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Net directed 180° aryl–aryl bond rotation in a prototypical achiral biaryl lactone synthetic molecular motor

Ying Lin, Bart J. Dahl and Bruce P. Branchaud*

Department of Chemistry, Materials Science Institute, Oregon Nanoscience and Microtechnologies Institute, University of Oregon, Eugene, OR 97403-1253, USA

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Abstract—Net directed 180° bond rotation was achieved through diastereoselective ring-opening reactions in an achiral biaryl lactone using a chiral nucleophile followed by re-lactonization. The efficiency of the directed bond rotation has been determined by HPLC–MS to be 50% and 20% with two different chiral nucleophiles. These results demonstrate the potential for a prototype of a chemically driven synthetic molecular motor which has the advantages of both simplicity and flexibility in operation and is the first example of the use of a chiral auxiliary to induce transient axial chirality resulting in net directed bond rotation.
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Synthetic molecular machines are designed to imitate the mechanical movements of everyday large scale machines and machine parts.[1] The design of these artificial molecular machines challenges organic chemists to synthesize molecules that conform to desired dynamic behaviors and the characterization of these systems provides a more lucid understanding of molecular motion.

Biological rotary molecular motors[2] are a spectacular group of biological molecular machines[3] that convert energy (from chemical and electrochemical sources) into a directed mechanical rotation, producing useful work. The most basic requirement of a totally synthetic rotary molecular motor analog is an iterative directed bond rotation via a controllable energetic input.[4] There must be a net rotation in one direction versus the other in order for the system to be useful as an artificial molecular motor.[5] To date there have been only two general synthetic systems that have been experimentally determined to achieve iterative 360° biased net directed bond rotation[6,7] and one synthetic system that has been experimentally determined to achieved 120° biased net directed bond rotation.[8] Several theoretical designs, syntheses, and studies of experimentally unverified proposed net unidirectionally rotating molecular systems have also been reported.[9] We have reported the design and synthesis of a chiral biaryl lactone that should function as a prototypical chemically driven molecular motor capable of repeated net directed 360° rotation.[9g] Practical uses for totally synthetic rotary molecular motors are still being hypothesized, however, preliminary studies have indicated that they may find useful applications in tuning the properties of liquid crystalline environments.[10]

In this letter, we report a new approach to the design of totally synthetic rotary molecular motors, using an achiral motor with chiral reagents to drive the unidirectional rotation. Bringmann et al. have found that ring openings of biaryl lactones with both chiral amides[11] and chiral alkoxides[12] lead to high diastereoselectivity in the formation of atropisomeric biaryls. Using chiral nucleophiles in diastereoselective ring openings to produce atropisomeric biaryls is also well established in the synthesis of natural products containing atropisomeric biaryl stereochemistry.[13] Herein, we report how this concept can be extended to the design of synthetic molecular motors.

Achiral lactone **1** (Scheme 1) should exist as a rapidly interconverting pair of enantiomers by a slight back and forth pivoting about the biaryl bond.[14] Diastereoselective (atropisoselective) ring opening of **1** with an appropriate chiral nucleophile, acting as a chiral auxiliary, should generate predominantly one axial diastereomer, shown as **2a** in Scheme 1, resulting in a net 90°

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* Corresponding author. Tel.: +1 541 346 4627; fax: +1 541 346 4645; e-mail: bbranch@oregon.uoregon.edu

