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Atroposelective Synthesis

Stereoselective Synthesis of Atropisomeric Acridinium Salts by the Catalyst-Controlled Cyclization of *ortho*-Quinone Methide Iminiums

*Xingxing Wu and Christof Sparr**

Abstract: Quinone methides are fundamental intermediates for a wide range of reactions in which catalyst stereocontrol is often achieved by hydrogen bonding. Herein, we describe the feasibility of an intramolecular Friedel–Crafts 6π electrocyclization through ortho-quinone methide iminiums stereocontrolled by a contact ion pair. A disulfonimide catalyst activates racemic trichloroacetimidate substrates and imparts stereocontrol in the cyclization step, providing a new avenue for selective ortho-quinone methide iminium functionalization. A highly stereospecific oxidation readily transforms the enantioenriched acridanes into rotationally restricted acridiniums. Upon ion exchange, the method selectively affords atropisomeric acridinium tetrafluoroborate salts in high yields and an enantioenrichment of up to 93:7 e.r. We envision that ion-pairing catalysis over ortho-quinone methide iminiums enables the selective synthesis of a diversity of heterocycles and aniline derivatives with distinct stereogenic units.

Introduction

The multitude of transformations proceeding over carbenium intermediates represents a striking opportunity for catalyst stereocontrol when applying common activation strategies.[1] Compared to systems devoid of proximal heteroatoms (R_3C^+),[1b–f] oxocarbenium-, iminium-, thiocarbenium- and related intermediates (XC^+R_2) provide a specific site to interact with catalysts to arrange for enantioface discrimination (Figure 1A).[2] Analogous benzylic carbocations stabilized by *para*- or *ortho*-positioned heteroatoms as represented by their quinoidal structure require longer-ranging interactions for catalyst stereocontrol. As they are common intermediates, quinone methides have enabled a multitude of applications in natural products synthesis, materials chemistry and the development of pharmaceuticals.[3] By the use of chiral Brønsted acid catalysts,[4] stereocontrol was thus recently established with *ortho*- or *para*-amino functionalized benzylic alcohols through the formation of quinone methide imines (Figure 1B, left).[5] Rearomatization of the neutral intermediates thereby provides an ideal driving force as evident by their high reactivity, which enables the preparation of a striking number of enantioenriched aromatic amines. By harnessing hydrogen-bond interactions, the quinone methide imines react stereoselectively in conjugate additions or cycloaddition reactions, as systematically demonstrated by Rueping,[5a,b] Schneider,[5c,d] Sun,[5e] Shi[5f] and other researchers. The transition state geometry and the proximity of the catalyst, pivotal to control reactions with high stereoselectivity, is thereby organized by discrete hydrogen bonds.[5] In contrast, stereoselective ion-pairing catalysis through *ortho*-quinone methide iminiums without hydrogen-bonding assistance is hampered by the variation of delocalized interactions (Figure 1B, right).[6] Nonetheless, given the analogies between common unsaturated carbonyl substrates and quinone methides[7] and their corresponding iminium-activated derivatives, such chiral contact ion pairs are deemed of general interest for stereoselective catalysis to prepare *ortho*-substituted anilines or heterocyclic products.

Based on the pioneering approaches for catalytic 6π electrocyclizations reported by Trauner, Bergmann, List, Smith and others,[8] the capacity of ion-pairing catalysis to induce stereoselectivity was elegantly demonstrated by Rueping and co-workers in particular for acyclic substrates (Figure 1C, ancillary aryl groups).[8d] Under chiral Brønsted acid catalysis, α,β-unsaturated aldehydes and hydrazines were thereby readily converted into hydrazonium ions, thus inducing the hexatomic ring formation by a highly stereoselective 6π electrocyclization.

