Communication

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Diastereo- and Atroposelective Synthesis of Bridged Biaryls Bearing an Eight-Membered Lactone through an Organocatalytic Cascade

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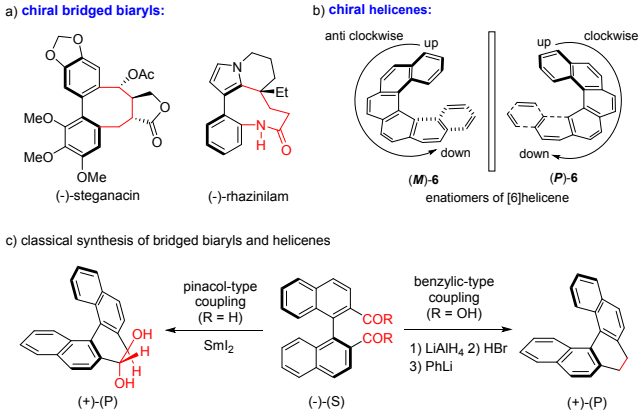
Supporting Information Placeholder

ABSTRACT: We present herein an unprecedented stereoselective synthesis of bridged biaryls with defined axial and central chirality from readily available starting materials. This NHC-catalyzed method proceeds through propargylic substitution of azolium enolates followed by two-directional cyclization as supported by DFT calculation. A range of benzofuran/indole-derived bridged biaryls bearing an eight-membered lactone are accessed with uniformly high stereoselectivity (>98:2 dr, mostly >98% ee).

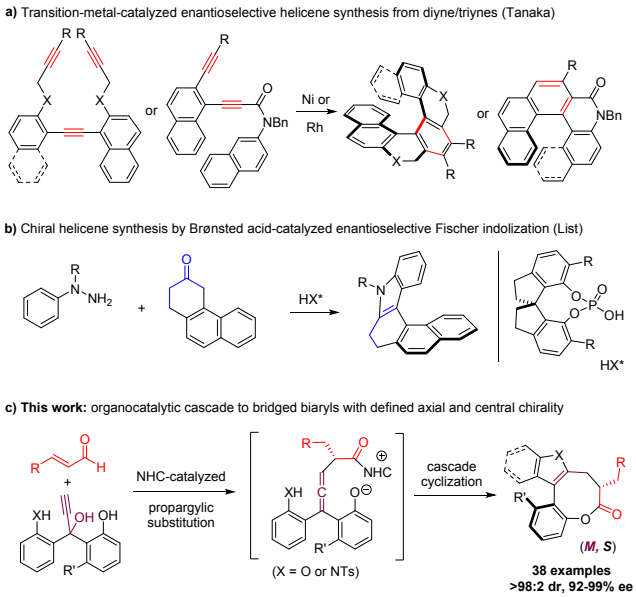
The significance of axially chiral biaryls has been widely recognized in catalysis and drug delivery, due to their exceptional, compact architectures and promising pharmacological profiles.[1] An important subclass is bridged biaryls, which bear an additional linkage between the two arenes and often with stereocenters (Scheme 1a). These structures are of high natural abundance, as exemplified by the *anti*-leukemic lignan (-)-steganacin[2] and tubin inhibitor (-)-rhazinilam.[3] Notably, these compounds are structurally related to helicenes (Scheme 1b), a significant class of helically chiral, *ortho*-condensed polycyclic compounds.[4]

Scheme 1. Bridged Biaryls and Helicenes



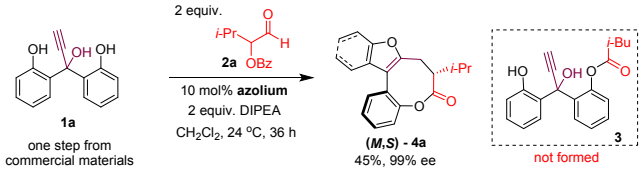
Due to their significant utility, extensive efforts were devoted to the atropoenantioselective synthesis of axially chiral biaryls.[5] The synthesis of bridged biaryls, however, still requires multi-step procedures. The control of both axial and central chirality in these compounds also represents a great challenge, which is typically achieved by sequential reactions utilizing substrate control. As exemplified in Scheme 1c, the pre-installed axial chirality of a bis-carbonyl substrate was exploited to control the installation of stereocenters in the linker or the helical chirality.[6] Only recently, elegant catalytic enantioselective syntheses of helicenes were reported, through either metal-catalyzed arene formation from alkynes (Scheme 2a)[7] or Brønsted acid-catalyzed Fischer indolization (Scheme 2b).[8] To the best of our knowledge, the direct catalytic synthesis of bridged biaryls with simultaneous control of axial and central chirality remains elusive in the literature.