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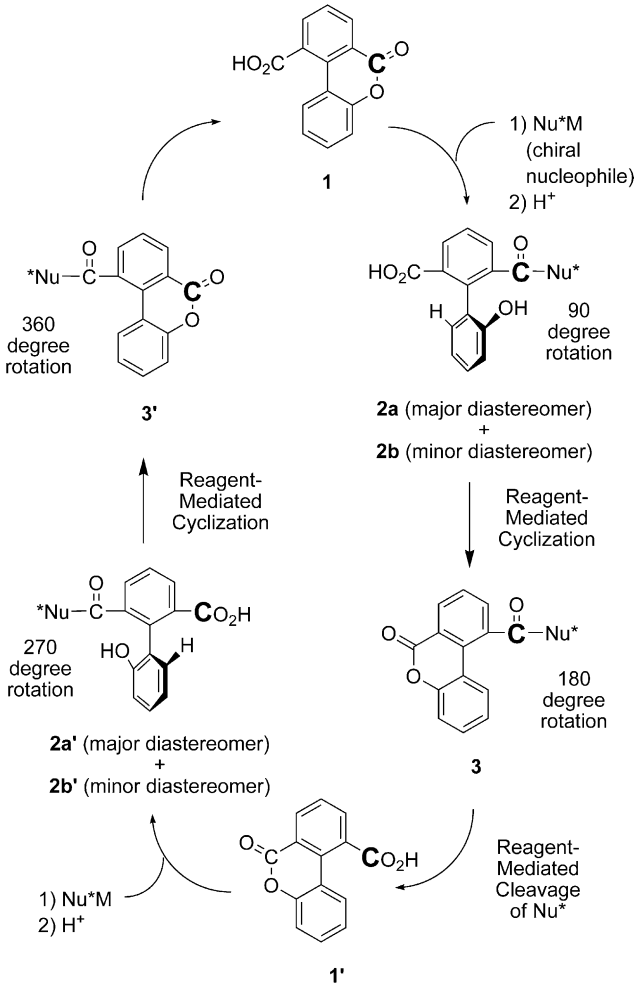
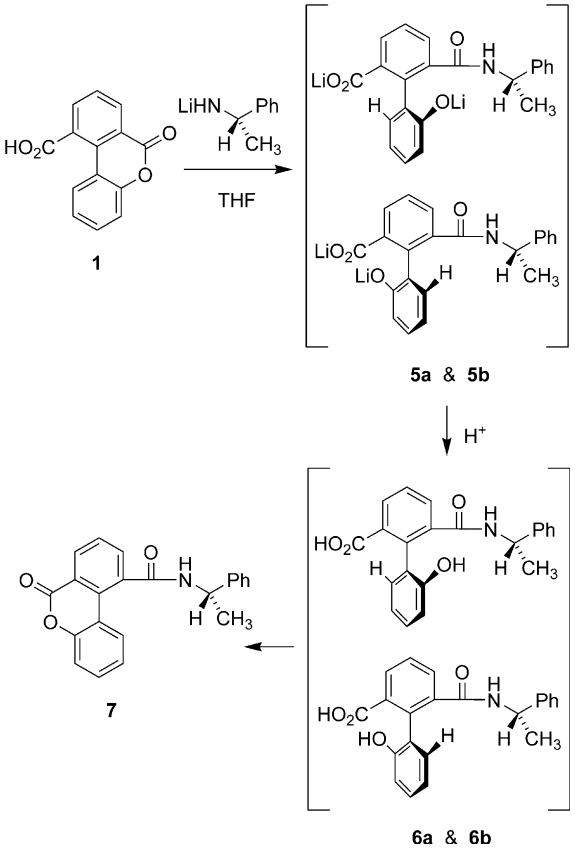


Scheme 1. General strategy to use repeated, iterative atropisoselective lactone ring opening reactions to achieved directed bond rotation in 180° increments.



Scheme 2. Reactions of lactone **1** to demonstrate directed bond rotation using an amine nucleophile (see text for detailed discussion).

directed rotation. Cyclization of **2a** with an appropriate reagent should generate lactone **3**, resulting in a net 180° directed rotation. Cleavage of the chiral auxiliary (Nu*) from **3** should generate **1′**, in which the carbonyl would be switched relative to its position in **1**. Another cycle of the same reactions would lead to **2a′** (270° rotation), then **3′** (360° rotation), then back to **1**. The entire process could then be repeated to result in iterative net unidirectional bond rotation. The overall energy for the bond rotation would come from the use of thermodynamically favorable reactions at each step to drive the directed bond rotation cycle forward.

The synthesis of lactone **1** was performed in two steps following the modified literature procedures from commercially available diphenic acid **4** by Haworth cyclization[15] followed by Baeyer–Villiger oxidation.[16] Lactone ring opening of **1** with lithio(*S*)-1-phenylethanamine in THF at room temperature resulted in the formation of amide axial diastereomers **5a** and **5b** (Scheme 2). Subsequent acidification of the mixture with 2 N HCl led directly to the isolation of lactone **7** in a 58% yield with expected products **6a** and **6b** being undetected. The biaryl lactone **7** should be thermodynamically favorable compared to **6a**/**6b** due to the adoption of a near-planar geometry, allowing for stabilizing delocalization across the two aryl rings of the biaryl system. Similar behavior of comparable biaryl lactones has been reported.[17] The ring opened form is favored only under basic conditions in which the carboxylic acid in its anionic form.

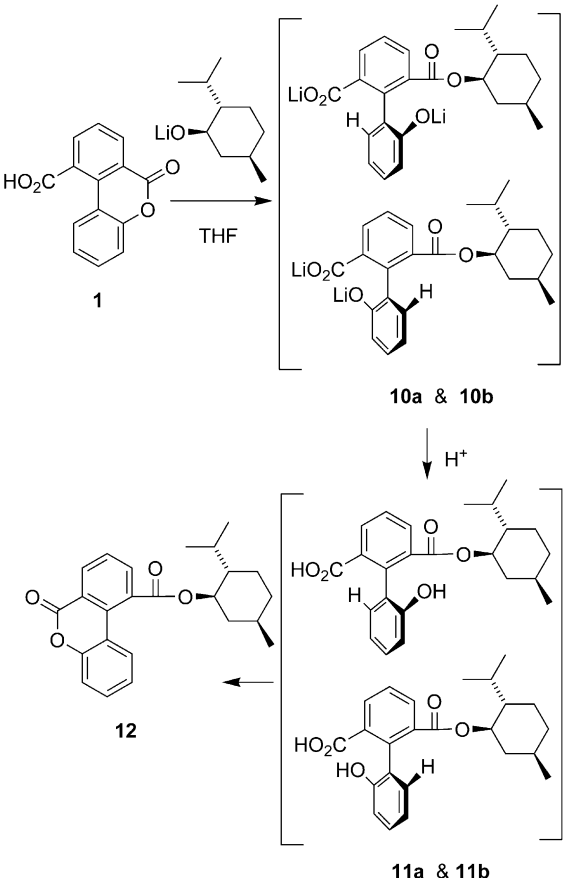
Attempts to isolate samples of **6a** and **6b** with milder acid additions (2 N HCl acidified to pH 2.0 and 4.0 or oxalic acid to pH 2.0 and 4.0) resulted in the desired products being transiently observed by ^{1}H NMR.[18] However, chromatographic purification necessary for analysis of diastereomer formation consistently resulted in complete conversion to cyclized lactone **7**.

