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Stereoselective Synthesis of Hexahydroimidazo[1,2-*a*]quinolines via S_N2-Type Ring-Opening Hydroarylation–Hydroamination Cascade Cyclization of Activated Aziridines with *N*-Propargylanilines

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Cite This: https://dx.doi.org/10.1021/acs.orglett.0c02801 Read Online

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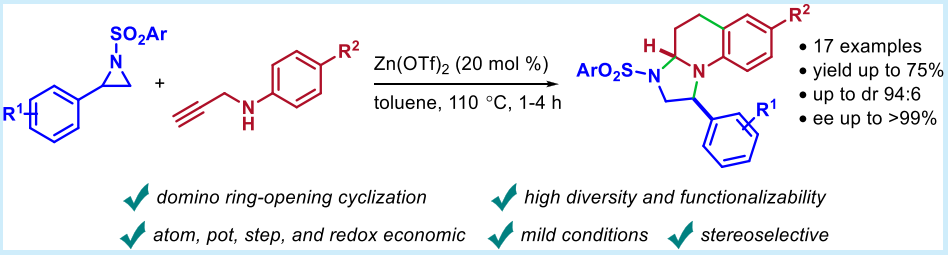


ABSTRACT: A novel synthetic approach for the construction of 1,2,3,3a,4,5-hexahydroimidazo[1,2-*a*]quinolines in good yields (up to 75%) with excellent stereoselectivity (dr up to 94:6, ee up to >99%) under one-pot domino ring-opening cyclization (DROC) conditions has been developed. The DROC protocol proceeds through a Lewis acid catalyzed S_N2-type ring-opening of activated aziridines with *N*-propargylanilines followed by intramolecular cyclization comprising concomitant hydroarylation and hydroamination steps in a domino fashion.

The cutting-edge discovery programs of new pharmaceutical agents warrant the development of ever more efficient synthetic methodologies to allow the rapid generation of structural complexity in the organic molecules.[1] In this context, the nitrogen-containing polyheteroaromatic compounds, particularly benzimidazo[1,2-*a*]quinolines (**I**, Figure 1), possess potent DNA intercalation and topoisomerase II inhibition activities. Structurally analogous phenanthridinium derivatives are also efficient DNA-intercalating agents with antitumor properties.[2] Recently, dihydro-1*H*-imidazophenanthridinum compounds (DIP, **II** and **III**),[3−5] more planar imidazophenanthridinium moieties (IP, **IV**),[6] as well as less planar tetrahydroimidazophenanthridines (TIP, **V** and **VI**)[7] have been found to exhibit interesting biological activities (Figure 1). Therefore, the development of efficient and novel synthetic routes to such compounds with greater selectivity and wide structural diversity is of significant research interest among organic and medicinal chemists.

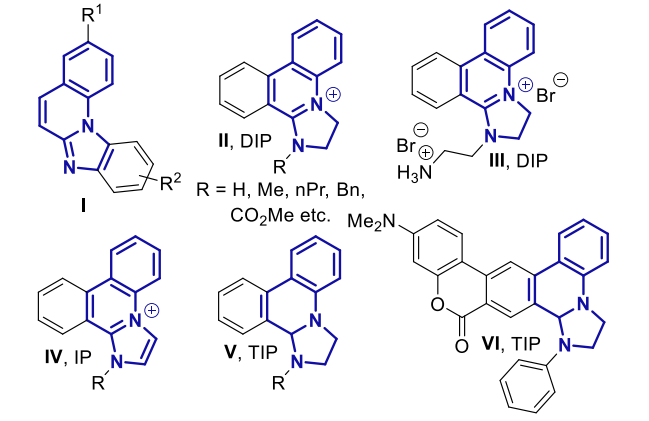


Figure 1. Various biologically active and useful benzimidazoquinoline and imidazophenanthridine frameworks.