We hence considered if the generation of *ortho*-quinone methide iminiums by means of ion-pairing catalysis[9] allows to induce a stereoselective Friedel–Crafts 6π electrocyclization by enantioface discrimination of the transient chiral contact ion pair (Figure 1D). Upon rearomatization and catalyst regeneration, such a heterocycle formation would provide substituted acridanes through a pathway unique for stereoselective catalysis. More specifically, the stereoconvergent Brønsted acid activation of racemic substrates with a benzylic leaving group (LG) would lead to a chiral ion pair in the form of an *ortho*-quinone methide iminium salt for

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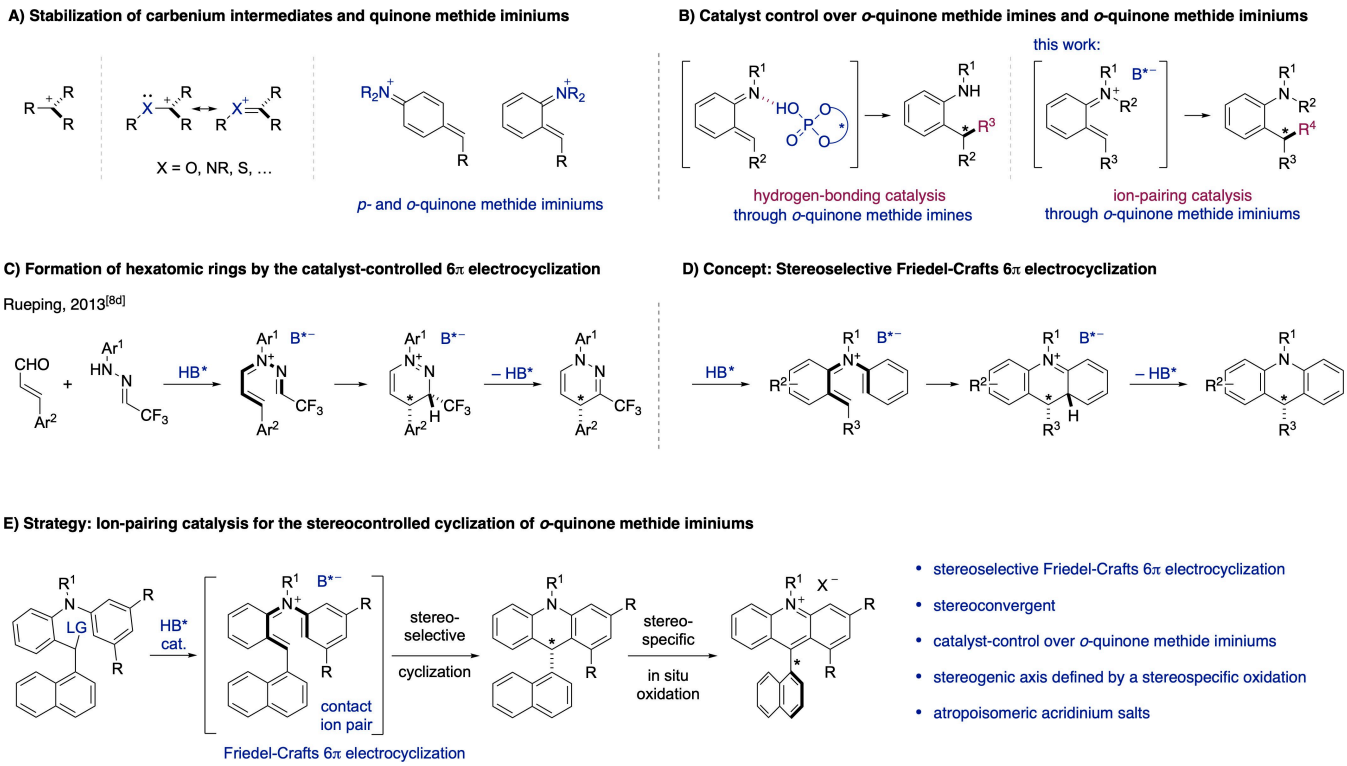


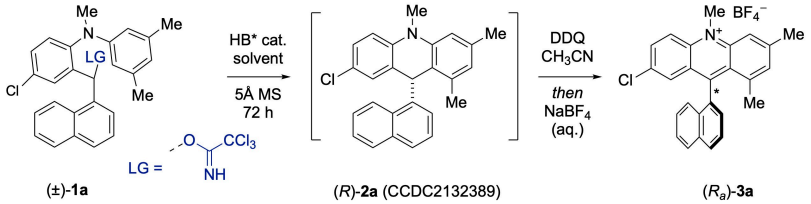
Figure 1. Background and concept of the work.

