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Dimerization–cyclization reactions of isocyanoaryl-tethered alkylidenecyclobutanes *via* a triplet biradical mediated process†

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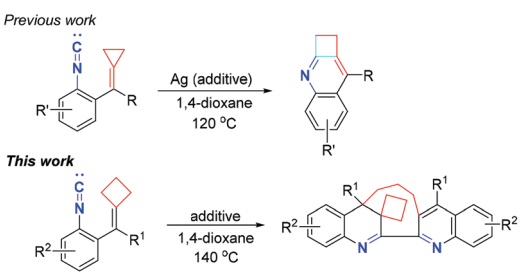
A triplet biradical mediated dimerization–cyclization reaction of isocyanoaryl-tethered alkylidenecyclobutanes has been reported in this paper, giving a new protocol for the construction of macrocyclic skeletons including dihydroquinoline and quinoline units in moderate yields. The reaction proceeded through a key 1,4-diazabutatriene intermediate along with intramolecular redox to produce a biradical intermediate species, which subsequently experienced bond-breaking and -making processes to give the desired product. The reaction mechanism was supported by density functional theory (DFT) calculations.

Introduction

Isocyanides are pivotal intermediates in organic synthesis and have been widely used to synthesize a diversity of nitrogen-containing compounds, including new drugs and natural products.[1] For example, they can easily insert into various C–C, C–X or X–X (X = heteroatom) chemical bonds to rapidly construct complex molecules.[2] Moreover, they can also undergo diverse radical cyclizations to provide aromatic heterocyclic compounds;[3] function as ligands to coordinate with transition metals to realize further transformations;[4] act as zwitterion intermediates to accept nucleophilic attacks;[5] and perform as key intermediates for multi-component reactions.[6,5h,i]

The dimerization of isocyanides has also been employed to furnish aromatic heterocyclic compounds,[7] which can be classified as homodimerization and heterodimerization. In 1977, Lange and Höfle reported the synthesis of 2,2-diphenyl-4,4′-bis-quinazolines *via* a head to head C–C bond homodimerization of two *N*-imidoyl isocyanides.[7a] Later on, Yamamoto and co-workers developed a new and efficient synthetic method to produce a novel class of 1,4-disubstituted imidazoles *via* heterodimerization of two different isocyanides in 2006.[7b] Subsequently, Cheng's group employed the homodimerization of 2-pyridylisonitriles to rapidly construct π-extended fused heteroarenes, which are novel selective colorimetric and optical probes for copper ions.[7c] Moreover, Hong and Xu also independently reported the cycloaddition of two different isocyanides to synthesize the corresponding 1,4-diaryl-1*H*-imidazoles and pyrrolo[3,4-*b*]indoles in good yields, respectively.[7d,e] However, to the best of our knowledge, the homodimerization of isocyanides through a biradical process has not been reported yet.

In 2017, our group reported a novel formal [3 + 1] cyclization reaction of isocyanoaryl-substituted alkylidenecyclopropanes for the synthesis of 1,2-dihydrocyclobuta[*b*]quinoline derivatives in moderate to excellent yields (Scheme 1, *previous work*).[8] We proposed that this cyclization reaction proceeded through an intramolecular nucleophilic attack of the isocyanide group to the C=C double bond, Ag ion elimination and cyclopropane ring expansion, furnishing 1,2-dihydrocyclobuta[*b*]quinoline derivatives. On the basis of this previous work, we envisaged that if isocyanoaryl-tethered alkylidenecyclobutanes are used as substrates to conduct the same reaction, the cyclobutane ring expansion could also be realized. However, we found that upon heating at 140 °C, an unexpected quinoline and dihydroquinoline product derived from homodimerization and cyclization was obtained in moderate yield (Scheme 1, this



Scheme 1 Previous work and this work.