Scheme 2. Catalytic Enantioselective Access to Helicenes and Bridged Biaryls



Herein, we present our discovery and development of a direct, catalytic synthesis of bridged biaryls from readily available propargylic alcohols and enals with excellent diastereo- and atropo-enantioselectivity (Scheme 2c). These products possess a benzofuran or indole-containing biaryl moieties with an eight-membered lactone bridge, and are produced under NHC-catalysis[9] through an enantioselective propargylic substitution followed by two-directional cyclization.

Scheme 3. Discovery of Bridged Biaryl Synthesis



Previous investigation in our laboratory has led to the development of NHC-catalyzed enantioselective acylative kinetic resolution of alcohols/phenols as well as desymmetrization of *meso*-bisphenols.[10] We became interested in the asymmetric acylation of the readily available triol **1a** to access enantioenriched propargylic tertiary alcohol **3** (Scheme 3). When we carried out the reaction of **1a** with aldehyde **2a** in the presence of catalytic azolium and DIPEA, to our great surprise, the expected acylation product **3** was not observed at all. Instead, a bridged biaryl with an eight-membered lactone linkage **4a** was obtained in moderate yield with excellent diastereo- and enantioselectivity (45% yield, >98:2 dr, 99% ee). Intriguingly, the incorporation of the reactive terminal alkyne completely switched the chemo-selectivity of this catalytic system. The formation of **4a** is believed to follow a pathway initiated by the attack of the azolium enolate intermediate to the alkyne moiety[11] followed by cascade cyclization. Attracted by this unprecedented one-pot catalytic synthesis of bridged biaryls, we turned our attention to the exploration of this transformation.

The representative optimization studies are included in the supporting information (SI). The use of commercially available α,β-unsaturated aldehydes instead of **2a** provided similar level of efficiency in most cases and was therefore a more convenient choice. With the optimal reaction conditions in hand, the generality of this catalytic desymmetrization was examined.

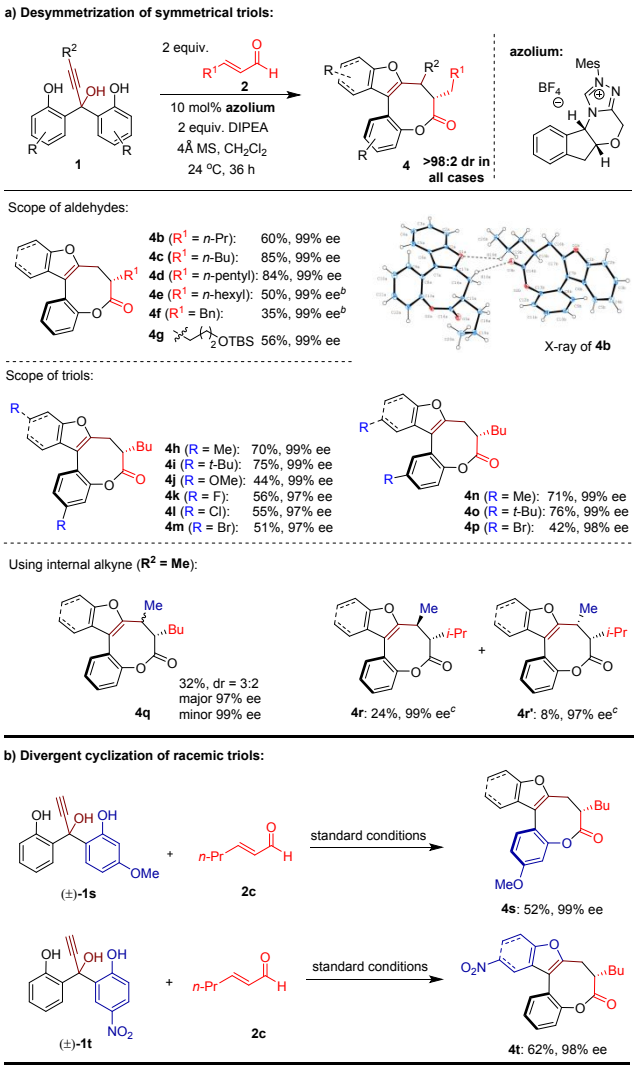
As shown in Scheme 4a, the scope of this system regarding the aldehydes proved to be general. A range of aldehydes **2** bearing simple alkyl or ether-containing substituents participated in the reaction equally well to yield **4b**-**4g** in moderate to high yield with uniformly >98:2 dr and ≥99% ee. The absolute configuration of **4b** was assigned by single crystal X-ray diffraction analysis.