the stereoselective cyclization to an enantioenriched acridane (Figure 1E). Notably, the naphthyl acridane bearing a configurationally defined stereogenic center at the 9-position could then directly undergo a stereospecific oxidation with control over the configuration of a stereogenic axis,[10] offering a strategy for the stereoselective synthesis of atropisomeric acridinium salts.[11,12] It is noteworthy that by using current methods, acridinium atropisomers are only accessible with the chromatographic separation of corresponding acridanes and an ensuing reoxidation.[12f]

We herein demonstrate the viability of a stereoconvergent *ortho*-quinone methide iminium formation using atropisomeric disulfonimide catalysts to induce a stereoselective Friedel–Crafts 6π electrocyclization with enantioface discrimination within the chiral ion pair. A subsequent stereospecific oxidation of the enantioenriched acridanes selectively provides atropisomeric acridinium salts in high yields and enantioenrichment.

Results and Discussion

We started our studies by an expeditious substrate preparation through a reaction sequence involving a C–N cross coupling and the addition of a corresponding organolithium reagent to 1-naphthaldehydes (see Supporting Information for details). A trichloroacetimidate was subsequently installed as leaving group given their efficient synthesis from hydroxy precursors and the known catalytic activation by phosphoric acids.[13] With an exploratory racemic trichloroacetimidate substrate (±)-**1a** in hand, the effect of different atropisomeric Brønsted acid catalysts **C1**–**C5**[5] was explored for their capability to stereoconvergently generate *ortho*-quinone methide iminium intermediates for the envisaged stereoselective cyclization (Figure 2). We anticipated that after the activation of the trichloroacetimidate group to induce the elimination step, an ion pair of the *ortho*-quinone iminium and the anionic form of the catalyst gives rise to enantiocontrol to furnish chiral acridane **2a**. We therefore first investigated the enantioselective Friedel–Crafts electrocyclization using (R_a)-configured catalysts separately (see Supporting Information) and were pleased to find that the acridane **2a** was formed with up to 94:6 e.r. with (*R*)-configuration when using **C4**, as established by X-ray crystallographic analysis. We next tackled the stereospecific oxidation of acridane (*R*)-**2a** to access the desired atropisomeric acridinium product **3a**. While $NOBF_4$ and MnO_2 as oxidants provided inconsistent outcomes or low conversion, chloranil and DDQ suitably afforded the anticipated acridinium products at ambient temperature or −78 °C. Employing DDQ to convert the acridane intermediate (*R*)-**2a** (94:6 e.r.), the highest level of enantiopurity for **3a** (91:9 e.r.) was obtained in CH_3CN at −45 °C. Notably, the acridinium salt **3a** shows a suitable configurational stability with a bond rotational barrier of $\Delta G^{\ddagger}_{348K} = 121.2\ kJmol^{-1}$. After the individual cyclization and oxidation steps allowed high stereoselectivity and conversion, the combined sequence was paired with a final anion exchange using $NaBF_4$. Consistent with our initial results, the BINOL-based phosphoric acid **C1**, which was previously used to activate



Entry	Catalyst	Solvent	Temperature	Yield[b]	e.r.[c]
1	**C1**	toluene	–20 °C	10	50:50
2	**C2**	toluene	–20 °C	67	63:37
3	**C3**	toluene	–20 °C	87	89:11
4	**C4**	toluene	–20 °C	85	89:11
5	**C5**	toluene	–20 °C	86	84:16
6	**C3**	toluene	–35 °C	81	89:11
7	**C3**	mesitylene	–35 °C	77	89:11
8	**C3**	$CHCl_3$/mesitylene (1:3 v/v)	–35 °C	75	90:10
9	**C3**	toluene/mesitylene (1:2 v/v)	–35 °C	82	91:9
10	**C4**	toluene/mesitylene (1:2 v/v)	–35 °C	85 (84)[d]	91:9