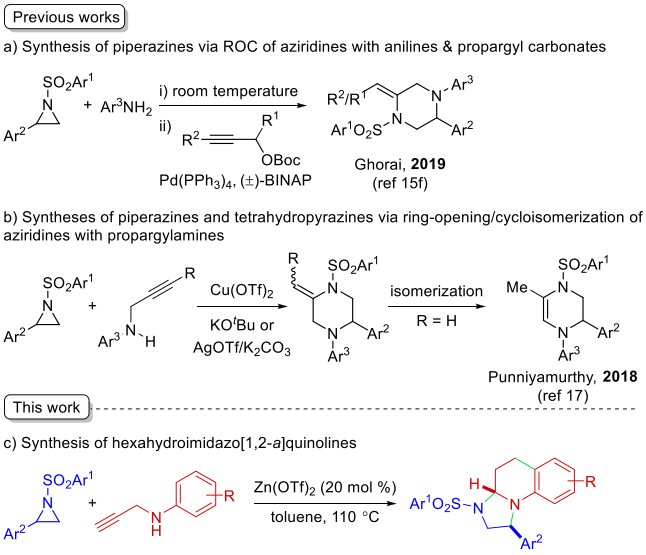
Various synthetic routes to benzimidazo[1,2-*a*]quinolines include sequential S_NAr and intramolecular Knoevenagel condensation of 2-methyl-1*H*-benzimidazoles and 2-fluorobenzaldehydes,[8] Pd-catalyzed intramolecular Buchwald–Hartwig aryl amination of 2-(2′-bromoanilino)quinolines,[9] photochemical dehydrocyclization reaction of benzimidazolyl-substituted acrylonitriles,[10] Cu-catalyzed cascade reactions,[11] Rh(III)-catalyzed C–H activation cascade reactions of imidamides and anthranils,[12] etc. On the other hand, only a few reports are known in the literature for the synthesis of dihydro-1*H*-imidazophenanthridinium compounds.[6,7,13] However, to date, there is no report available in the literature for the synthesis of 1,2,3,3a,4,5-hexahydroimidazo[1,2-*a*]quinolines.

Received: August 24, 2020

The activated aziridines and azetidines are attractive building blocks for the synthesis of high-value acyclic and cyclic nitrogenous compounds.[14] Over the years, we have been involved in exploring and exploiting Lewis acid catalyzed S_N2-type ring-opening transformations of activated aziridines and azetidines to synthesize biologically relevant aza-heterocycles via ring-opening cyclization (ROC)[15] or domino ring-opening cyclization (DROC).[16]

We recently reported the synthesis of highly substituted 1,4-piperazines via one-pot ring-opening cyclization involving aziridines, anilines, and propargyl carbonates (Scheme 1a).[15f]

Scheme 1. Reactions of *N*-Activated Aziridines with Anilines and Tethered and Nontethered Propargyl Moiety

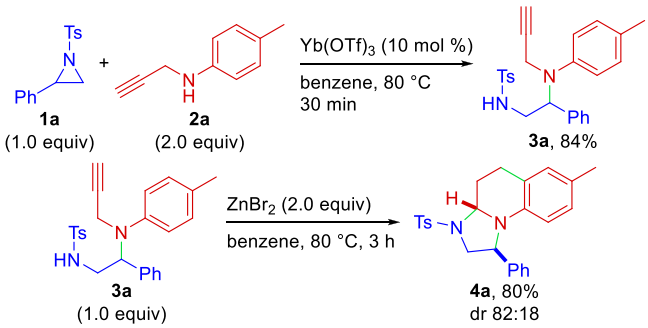


In another report, Punniyamurthy et al. reported the synthesis of piperazines/tetrahydropyrazines via ring-opening cyclization/cycloisomerization of aziridines with *N*-propargylanilines (Scheme 1b).[17] While exploring the Lewis-acid catalyzed ring-opening of activated aziridines with *N*-propargylanilines (Scheme 1c), to our great surprise, instead of the expected piperazine scaffold, we observed the unprecedented formation of a hexahydroimidazo[1,2-*a*]quinoline framework with multiple stereogenic centers via S_N2-type ring-opening with *N*-propargylanilines followed by intramolecular cyclization comprising concomitant hydroarylation and hydroamination steps in a domino fashion. Herein, we report our preliminary results of the aforementioned novel findings.

Our study commenced with the ring opening of 2-phenyl-*N*-tosylaziridine (**1a**) with 2.0 equiv of 4-methyl-*N*-(prop-2-yn-1-yl)aniline (**2a**) as the nucleophile in the presence of 10 mol % of $Yb(OTf)_3$ as the Lewis acid in benzene at 80 °C to furnish the corresponding ring-opened product **3a** in excellent yield (84%, Scheme 2) as the single regioisomer.