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work). Quinoline and dihydroquinoline skeletons are an important class of heterocycles in natural products, and are widely found in alkaloids and pharmaceuticals, possessing diverse pharmacological properties such as anti-bacterial,[9] anti-cancer,[10] anti-HIV[11] and so on.[12] In particular, in 2015, Pal and co-workers reported the design and preparation of a new hybrid template by linking quinoline, triazole and dihydroquinoline together as pharmacophoric groups, disclosing that this library of molecules could work as potential cytotoxic agents for the inhibition of cancer cells and PDE48 *in vitro*.[13] Although numerous useful synthetic methods have been developed to construct quinoline[14] and dihydroquinoline[15] related core structures, the exploration of novel and efficient synthetic protocols for the rapid construction of quinoline and dihydroquinoline skeletons is still required at the present stage. This unprecedented result stimulated us to further explore this reaction because the mixed quinoline and dihydroquinoline scaffold may have special biological activities. Herein, we wish to report a novel biradical-mediated dimerization–cyclization reaction of isocyanoaryl-tethered alkylidenecyclobutanes to synthesize macrocyclic skeletons containing dihydroquinoline and quinoline units.

Results and discussion

Experimental investigations

We first utilized substrate **1a** as a model substrate for the initial examination in the presence of Ag_2CO_3 (5 mol%) as the additive at 140 °C in 1,4-dioxane under an argon atmosphere and found that the desired macrocyclic product **2a** was obtained in 33% NMR yield within 24 h (Table 1, entry 1). The structure of **2a** has been unambiguously determined by X-ray diffraction, and its crystal data are presented in the ESI.† We further optimized the reaction conditions, and the results are summarized in Table 1. Using various Lewis acidic additives such as $AgNTf_2$, $Zn(NTf_2)_2$, $Cu(OTf)_2$, TlOAc, $In(OTf)_3$, $Fe(OTf)_2$ and $BF_3{\cdot}Et_2O$ in this reaction, we identified that TlOAc was the best Lewis acidic additive for this dimerization–cyclization reaction, affording **2a** in 42% yield, presumably due to that it is the most stable additive at such high temperature (entries 2–8). Next, we found that the reaction could also proceed in the absence of any additive, giving **2a** in 37% yield (entry 9). The examination of solvent effects revealed that the use of other organic solvents such as DMF, toluene, anisole and cyclohexanone could also afford **2a** in moderate yields ranging from 32% to 42%, indicating that 1,4-dioxane, toluene and anisole were the solvent of choice (entries 10–13). Then, we chose 1,4-dioxane as the solvent and TlOAc as the additive for further optimization of the reaction conditions. Lowering the reaction temperature to 130 °C furnished **2a** in 20% yield, and raising the reaction temperature to 150 °C did not improve the yield of **2a** in 1,4-dioxane (entries 14 and 15). Further increasing the employed amount of TlOAc did not improve the yield of **2a**, suggesting that 5 mol% of TlOAc should be used in this reaction (entry 16). In addition, lengthening or shortening the reaction time did not give **2a** in better yields (entries 17 and 18). Purging the oxygen gas from the solvent could improve the yield of **2a** to 45% NMR yield (40% isolated yield) and adding molecular sieves 4 Å to get rid of the trace water in the solvent did not improve the yield of **2a** (entries 19 and 20). To summarize, this dimerization–cyclization reaction should be carried out in degassed 1,4-dioxane using TlOAc (5 mol%) as the additive at 140 °C within 24 h (for more detailed information, see Tables S1–S3 in the ESI†).