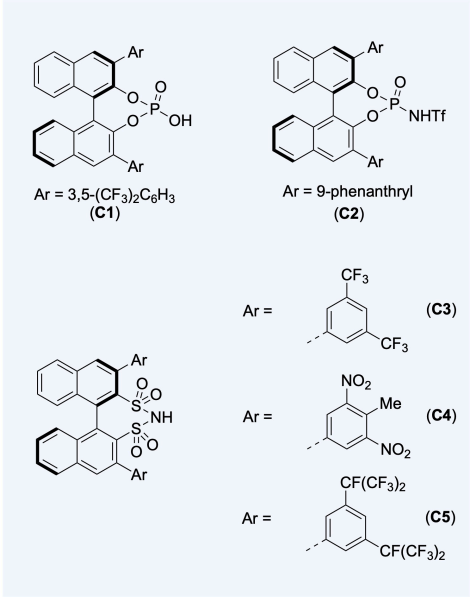


Figure 2. [a] The reactions were performed with **1a** (15.0 μmol), catalyst (5.00 mol%) and 5 Å MS (30.0 mg) in the specified solvent (8.0 mmol L^{-1}) at the specified temperature for 72 h; Oxidation of the acridane intermediate (*R*)-**2a** was performed with DDQ (2.00 eq.) in CH_3CN at −45 °C for 15 minutes, followed by anion exchange with $NaBF_4$ (aq., sat.). [b] NMR yield of **3a** in % using durene as internal standard. [c] Enantiomeric ratio determined for the isolated product by HPLC on a chiral stationary phase after reduction of (R_a)-**3a**. [d] Isolated yield in parentheses. MS = molecular sieves. DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone.

trichloroacetimidates,[13] showed only low conversion to a racemic product (Figure 2, entry 1). However, utilizing 5.0 mol% of the more acidic *N*-triflyl phosphoramide catalyst **C2** gave acridinium **3a** in 67 % yield and a promising enantioselectivity of 63:37 upon ensuing oxidation with DDQ and anion exchange (entry 2). Gratifyingly, disulfonimide catalysts **C3**–**C5**[14] were particularly effective in this reaction (entries 3–5) and catalyst **C3** and **C4** were identified to be also superior in terms of stereocontrol (both 89:11 e.r., entries 3 and 4). By evaluating the effects of the reaction medium and temperature (entries 6–10), we found that the highest selectivities are achieved in a toluene-mesitylene solvent mixture at −35 °C and that catalyst **C4** provided slightly higher yields (entry 10, 84 %, 91:9 e.r.). We next studied the stereochemical outcome of the oxidation from the intermediate (*R*)-**2** to the atropisomeric acridinium salts **3**.[15] However, after numerous attempts, all inspected crystals of the acridinium salts were unsuitable for X-ray crystallographic studies. The absolute configuration of **3a** was thus determined by X-ray crystallography of an enantioenriched demethylated acridine derivative after a conclusive comparison to assign a (R_a)-configuration for **3a**, followed by the comparison of the CD spectra of all acridinium products, hence providing a basis for a stereochemical model in combination with the previously deduced (*R*)-configuration of **2a**.[16]

With the optimal reaction procedure established, we set out to verify the generality of the catalyst-controlled Friedel–Crafts electrocyclization of *ortho*-quinone methide iminiums (Figure 3A). Trichloroacetimidate substrates **1a**–**1e** possessing various residues at the polyaromatic residue (Ar^3), such as substituted naphthyl, phenanthryl and pyrene units, were initially explored, leading to corresponding acridiniums (R_a)-**3a**–**3e** in excellent yields (84–94 %) and high enantioselectivities. Notably, a substrate with a benzyl moiety at the nitrogen atom was also readily converted, affording product **3f** in 85 % yield with 93:7 atroposelectivity. We next examined the variations of the *ortho*-quinone methide iminium-forming moiety (Ar^2) for their impact on the stereoselective transformation. Substrates **1g**–**1i** with F, H or Me groups at the *para*-position thereby delivered the products (R_a)-**3g**–**3i** smoothly under identical reaction conditions. Gratifyingly, yields of up to 96 % were obtained over both steps after anion exchange. Notably, substitution on the 5-position of the Ar^2-residue resulted in a slightly lower enantioselectivity, which was observed for the Cl-substituted product (R_a)-**3j** (84:16 to 91:9 e.r., (R_a)-**3j** versus (R_a)-**3a**). The benzene ring undergoing aromatic substitution (Ar^1) was next replaced by a 2-naphthyl unit, furnishing product (R_a)-**3k** in good yield but modest selectivity through an acridane (*R*)-**2k** with 68:32 e.r., likely because of the different reactivity of the substrate in the cyclization process. Furthermore, the electron-deficient 3,5-dichloro phenyl group was also compatible with the reaction sequence, thus yielding the corresponding atropisomeric product (R_a)-**3l**. For this substrate, the reaction was carried out in $CHCl_3$/mesitylene at slightly higher temperature to ensure full conversion (−18 °C), providing (R_a)-**3l** in 79 % yield and an e.r. of 86:14.