Next, **3a** was treated with a superstoichiometric amount of a second Lewis acid (2.0 equiv of zinc(II) bromide) in benzene at 80 °C, and after 3 h, to our delight, the corresponding 1,2,3,3a,4,5-hexahydroimidazo[1,2-*a*]quinoline derivative **4a** was formed in high yield (80%) with high diastereoselectivity (dr 82:18, Scheme 2) instead of the formation of the expected piperazine derivative (Scheme 1). The compound **4a** was characterized by spectroscopic data.[18] To make our strategy more practical as a general synthetic methodology, the reaction

Scheme 2. Synthesis of Hexahydroimidazo[1,2-*a*]quinoline 4a via Ring-Opening Cyclization of 2-Phenyl-*N*-tosylaziridine (1a) with 4-Methyl-*N*-(prop-2-yn-1-yl)aniline (2a)

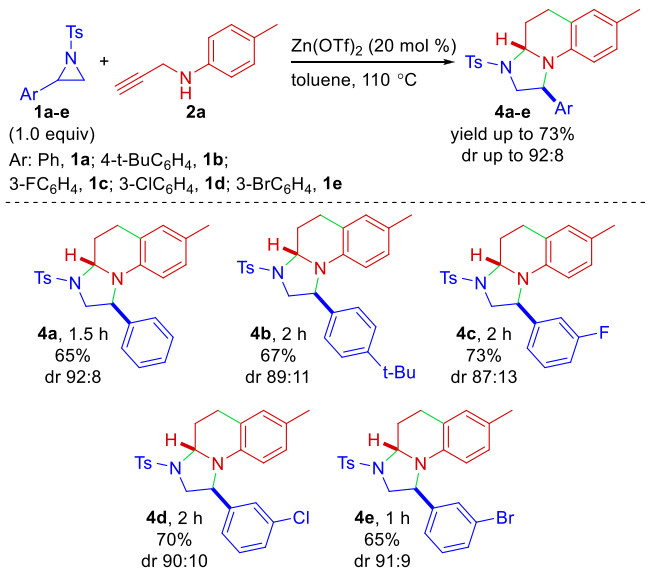


was studied under one-pot conditions. The ring-opening of **1a** with **2a** in the presence of 10 mol % $Yb(OTf)_3$ in benzene at 80 °C followed by treatment with 2.0 equiv of $ZnBr_2$ in the same pot afforded the corresponding quinoline derivative **4a** in 46% overall yield with identical stereoselectivity (dr 82:18).[18]

To optimize the reaction conditions in terms of better yield and diastereoselectivity of the product, several conditions (Lewis acid, temperature, solvent, etc.) were studied. A generic Lewis acid serving both the initial ring-opening step and the concomitant cascade intramolecular cyclization steps of the DROC strategy was explored. When **1a** was treated with **2a** in the presence of 20 mol % $Zn(OTf)_2$ in toluene at 110 °C, we were pleased to observe the formation of **4a** in 65% yield in 1.5 h with excellent diastereoselectivity (92:8). Since no improvement was observed in terms of the yield or the diastereoselectivity of the product **4a** with further change in the amount of $Zn(OTf)_2$, we identified this as the optimized DROC condition.[18]

Next, to generalize our protocol, the reactions of a diverse range of 2-aryl-*N*-tosylaziridines with the aniline **2a** were studied, and the results are shown in Scheme 3. When

Scheme 3. Synthesis of Various 1-Aryl-Substituted Hexahydroimidazo[1,2-*a*]quinolines from 2-Aryl-*N*-tosylaziridines and *N*-Propargylanilines



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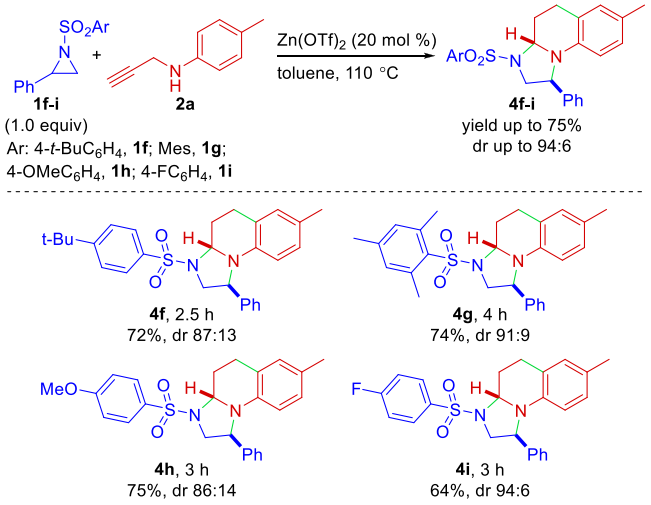
electron-rich 2-(4-*tert*-butylphenyl)-*N*-tosylaziridine (**1b**) and the 3-fluoro variant of the 2-aryl-*N*-tosylaziridine **1c** were reacted with **2a** under the optimized DROC conditions for 2 h, the corresponding quinoline derivates **4b** and **4c**, respectively, were obtained in very good yields with high diastereoselectivity. It is noteworthy that various organic compounds and drug molecules with fluorine substituents can exhibit special biological properties.[19] For further functionalization of the products, halo-aryl substituted aziridines were studied. When 2-(3-chlorophenyl)-*N*-tosylaziridine (**1d**) and 2-(3-bromophenyl)-*N*-tosylaziridine (**1e**) were reacted with **2a** under the optimized DROC conditions, the corresponding products **4d** and **4e** were obtained in very good yields with excellent diastereoselectivity (Scheme 3).