The variation on the triol substrates was explored next. It is noteworthy that triols **1** bearing various substituents are easily accessible within two steps from commercial materials. The variations of either electron-donating or withdrawing character on **1** could be well-tolerated to yield the corresponding products **4h**–**4p** in good yield and again with >98:2 dr and excellent enantioselectivity (97-99% ee).

To further expand the substrate scope, triol containing an internal alkyne was tested. When hex-2-enal was used as the aldehyde, the corresponding product **4q** was obtained in relatively low yield and dr (of the two stereocenters). Nonetheless, the enantioselectivities for both isomers are excellent. Alternatively, by the use of the bulky aldehyde **2a**, two diastereomeric compounds **4r** and **4r´** (3:1 dr), each being diastereomerically pure regarding the axial chirality, could be easily separated by column chromatography; both isomers were obtained with high ee of 97-99%. The use of related substrates bearing a more bulky substituent on the internal alkyne (e.g., R^2 = *i*-Pr or Ph) led to no reactivity.

In addition to desymmetrization of symmetrical triols, we were curious whether chemo-selective cascade cyclization could be achieved for unsymmetrical racemic triols as well. As shown in Scheme 4b, when triols **1s** or **1t** possessing electronically differentiated arenes were examined, the formation of a single product **4s** or **4t** was observed. The more electron-rich/nucleophilic phenol moiety attacked the acyl group selectively to form the lactone functionality in the products. The level of diastereo- and enantioselectivity remained at the same level of >98:2 dr, 98-99% ee. It is also noteworthy that these reactions proceeded in a stereoconvergent fashion. Both enantiomers of the racemic substrate were converted to the desired product in excellent enantiopurity.

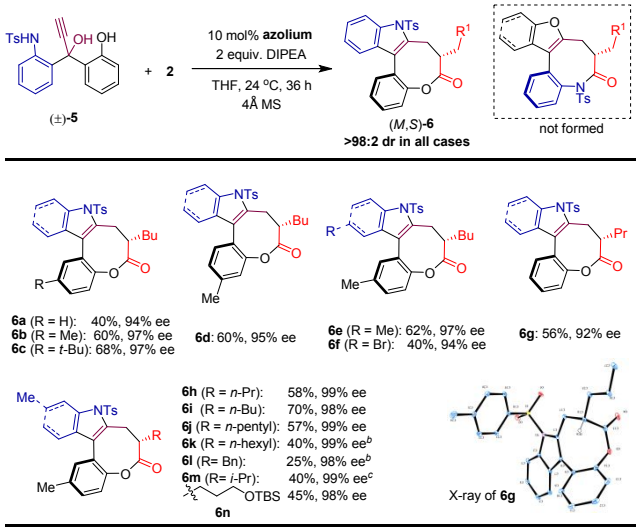
Scheme 4. Scope of Benzofuran-Derived Bridged Biaryls[a]



[a]The reactions were carried out using **1** (0.15 mmol), **2** (2.0 equiv.), azolium (10 mol%), DIPEA (2.0 equiv.) and 4Å molecular sieves (100 mg) in CH_2Cl_2 (2.0 mL) at 24 °C for 36 h. [b]2-chloroaldehyde was used instead of **2**. [c] Aldehyde **2a** was used.