While (R_a)-**3l** was formed with somewhat lower selectivity, a simple recrystallization of the acridane (*R*)-**2l** readily provided a highly enantioenriched intermediate (99:1 e.r.) for subsequent transformations (Figure 3B). Intriguingly, we observed that upon oxidation of (*R*)-**2l** with DDQ, the

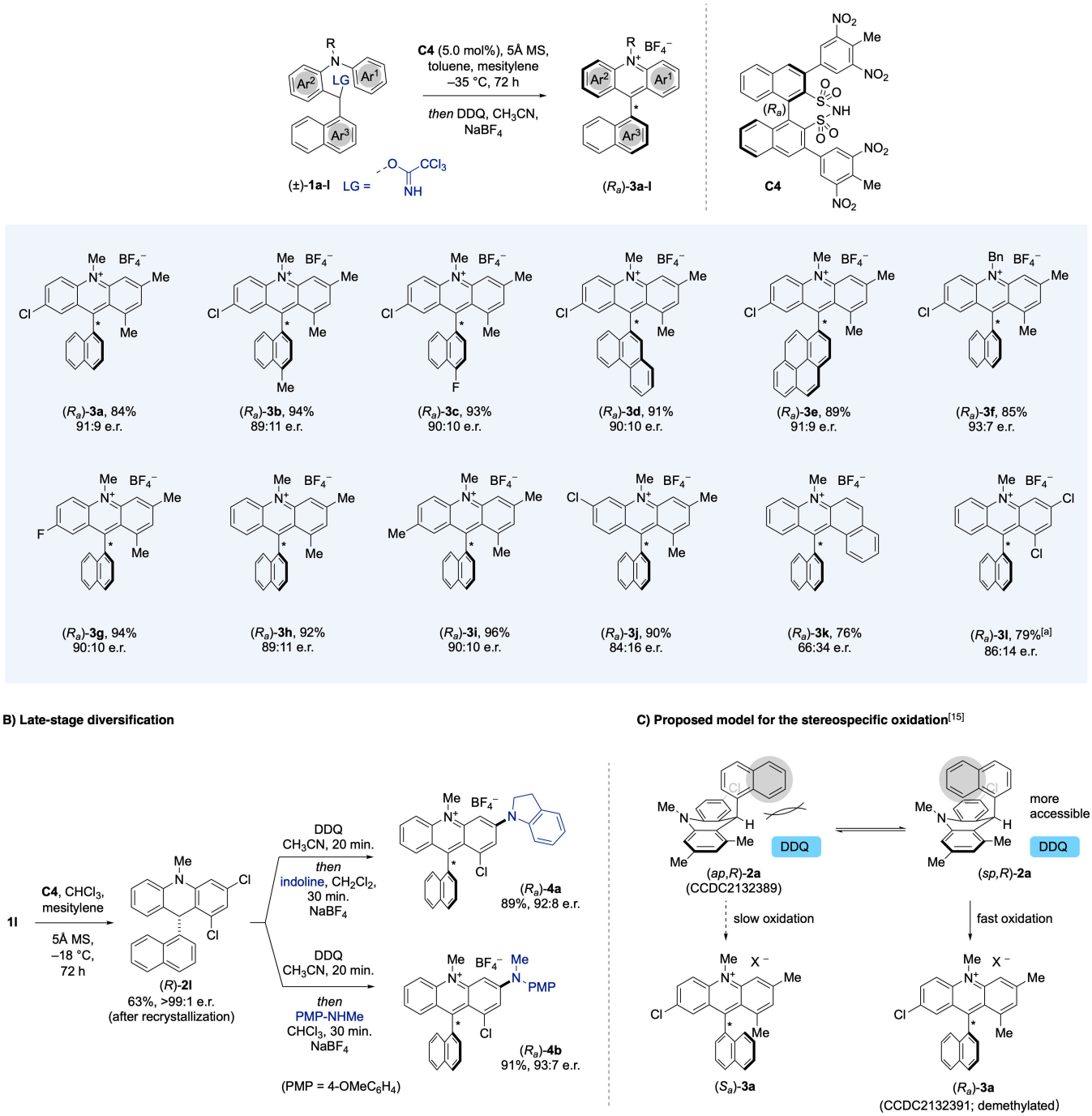


Figure 3. A) Scope of the catalyst-controlled stereoselective cyclization of *ortho*-quinone methide iminiums, B) late-stage diversification by nucleophilic aromatic substitution to access aminoacridinium salts and C) the proposed stereoselectivity model for the stereospecific oxidation of acridane (*R*)-**2a** to acridinium product (R_a)-**3a**, in agreement with related literate-known processes.[15] The cyclizations were performed with substrates **1** (70.0 μmol), 5.00 mol% catalyst **C4**, in a mixture of toluene (2.9 mL) and mesitylene (5.9 mL) at −35 °C for 72 h; The oxidation was carried out with DDQ (2.00 eq.) in CH_3CN (10 mL) at −45 °C for 15 minutes. Isolated yield of **3** after anion exchange with aq. sat. $NaBF_4$. The enantiomeric ratio was determined for the isolated product by HPLC on a chiral stationary phase after reduction of (R_a)-**3a–3l**. [a] Reaction performed in a mixture of $CHCl_3$ (1.95 mL) and mesitylene (5.85 mL) at −18 °C. MS = molecular sieves. DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone.

dichloro-substituted acridinium salt (R_a)-**3l** (97:3 e.r.) was capable of undergoing nucleophilic aromatic substitutions with appropriate nucleophiles.[12h] A late-stage diversification of (R_a)-**3l** was thus successfully carried out, providing the amino-functionalized, atropisomeric acridiniums (R_a)-**4a** and (R_a)-**4b** with an e.r. of 92:8 and 93:7, respectively.

Whereas this process renders the acridinium salts modular for structural modifications, the slight impact on enantiopurity is likely a consequence of reversible additions to the electrophilic 9-position of the acridinium salt (R_a)-**3l** (see Supporting Information).