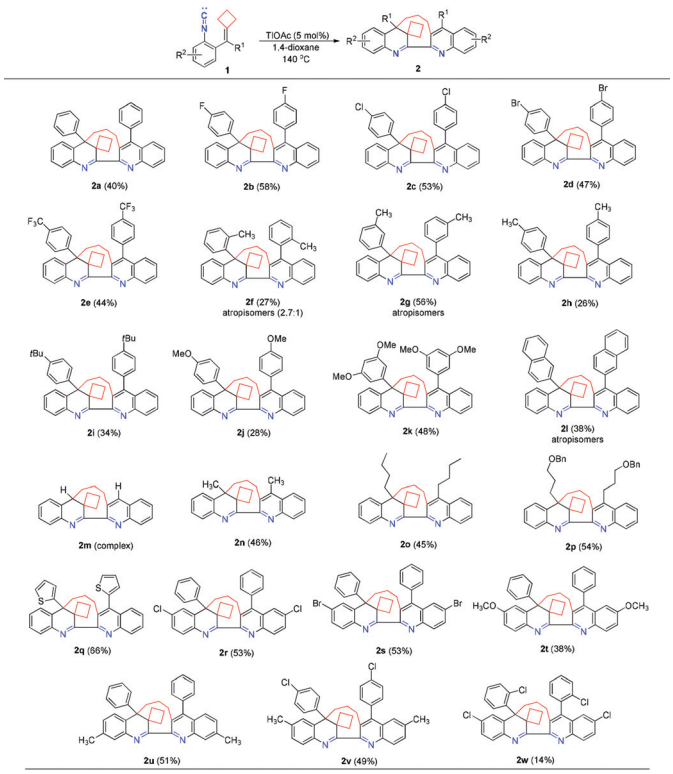
Table 1 Optimization of the reaction conditions[a]

Entry	Additive	Temp. (°C)	Solvent	Yield[b]/%
1	Ag_2CO_3	140	1,4-Dioxane	33
2	$AgNTf_2$	140	1,4-Dioxane	21
3	$Zn(NTf_2)_2$	140	1,4-Dioxane	—
4	$Cu(OTf)_2$	140	1,4-Dioxane	—
5	TlOAc	140	1,4-Dioxane	42
6	$In(OTf)_3$	140	1,4-Dioxane	—
7	$Fe(OTf)_2$	140	1,4-Dioxane	20
8	$BF_3{\cdot}Et_2O$	140	1,4-Dioxane	—
9	—	140	1,4-Dioxane	37
10	TlOAc	140	DMF	37
11	TlOAc	140	Toluene	42
12	TlOAc	140	Anisole	42
13	TlOAc	140	Cyclohexanone	32
14	TlOAc	130	1,4-Dioxane	20
15	TlOAc	150	1,4-Dioxane	37
16[c]	TlOAc	140	1,4-Dioxane	41
17[d]	TlOAc	140	1,4-Dioxane	18
18[e]	TlOAc	140	1,4-Dioxane	40
19[f]	***TlOAc***	***140***	***1,4-Dioxane***	***45 (40)***
20[g]	TlOAc	140	1,4-Dioxane	39

[a] Unless otherwise specified, all reactions were carried out using **1a** (0.1 mmol), additive (5 mol%) in solvent (1.0 mL), 140 °C, 24 h. [b] Yields were determined by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard and isolated yield is given in parentheses. [c] Additive: 20 mol%. [d] Reaction time: 12 h. [e] Reaction time: 36 h. [f] Purging oxygen gas in the solvent. [g] Adding molecular sieves 4 Å (50 mg).

With the optimal conditions in hand, we investigated the generality of this dimerization–cyclization reaction using various isocyanoaryl-tethered alkylidenecyclobutanes **1b–1w** as substrates and the results are elucidated in Table 2. When the R^1 group is an aromatic substituent, substrates **1b–1e**, having an electron-poor aromatic ring, gave the desired products **2b–2e** in moderate yields ranging from 44% to 58%. However, substrates **1f–1k**, having an electron-rich aromatic ring, furnished the corresponding products in the yields depending on the position of the substituent at the aromatic ring. When the $-CH_3$ or $-OCH_3$ group was present at the *meta*-position of the benzene ring, the corresponding products **2g** and **2k** were obtained in 56% and 48% yields, respectively. However, when the $-CH_3$ or $-OCH_3$ group was present at the *ortho*- or *para*-position, products **2f**, **2h** or **2j** were obtained in lower yields, indicating that the substituent position effects have a signifi-

Table 2 Substrate scope of **1** for the homodimerization reaction[a,b]