Recognizing the possibility of using unsymmetrical substrates to realize convergent reactions, we then turned our attention to the reaction of compounds bearing different functionalities such as amino phenols **5** (Scheme 5). To our delight, these racemic substrates underwent a highly chemo-selective reaction to deliver indole-based bridged biaryls **6** with the eight-membered lactone exclusively. Notably, no benzofuran-fused lactam product was observed at all. This is consistent with the intriguing preference for ester formation over amide formation under NHC catalysis.[12]

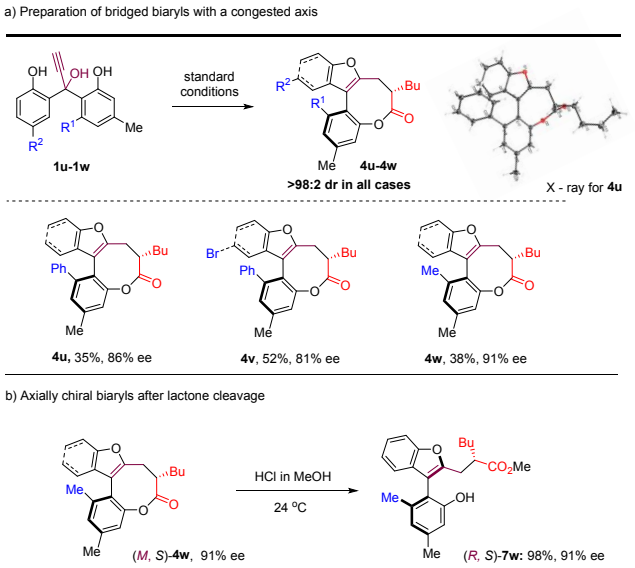
Scheme 5. Scope of Indole-Derived Bridged Biaryls[a]



[a]The general procedure was followed with THF as the solvent. [bc]See Scheme 4.

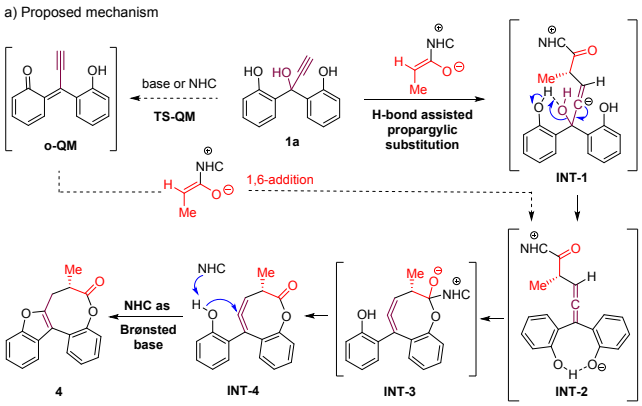
The synthesis of indole-derived bridged biaryls dramatically expanded the scope of this catalytic system.[13] The switch of solvent from CH_2Cl_2 to THF proved to be crucial to achieve higher efficiency of the reaction. A wide range of substituents on the aryl ring in **5** and the substituents in **2** could be well-tolerated to produce **6a-6f** and **6g-6n** in uniformly high diastereo- and enantioselectivity. The absolute configuration of **6g** was unambiguously assigned by single crystal X-ray diffraction analysis. The relatively low yields were due to a side reaction pathway, the details are included in the SI. Fused indoles represent large families of natural products and biologically active compounds in general, and our method provides access to new scaffolds of indole-based bridged biaryls linked by an eight-membered lactone. The evaluation of these new compounds against various *anti*-cancer assays is currently underway.

