriched form. 2-Alkyl-, 2-aryl-, and 2-heteroaryl-substituted tetrahydroquinolines were all obtained in good yields and typically excellent diastereoselectivity.

Moreover, the vinyl substituent intrinsically present in the 4-position of the heterocyclic skeleton offers some interesting possibilities for modification (Scheme 3). Thus, cross me-

Scheme 3. Elaboration of Tetrahydroquinolines **5a**



tathesis employing the Hoveyda–Grubbs second-generation catalyst²¹ furnished α β -unsaturated ester **6** in 74% yield along with 11% of the readily separable *Z*-isomer. Furthermore, hydroboration²² followed by oxidative workup afforded tetrahydroquinoline alcohol **7** in 85% yield. Finally, oxidative degradation of the vinyl group was readily ac-

complished after conversion into *N*-acetyl tetrahydroquinoline **8** through a sequence comprising dihydroxylation,²³ diol cleavage, and reduction to provide tetrahydroquinoline alcohol **9** in excellent overall yield.

In conclusion, we have developed a novel, flexible, and highly stereoselective process for the synthesis of a broad range of 1,2,3,4-tetrahydroquinolines through an InCl_3 -catalyzed Friedel–Crafts reaction. Allyl chlorides with both electron-rich and electron-poor *N*-aryl groups successfully underwent the cyclization with high 2,4-*cis*-diastereoselectivity, delivering products with diverse substitution patterns. An additional key element of the strategy is the Brønsted acid-catalyzed vinylogous Mannich reaction to provide the substrates in highly optically enriched form.

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Supporting Information Available: Detailed experimental procedures, characterization, and copies of spectra for the products. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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