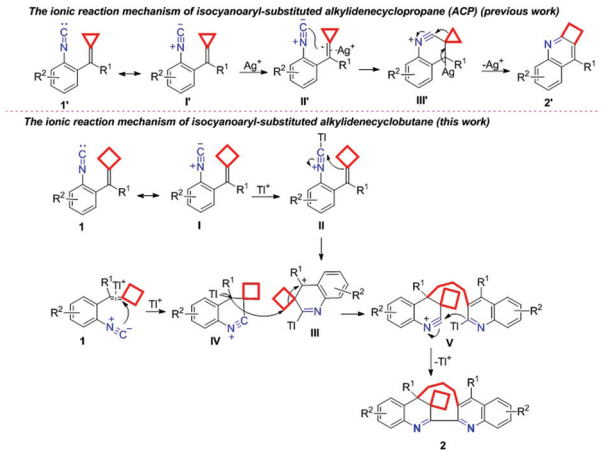


[a] Unless otherwise specified, all reactions were carried out using **1** (2 mmol), TlOAc (5 mol%) in degassed 1,4-dioxane (4.0 mL), 140 °C, 24 h, under an Ar atmosphere. [b] Isolated yield.

cant impact on product yields. Substrate **1i** bearing a sterically bulky and electron-rich *tert*-butyl group at the *para*-position of the benzene ring could deliver the desired product **2i** in 34% yield. Substrate **1l**, in which the R^1 group is a 2-naphthyl group, provided the desired product **2l** in 38% yield as atropisomers. When R^1 is a hydrogen atom, the reaction only gave a complex product without the formation of the desired product. Substrates **1n–1p** with aliphatic substituents were also tolerated, giving the corresponding products **2n–2p** in 46%, 45% and 54% yields, respectively. When R^1 is a thiophene substituent, the corresponding product **2q** could be obtained in 66% yield, suggesting that this reaction is compatible with heteroaromatic rings. We also examined the substituent effect at the isocyanoaryl moiety and found that the substituents could be halogen atoms, methyl or methoxy groups and had little influence on the reaction proceeding, affording the desired products **2r–2u** in 38%–53% yields. Substrates **1v** and **1w** having a substituent on each benzene ring were also tolerated, furnishing the desired products **2v** and **2w** in 49% and 14% yields.

Mechanistic studies

Next, we focused on investing the mechanism of this dimerization–cyclization reaction. The suggested ionic reaction mechanism of isocyanoaryl-substituted alkylidenecyclopropane (ACP) **1′** is shown in Scheme 2 (previous work).[8] Initially, the C=C



Scheme 2 The proposed reaction mechanisms for previous work and this work.

double bond of ACP **I′** was activated by Ag^+ ions to furnish an intermediate **II′**, which subsequently underwent an intramolecular nucleophilic attack to afford intermediate **III′**. Finally, the elimination of Ag^+ and cyclopropane ring expansion gave the corresponding product **2′**. According to the above mechanism, a plausible ionic reaction mechanism for isocyanoaryl-substituted alkylidenecyclobutane is first proposed as shown in Scheme 2. Substrate **1** can have its resonance structure **I**, in which the isocyanide group is initially activated by Tl^+ ions to receive the intramolecular nucleophilic attack of the cyclobutyl group, affording an intermediate **III**. On the other hand, the C=C double bond in another molecule of substrate **1** can also receive the intramolecular nucleophilic attack of the isocyanide group at high temperature to give an intermediate **IV**, which reacts with intermediate **III** through an intermolecular nucleophilic attack along with the cyclobutane ring-opening process to afford intermediate **V**. The subsequent intramolecular addition along with the release of TI^+ delivers the desired product **2**.