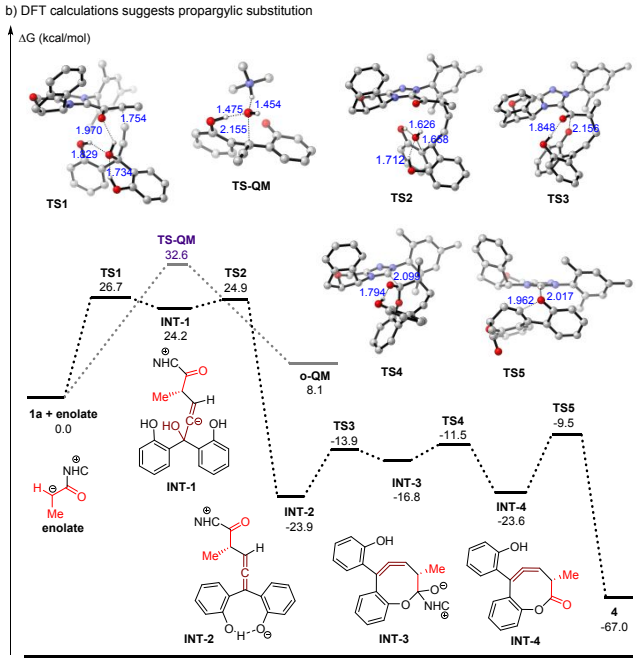
Scheme 6. Access to New Axially Chiral Biaryls



To probe the independent stability of the axial and central chirality in these bridged biaryls, we explored the reaction of triols **1u-1w** to access **4** with an ortho-group on the bottom arene (Scheme 6a). These bulky substrates participated in the reaction and produced **4u-4w** with high stereoselectivity, albeit with lower efficiency. With these bridged biaryls in hand, the cleavage of the lactone to release the rigidity of the compounds was carried out smoothly by the use of HCl in MeOH (Scheme 6b). Biaryl **7w** was obtained in excellent yield and as a single diastereomer.[14] This thus represents a new entry to axially chiral benzofuran/indole-derived biaryls.[15]

Scheme 7. DFT Calculation on Reaction Mechanism





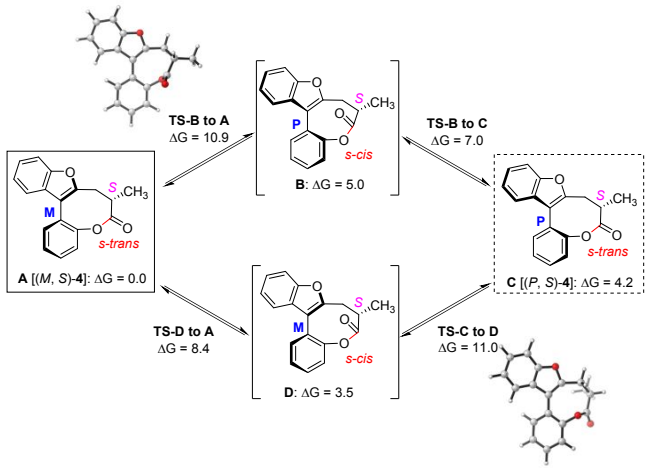
Regarding the mechanism for this NHC-catalyzed cascade cyclization, we hypothesized two possible initiation pathways. Firstly, this reaction could proceed through an alkyne-conjugated *ortho*-quinone methide (Scheme 7a in the box),[16] which would then react with azolium enolate in a 1,6-conjugate addition fashion followed by cascade cyclization. Alternatively, a direct propargylic substitution of the azolium enolate could generate the same allene **INT-2**. Such a transformation under NHC catalysis was realized by our group very recently.[17] **INT-2** could then undergo two-directional cyclization to deliver the desired product **4**. To gain more insight on the reaction mechanism, DFT computations at M06-2X/6-311+G(2d,p)//M06-2X/6-31G* level[18] were performed (Scheme 7). Solvent effect (in THF) was taken into account using the SMD continuum solvent method.[19]

The postulated formation of *o*-quinone methide (**o-QM**) through a base-catalyzed dehydration of **1a** was examined first. Although ***o*-QM** was calculated to be reasonably stable with only 8.1 kcal/mol higher in energy than **1a**, the activation barrier for the formation of such species is too high (32.6 kcal/mol for transition state **TS-QM**) for the reaction to take place. In fact, all the literature precedence involving *o*-quinone methide is carried out in acidic instead of basic conditions.[20]