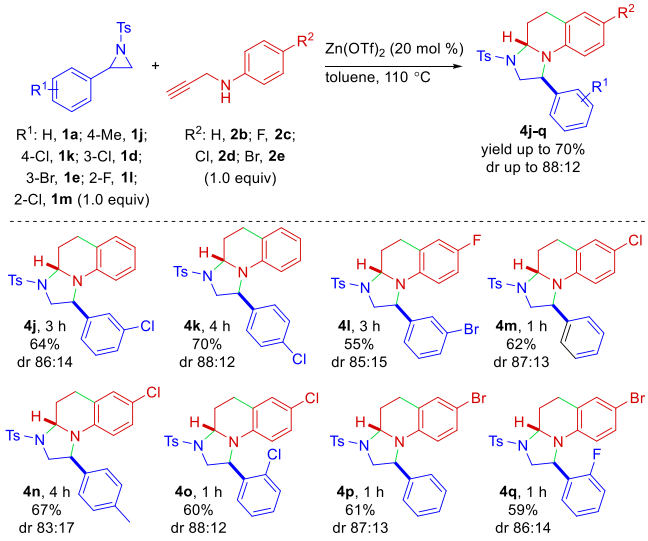
To study the electronic effect of the *N*-arylsulfonyl group, several 2-phenyl-*N*-arylsulfonylaziridines were investigated as substrates. When aziridines bearing aryl groups with + I effect such as 4-*tert*-butylphenyl (**1f**) and mesityl (**1g**) on the *N*-sulfonyl group or aziridine **1h** with a 4-methoxyphenyl group on the sulfonamide nitrogen exerting a strong + R effect were used, the corresponding products **4f–h** were obtained in high yields with high diastereoselectivity (up to 91:9 dr). The transformation also effectively worked with aziridine **1i** bearing an electron-withdrawing 4-fluorophenylsulfonyl group on the nitrogen to furnish the corresponding hexahydroimidazo[1,2-*a*]quinoline derivative **4i** in good yield with excellent diastereoselectivity (94:6 dr). All of the results are summarized in Scheme 4.

Scheme 4. Synthesis of *N*-Arylsulfonyl-Substituted Hexahydroimidazo[1,2-*a*]quinolines from 2-Phenyl-*N*-arysulfonylaziridines and *N*-Propargylaniline



To extend the scope of the strategy further, a wide range of 2-aryl-*N*-tosylaziridines and 4-substituted *N*-(prop-2-yn-1-yl)-anilines were subjected to the optimized DROC conditions. The results are shown in Scheme 5. When *N*-(prop-2-yn-1-yl)aniline (**2b**) was used with aziridines **1d** and 2-(4-chlorophenyl)-*N*-tosylaziridine (**1k**) in two separate sets of experiments, the respective quinolines **4j** and **4k** were obtained in very good yields with high diastereoselectivities. Similar DROC of 4-fluoro-*N*-(prop-2-yn-1-yl)aniline (**2c**) with **1e** for 3 h gives the corresponding quinoline derivative **4l** in 55% yield with high diastereoselectivity (Scheme 5).