In order to quantify the diastereoselectivity of the ring opening, and hence determine the efficiency of the 180° directed rotation, it was necessary to determine the ratio of the stable anionic products of ring opening (**5a** and **5b**) prior to treatment with acid. Lactone ring cleavage of **1** with lithio(*S*)-1-phenylethanamine was performed as described above. However, the solution was not acidified and the resulting crude mixture of **5a** and **5b** was isolated via evaporation. Analysis of the mixture was achieved by reverse-phase HPLC–MS, reproducibly resulting in a clean separation and identification of the two major peaks (**5a** and **5b**) in a ratio of 3:1.[18] Net 180° directed rotation is inherent in the diastereoselective ring opening and subsequent lactonization. Due to the instability of the intermediate products, the absolute

stereochemistry of the major and the minor axial diastereomers could not be elucidated.[19]

In a similar system, net unidirectional 180° aryl–aryl bond rotation of lactone **1** was again achieved using a menthol nucleophile, lithio(1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexanol (Scheme 3). Subsequent acidification did not lead to isolable samples of **11a** and **11b** but instead led directly to lactone **12** in a 34% yield. After direct evaporation of the crude product, HPLC–MS analysis of anions **10a** and **10b** reproducibly led to a clean separation of the diastereomers in a ratio of 3:2.[18] Net 180° directed rotation is inherent in the diastereoselective ring opening and subsequent lactonization. Due to the instability of the intermediate products, the absolute stereochemistry of the major and the minor axial diastereomers could not be elucidated.[19]

These two examples demonstrate directed bond rotation in a new prototypical biaryl molecular motor system. In the case of the amide system, the directed 180° bond rotation of **1** to **7** is 50% efficient and in the ester system the directed 180° bond rotation of **1** to **12** is 20% efficient. Although the rotational efficiency may be a drawback,[20] the overall simplicity of this biaryl system should be advantageous. In principle, systems analogous to prototypical molecular motor **1** could be used for processive (iterative, repeated) cycles of net unidirectional bond rotation. Simple one-pot switching of basic (nucleophilic) and acidic conditions would drive the continuous rotation of **1**. Flexibility in the choice of fuel usage is also a key advantage, in that any chiral nucleophile could potentially drive net unidirectional rotation in this system. These two factors are especially relevant when considering the more sophisticated chemically driven synthetic motor systems reported to date: one of which is reversible and more efficient[6b] in rotation but makes use of very specific and time-consuming multistep reaction sequences[6] and the other being unable to surpass a 120° directed rotation.[7]



Scheme 3. Reactions of lactone **1** to demonstrate directed bond rotation using an alcohol nucleophile (see text for detailed discussion).

Current efforts are focused on discovering reaction conditions to selectively hydrolyze amide **7** and ester **12** in the presence of the lactone group. The relative reactivities of the aforementioned functionalities to conventional acid or base hydrolysis makes this a difficult task and previous attempts have been unsuccessful. An alternate approach is also currently being pursued using different chiral nucleophiles which generate intermediates from which the chiral auxiliary is more easily cleaved or that can be cleaved under orthogonal (e.g., redox or light) conditions. Realization of these studies would result in 360° iterative directed rotation in a new biaryl molecular motor system with the advantages of greatly simplified operation and flexibility in fuel usage.

In summary, these results are the first examples of prototypical molecular motors driven by chiral auxiliaries. In each case, the chiral auxiliary induces transient axial chirality, resulting in net directed bond rotation.

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Supplementary data

Experimental procedures and characterization of all compounds as well as HPLC–MS procedures and data. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.09.151.

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18. See Supplementary data for experimental details.
19. This characterization is useful for determining the specific direction of rotation but is unnecessary in verifying that net unidirectional 180° rotation has occurred.
20. Note that in a bulk molecular motor system this seemingly limited efficiency of the proposed system may be sufficient to statistically generate useful work and/or change the properties of the surrounding environment.