We next investigated the direct propargylic substitution of azolium enolate.[16] Our results showed that the nucleophilic addition to the unactivated alkyne moiety step (via **TS1**) has a lower barrier of 26.7 kcal/mol (5.9 kcal/mol lower than that of **o-QM** formation). The intermediate **INT-1** formed in this way can readily undergo a facile dehydration to form allene **INT-2**. At this stage, the formation of the eight-membered lactone **INT-4** proceeds smoothly by the attack of the phenoxide onto the acyl azolium moiety via **TS3** to **INT-3** and then **TS4** with an overall low activation barrier of 12.4 kcal/mol. Finally, the attack of the remaining phenol to the allene unit is facilitated by NHC as a Brønsted base catalyst[21] to deliver product **4** with an activation barrier of 14.1 kcal/mol (via **TS5**).[22]

Regarding the enantioselectivity at the stereocenter of **4**, we propose that it is determined by **TS1** in the slow irreversible addition of enolate to **1a**. Calculations of *R*-producing transition states showed that the high enantioselectivity of the reaction is governed by steric factors imparted by the catalyst moiety on the conformation of the enolate moiety in **TS1**, resulting in a preferred addition of the Re face to **1a** (see SI for details).

Scheme 8. DFT Calculation of Conformers of 4.



To unravel the origin of the high diastereoselectivity of the reaction, we investigated computationally the different conformers of both (*M*, *S*)-**4** and (*P*, *S*)-**4**, and the rotational transition states that interconvert the conformers (Scheme 8). The structure of the eight-membered lactone was found to be quite rigid, and the conformation of the bridging axis was highly correlated with that of the lactone moiety. Notably, the interconversion between *M* and *P* isomers involves a key intermediate s-cis conformer. The low energies of these transition states, <15 kcal/mol with respect to the lowest energy s-trans (*M*, *S*)-**4**, indicates that the interconversion is rather facile and the selectivity between (M, *S*)-**4** and (P, *S*)-**4** is controlled thermodynamically by their relative stability. The calculated energy difference of 4.2 kcal/mol between MS-trans-**4** and PS-trans-**4** also agrees well with the high level of diastereoselectivity observed experimentally.

In summary, we have developed a catalytic, diastereo- and atropoenantioselective synthesis of bridged biaryls from readily available starting materials. This NHC-catalyzed transformation proceeds through propargylic substitution-two directional cyclization cascade, and delivers the products with uniformly excellent control of axial and central chirality. The development of new catalytic procedures to access other challenging structures bearing different types of chirality is currently under investigation.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization data for all the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(13) The overall moderate yield of **6** was due to a competitive intramolecular reaction of **5** (see SI for details).

(14) It is noteworthy that the *ortho*-substituent in these biaryls is important for its configurational stability. The cleavage of lactone in **6c**, e.g., led to the formation of biaryl product with a low dr of 1.5:1.

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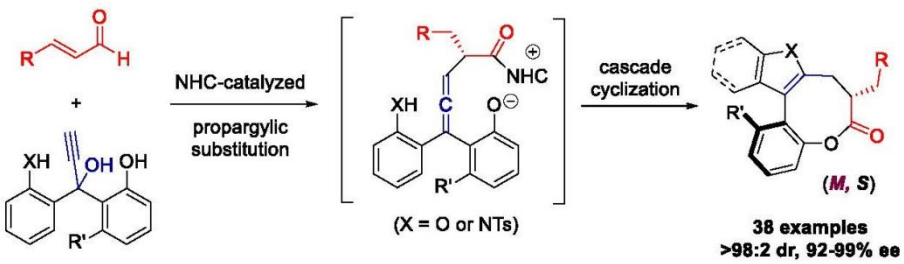
(22) An alternative conversion of **INT-2** to **4** that differs in the sequence of five- and eight-membered ring formation was determined to be a competitive pathway (see SI for details).

TOC Graphic:



- NHC-catalyzed propargylic substitution & cyclization
- Bridged biaryls with an eight-membered lactone
- Excellent control of both axial & central chirality