Scheme 5. Synthesis of Hexahydroimidazo[1,2-*a*]quinolines from 2-Aryl-*N*-tosylaziridines and 4-Substituted *N*-(Prop-2-yn-1-yl)anilines



In order to increase the available sites for substructural variation of the products, 4-chloro-*N*-(prop-2-yn-1-yl)aniline (**2d**) was used as the functionalized nucleophile for the DROC with **1a**, and the desired product **4m** was obtained in 62% yield with 87:13 dr. Electron-rich 2-(*p*-tolyl)-*N*-tosylaziridine (**1j**) also performed well, and in 4 h, the corresponding quinoline product **4n** was obtained in good yield with high dr. When 2-(2-chlorophenyl)-*N*-tosylaziridine (**1m**) was used as the substrate with **2d**, within just 1 h, **4o** was formed in 60% yield with high diastereoselectivity. When 4-bromo-*N*-(prop-2-yn-1-yl)aniline (**2e**) was reacted with **1a** and 2-(2-fluorophenyl)-*N*-tosylaziridine (**1l**) separately under the DROC conditions, the respective quinolines **4p** and **4q** were obtained in good yields with high diastereoselectivities (87:13 and 86:14 dr). The structure of compound **4** was confirmed by the single-crystal X-ray analysis of **4q** as a representative example. The relative stereochemistry of the 2-fluorophenyl group at carbon **1** and the hydrogen at **3a** carbon were found to be *syn* to each other.[18]

Finally, the strategy was extended for the synthesis of nonracemic hexahydroimidazo[1,2-*a*]quinolines starting from enantiopure (*R*)-2-phenyl-*N*-tosylaziridine, (*R*)-**1a** (>99% ee). When (*R*)-**1a** was reacted with **2a** under the DROC conditions, the corresponding nonracemic hexahydroimidazo-[1,2-*a*]quinoline derivative (1*S*,3a*R*)-**4a** was obtained with poor enantioselectivity (25% ee). The reduced ee of (1*S*,3a*R*)-**4a** was probably due to the partial racemization of the enantiopure starting material (*R*)-**1a** during the reaction.[20] To enhance the enantioselectivity of the reaction, the ring-opening step was carried out in the presence of 20 mol % $Zn(OTf)_2$ in toluene at room temperature. Upon complete consumption of the starting aziridine, the temperature of the reaction was elevated to 110 °C and in 2 h, (1*S*,3a*R*)-**4a** was obtained with 54% enantiomeric excess. Next, a milder Lewis acid, $Yb(OTf)_3$, was used (10 mol %) to effect the initial ring-opening of (*R*)-**1a** in toluene at 80 °C followed by treatment of the reaction mixture with 20 mol % $Zn(OTf)_2$ at 110 °C for 2.5 h to obtain the corresponding cyclized product in 57% yield with very poor enantioselectivity (19%). Gratifyingly, when (*R*)-**1a** was subjected to the ring-opening with **2a** in the presence of 10

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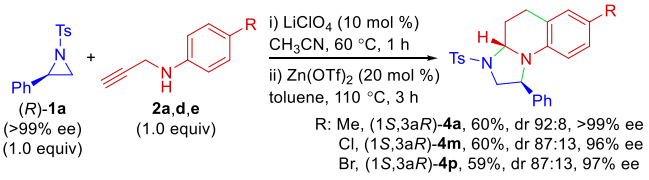
mol % $LiClO_4$ in acetonitrile at 60 °C for 1.5 h, followed by treatment with 20 mol % $Zn(OTf)_2$ in toluene at 110 °C, the nonracemic hexahydroimidazo[1,2-*a*]quinoline derivative (1*S*,3a*R*)-**4a** was obtained in the enantiopure form (>99% ee, Scheme 6).[18]

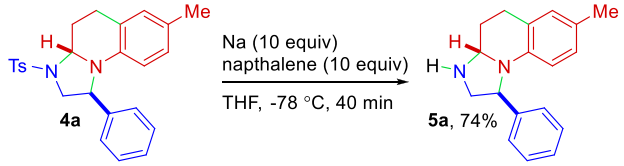
Scheme 6. Enantioselective Synthesis of Hexahydroimidazo[1,2-*a*]quinolines from Enantiopure Aziridines



Next, we generalized this approach by employing a couple of the 4-substituted *N*-propargylanilines. When **2d** was reacted with enantiopure (*R*)-**1a** (>99% ee) under the optimized reaction conditions, the corresponding nonracemic hexahydrimidazo[1,2-*a*]quinoline derivative (1*S*,3a*R*)-**4m** was obtained with excellent enantioselectivity (96% ee). Similarly, when **2e** was reacted with (*R*)-**1a** (>99% ee), the expected product (1*S*,3a*R*)-**4p** was also formed with excellent enantioselectivity (97% ee). The results are shown in Scheme 6.