Then, we embarked DFT studies on these proposed ionic mechanisms for previous work and this work. For the DFT studies on the proposed ionic mechanism of previous work, all calculations have been performed at the SMD/M06/6-311+G(d,p)/LANL2DZ//B3LYP/6-31G(d)/LANL2DZ level with the Gaussian 09 program. The solvation Gibbs free energy profile in 1,4-dioxane for the suggested reaction pathway is shown in Fig. 1 (ΔG_{298} (kcal mol^{-1}), see ESI† for the details). This reaction pathway includes two steps. The first one is the activation of the C=C double bond of isocyanoaryl-substituted alkylidenecyclopropane by silver(I) ions to undergo an intramolecular nucleophilic attack, giving intermediate **A′** through transition state **TS1′** with an energy barrier of 22.3 kcal mol^{-1}. The second step is the intermediate **A′** passing through **TS2′** with an energy barrier step up to 35.1 kcal mol^{-1} to furnish the corresponding product *via* the elimination of Ag^+ and cyclopropane ring expansion process, which is the rate-determining step in the reaction. Moreover, the total $\Delta G_{298,\ rxn}$ in

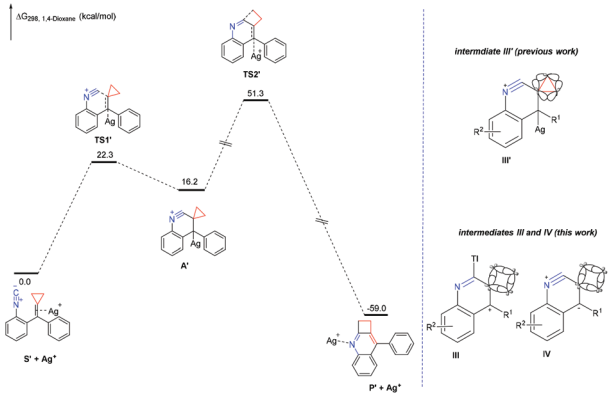
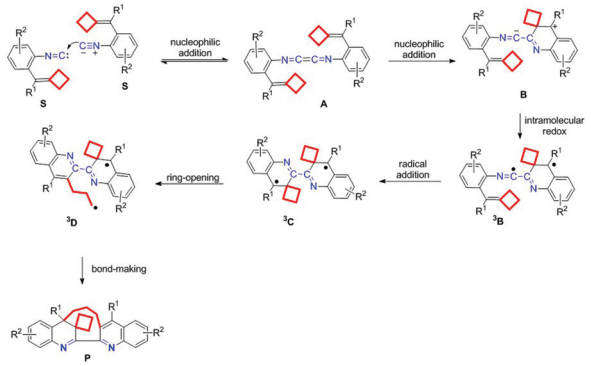


Fig. 1 DFT calculation on the reaction pathway *via* the ionic mechanism of previous work (relative Gibbs energy values in 1,4-dioxane solution are given in kcal mol^{-1}).



Scheme 3 Proposed biradical reaction mechanism.

1,4-dioxane of this reaction is −59.0 kcal mol^{-1} overall, accounting for a thermodynamically favorable process.

The proposed ionic mechanism of this work was also investigated by DFT calculations using the SMD/M06/6-311+G(d,p)//B3LYP/6-31G(d) level of theory with the Gaussian 09 program. To simplify the calculation process, we investigated the reaction pathway starting from substrate **1a** without TlOAc additive. However, the suggested intermediates **III** or **IV** could not be located after several attempts by the DFT calculations. Moreover, another plausible ionic reaction mechanism is also investigated and shown in Scheme S6 in the ESI,† which could not be supported by the DFT calculations as well. Therefore, we hypothesize that this dimerization–cyclization reaction may proceed through a different pathway from the aforementioned proposed ionic mechanism. Through the comparison of these two ionic reactions, we could recognize that the difference is the instability of intermediates **III** and **IV**. According to the Fröster–Coulson–Moffitt model, Walsh model[16] and Dewar's σ conjugation conception,[17] the carbon–carbon bond of cyclopropane is similar to an unsaturated C=C double bond. Therefore, the cyclopropane moiety could conjugate to the neighbouring electron-deficient part, contributing to the stability of intermediate **III′**. For cyclobutane units lacking similar properties, the formations of intermediate **III** or **IV** are impossible (Fig. 1).