With the configuration of the intermediate acridane (*R*)-**2** and the atropisomeric acridinium (R_a)-**3** determined by X-ray crystallography, we suggest a mechanism for the observed stereoselectivity in agreement with the model proposed by Straub, Bonne, Bressy, Bugaut and Rodriguez (Figure 3C).[15] Notably, NMR studies of (*R*)-**2a** in CD_2Cl_2 showed consistent ^1H spectra over the entire temperature range from 208 K to 298 K. Nonetheless, while the solid-state structure illustrates a boat conformation of the acridane with the naphthalene unit in pseudo-axial orientation that would lead to (S_a)-**3a**, a prompt rotation of the naphthyl group to the (*sp*,*R*)-**2a** conformer reduces shielding of the hydrogen at the C-9 position, leading to a faster oxidation with DDQ to provide the (R_a)-**3a** atropisomer with high stereospecificity. The reliable stereospecific oxidation to form congested aromatic products[15] is thus confirmed as a versatile method for controlling unique stereogenic units in order to define the topology of rotationally restricted products. On the other hand, the viability of ion pairing catalysis to direct stereoselective reactions through *ortho*-quinone methide iminiums (Figure 1B, right) is expected to provide a general means for conjugate additions to *ortho*-substituted anilines and a suitable entry to a variety of enantioenriched heterocycles by distinct cyclization strategies.

Conclusion

We developed a catalytic stereoselective Friedel–Crafts 6π electrocyclization of *ortho*-quinone methide iminiums formed by a stereoconvergent activation of trichloroacetimidate substrates, validating that stereocontrol over quinoidal iminium intermediates is tractable by a contact ion pair with an atropisomeric disulfonimide catalyst. Electrocyclic ring formation was furthermore verified as expedient approach for the selective synthesis of atropisomeric products when combined with a stereospecific oxidation. The rapid assembly of enantioenriched acridane intermediates and atropisomeric acridinium products furthermore demonstrates the suitability of the method for the efficient synthesis of pertinent heterocycles. We hence anticipate that catalyst control over the activated iminium form of quinone methides will allow the synthesis of a broad range of enantioenriched aniline derivatives and corresponding heterocyclic structures by employing ion pairing catalysis.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: Acridiniums · Atropisomers · Brønsted Acid Catalysis · Ion-Paring Catalysis · *Ortho*-Quinone Methide Iminiums

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