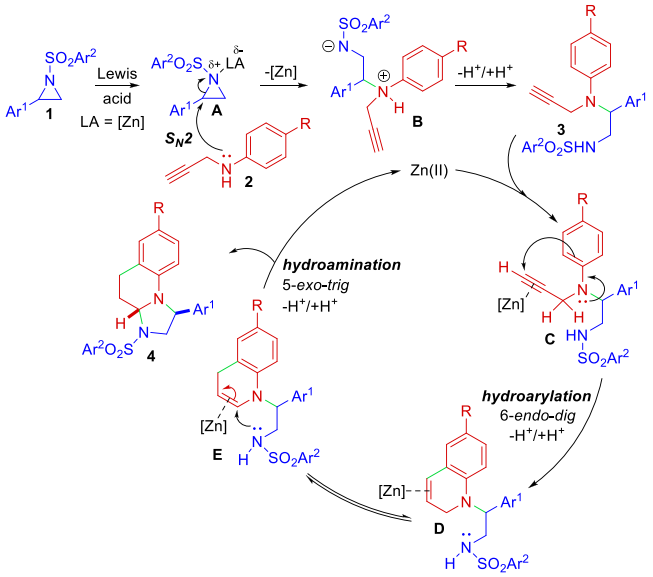
To enhance the scope and applicability of the products hexahydroimidazo[1,2-*a*]quinolines in medicinal chemistry,[21] the synthesized compounds were detosylated. As a representative example, the detosylation of **4a** was accomplished in the presence of sodium naphthalenide in THF at −78 °C and the corresponding hexahydro-imidazo[1,2-*a*]quinoline derivative **5a** with a free NH group was obtained in high yield (74%, Scheme 7).

Scheme 7. Synthesis of Hexahydroimidazo[1,2-*a*]quinoline with Free NH Group via Detosylation



Based on our experimental observations, a plausible mechanism is depicted in Scheme 8. At first, the Lewis acid coordinates with the nitrogen of the aziridine (or one of the sulfonamide oxygens) to generate a highly reactive intermediate species **A**. The nitrogen lone pair of *N*-propargylaniline then attacks the benzylic position of **A** in an S_N2-type fashion to generate the corresponding ring-opened product **3** via the formation of **B**. Subsequently, **3** enters into the zinc-catalytic cycle via formation of zinc-coordinated alkynyl complex **C**. In the next step, **C** undergoes 6-*endo*-*dig* cyclization at the terminal carbon of the alkynyl group by the neighboring tertiary nitrogen group-assisted nucleophilic substitution through the *ortho*-position of the aniline moiety to form the intermediate **D** via net hydroarylation process.[22] Presumably, **D** exists in an equilibrium with **E** that undergoes a concomitant second intramolecular cyclization (a net hydroamination process) by the attack of the pendant sulfonamide

Scheme 8. Plausible Mechanism for the Formation of Hexahydro[1,2-*a*]quinolines from Activated Aziridines and *N*-Propargylanilines



group through the nitrogen in a 5-*exo*-*trig* fashion to furnish the quinoline derivative **4**.

Notably, during the second hydroamination-type step, the stereochemical orientation of the aryl group on the acyclic chain spatially guides the intramolecular cyclization step leading to the formation of the products with excellent diastereoselectivity.

To conclude, we have developed an advanced synthetic route to expeditiously access a novel class of hexahydroimidazo[1,2-*a*]quinolines via a one-pot Lewis acid-catalyzed S_N2-type ring-opening of activated aziridines with *N*-propargylanilines followed by cascade cyclization steps comprising of intramolecular hydroarylation and hydroamination reactions. The developed high-yielding strategy remarkably upholds all the economic principles of modern organic synthesis, viz., atom, step, and redox economy (the consecutive hydroarylation and hydroamination steps on the same alkynyl moiety), and delivers the desired products with excellent diastereoselectivity (up to 94:6 dr) and enantiospecificity (up to >99% ee). The generality of the methodology has also been successfully demonstrated by employing a wide range of activated aziridines and substituted *N*-propargylanilines. We believe that the developed synthetic strategy will be extremely useful to practicing organic and medicinal chemists.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c02801.

Experimental procedure, optimization study, characterization data, NMR spectra (^1H and ^{13}C), crystal data, and HPLC chromatograms of the products (PDF)

Accession Codes

CCDC 1832327 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 Cam-

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Notes

The authors declare no competing financial interest.

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ACKNOWLEDGMENTS

M.K.G. is grateful to IIT Kanpur, India and DST (SERB), India, for financial support. S.P. thanks CSIR, India, and N.C. thanks DST, India, for a research fellowships.

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