The ionic mechanism of this dimerization–cyclization reaction does not work, leading us to think about other possibilities for the mechanism. According to Xu's work,[7e–i] we think that our work may also go through a 1,4-diazabutatriene mechanism. We first proposed a similar ionic mechanism shown in Scheme S7 in the ESI.† Unfortunately, this ionic mechanism cannot be supported by the DFT calculations since the key intermediate cannot be located. Considering that the reaction was conducted at 140 °C, we hypothesize that this reaction may involve a free-radical mechanism, which is generated by intramolecular redox at high temperature.

As a radical mediated process, a plausible biradical mechanism for this dimerization–cyclization reaction is outlined in Scheme 3. Initially, the isocyanide carbon of one substrate undergoes a nucleophilic attack on the isocyanide carbon of another substrate to give a 1,4-diazabutatriene intermediate **A**. Then, one C=C double bond of intermediate **A** undergoes the intramolecular nucleophilic attack on the 1,4-diazabutatriene unit, generating the intermediate **B**, which subsequently experiences an intramolecular redox process to furnish a biradical intermediate ^{3}**B**. Next, a radical addition to the C=C double bond takes place to furnish an intermediate ^{3}**C**, which initiated the cyclobutane ring-opening to produce a biradical intermediate ^{3}**D**. Finally, the intermediate ^{3}**D** undergoes a bond-making process to give the desired product. The Lewis acidic additive of TlOAc, which is quite stable at high temperature, probably can activate both the isocyano-group through σ-coordination and the C=C double bond by π-coordination, facilitating the reaction proceeding and improving the yield of this dimerization–cyclization reaction product. The key issue of this newly proposed reaction mechanism is the formation of 1,4-diazabutatriene and the biradical intermediates as well as their reaction properties.

The possible reaction mechanisms along the singlet or triplet pathways were all investigated theoretically. We first calculated the possible singlet pathway. The species reported in this paper are denoted as ^{m}ITEMx, where m = 1 for singlet and 3 for triplet spin state multiplicities; ITEMx = TSx for a transition state, **A–D** for a reaction intermediate, **S** for the substrate and **P** for the product. The solvation Gibbs free energy profile in 1,4-dioxane for the suggested reaction pathway is shown in Fig. 2 (ΔG_{298} (kcal mol^{-1}), see ESI† for the details). First, the reaction starting from substrate complex **S** proceeds through nucleophilic attack of the isocyanide carbon of one substrate on the isocyanide carbon of another substrate, to form 1,4-diazabutatriene **A** *via* **TS1** with an energy barrier of 18.0 kcal mol^{-1}. Subsequently, the intramolecular nucleophilic attack of the C=C double bond on the 1,4-diazabutatriene unit furnishes the intermediate **B** *via* transition state **TS2** with an energy barrier up to 14.4 kcal mol^{-1}. Then, the intermediate **B** is excited from the ground state to the triplet state biradical species ^{3}**B** with 14.0 kcal mol^{-1}. Next, a subsequent radical addition process takes place to generate an intermediate ^{3}**C**

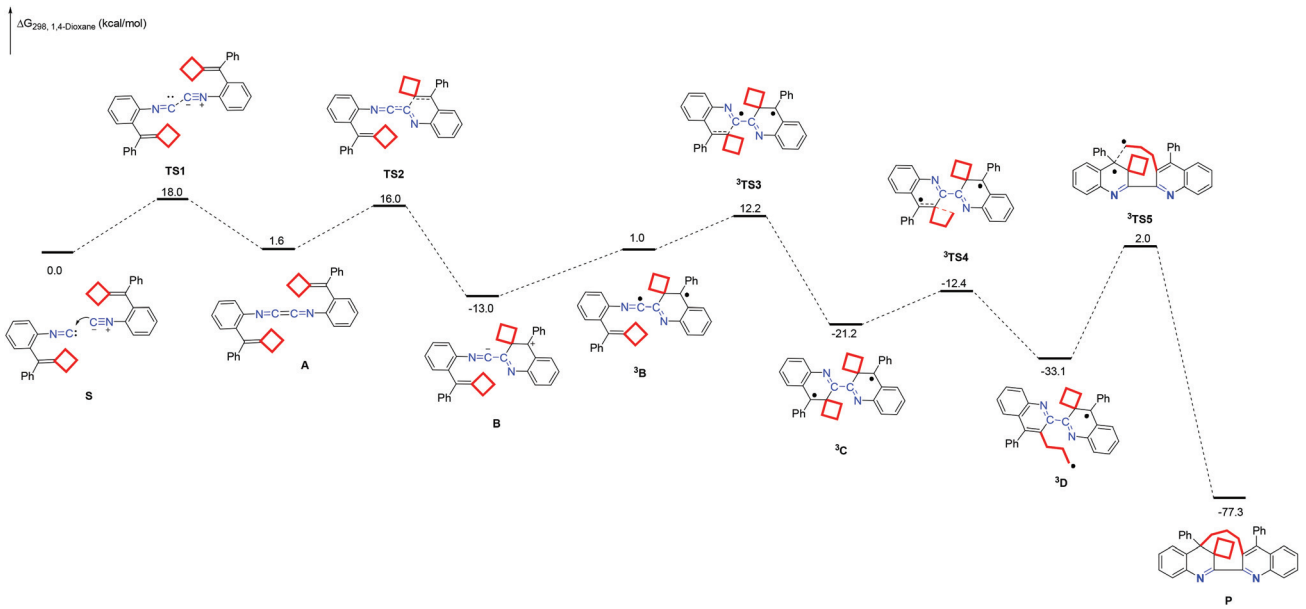
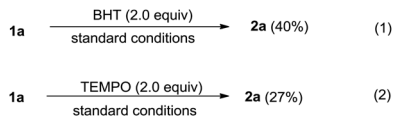


Fig. 2 Solvation Gibbs free energy profile for the reaction of **1a**. (Relative Gibbs energy values in 1,4-dioxane solution are given in kcal mol^{-1}.)

through ^{3}**TS3** with an energy barrier of 11.2 kcal mol^{-1}. Subsequently, the intermediate ^{3}**C** undergoes a cyclobutane ring-opening to deliver an intermediate ^{3}**D** through the transition state ^{3}**TS4** peaked at 8.8 kcal mol^{-1}. Finally, a C–C bond-formation step generates the desired product **P** through ^{3}**TS5** with an energy barrier of 35.1 kcal mol^{-1}, which is the rate-determining step in the reaction. This result is in line with the experimental conditions in which high temperature is required for this reaction. Moreover, the total $\Delta G_{298,\ rxn}$ in 1,4-dioxane of this reaction is −77.3 kcal mol^{-1} overall, accounting for a thermodynamically favorable process. The calculation results support that this reaction proceeds involving a biradical reaction mechanism in a triplet. In addition, we calculated another possible triplet biradical mediated reaction mechanism which is also supported by the DFT calculations (Scheme S8 in the ESI†). In this mechanism, the energy barrier of the rate-determining step is 45.5 kcal mol^{-1}, and the total $\Delta G_{298,\ rxn}$ in 1,4-dioxane of this reaction is −77.3 kcal mol^{-1} overall. Through the comparison of these two ionic reactions, we conclude that the mechanism shown in Scheme 3 is more reasonable than the mechanism shown in Scheme S8.†

To verify the reaction mechanism, two control experiments were conducted, and the results are shown in Scheme 4. Using butylated hydroxytoluene (BHT) and 2,2,6,6-tetramethylpiperidinooxy (TEMPO) as radical inhibitors, the yields of desired product **2a** obtained were 40% and 27%, respectively under the standard conditions. The extent of quenching is not significant. Based on our proposal, the biradical intermediate is generated in an intramolecular manner; thus, it is difficult to quench significantly by TEMPO.



Scheme 4 Control experiments.

Conclusions

In conclusion, we have discovered a novel triplet biradical mediated dimerization–cyclization reaction of isocyanoaryl-tethered alkylidenecyclobutanes, furnishing macrocyclic products containing dihydroquinoline and quinoline units in moderate yields. This new synthetic protocol represents a new entry for the rapid construction of macrocyclic skeletons with simple substrates. Further investigations on expanding the applications of this synthetic method are ongoing in our laboratory.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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