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Enantioselective Syntheses of Furan Atropisomers by an Oxidative Central-to-Axial Chirality Conversion Strategy

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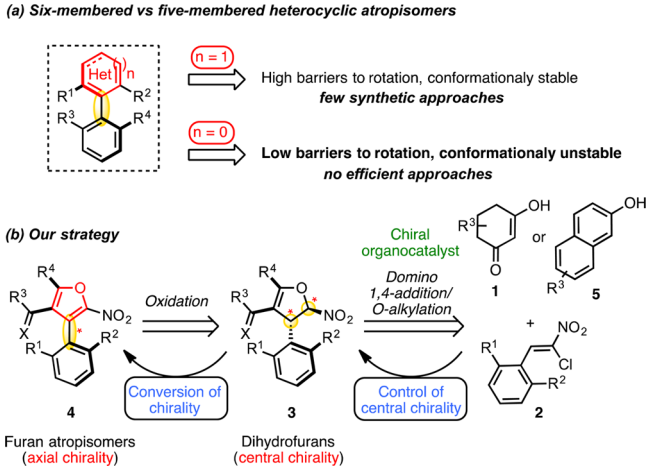
Supporting Information

ABSTRACT: For the first time, enantiomerically enriched atropoisomeric furans have been accessed using a central-to-axial chirality conversion strategy. Hence, oxidation of the enantioenriched dihydrofuran precursors gave rise to axially chiral furans with high enantiopurities accounting from excellent conversion percentages (cp) in most cases.

Nonracemic axially chiral molecules are of utmost interest for a wide cross section of chemists due to their numerous applications as chiral ligands,[1] organocatalysts,[2] and materials[3] but also for their biological relevance.[4] Among them, biaryl atropisomers are the most common ones and many synthetic approaches are available.[5] In sharp contrast, the much more challenging enantioselective construction of atropisomeric heteroaryl structures still constitutes a daunting challenge of modern organic synthesis.[6] The presence of a heteroatom not only can bring new synthetic and biologic perspectives but also can be used for the control of the reactivity based on the possible establishment of additional hydrogen-bonding interactions. Therefore, the design of new dedicated enantioselective synthetic strategies to access new families of atropisomeric heteroaryls is highly desirable.[7] However, the situation becomes drastically more difficult when the targeted heteroatropisomeric species display a five-membered heterocycle because of the increased distance between aryl substituents resulting in generally much lower barriers to rotation hampering the conformational stability (Scheme 1a).[8] To the best of our knowledge, the only example concerning the enantioselective construction of five-membered heteroatropisomers has been reported by Itami and Yamaguchi in 2012. They described a Pd-catalyzed enantioselective C−H coupling methodology between the two preformed aromatic partners affording a thiophene atropisomer isolated in only 27% yield and 72% ee.[9,10] A more appealing but challenging approach would rely on the construction of the heteroaromatic ring with the concomitant creation of the stereogenic axis. We decided to tackle this synthetic defiance considering the easy formation of a furan ring **4** by oxidation of a chiral dihydrofuran precursor **3** in line with the central-to-axial chirality conversion[11,12] strategy developed in our group.[13] This will open a new synthetic way to access hitherto unknown atropisomeric furans **4** in optically active form (Scheme 1b). The overall sequence is initiated by an enantioselective organocatalyzed 1,4-addition of diverse pronucleophiles such as 1,3-dicarbonyls[14] **1** or β-naphthols[15] **5** to (*Z*)-(2-halo-2-nitroethenyl)benzenes[16] **2** triggering an intramolecular diastereoselective *O*-alkylation leading to *trans*-dihydrofurans precursors of the final furans upon oxidation.

Scheme 1. Synthetic Plan to Furan Atropisomers



To reach this goal, two main difficulties needed to be addressed: first, the efficient enantioselective synthesis of dihydrofurans bearing bulky 2,6-disubstituted phenyl moieties, in order to reach high enough barriers to rotation. Second, mild and selective oxidative conditions in order to preserve enantiomeric purity during the conversion of chirality step. Our initial investigations started by the optimization of the dihydrofuran synthesis by screening of various organocatalysts with dimedone (**1a**) and bulky β-substituted nitroolefin **2a** as model substrates (Scheme 2). Among different bifunctional organocatalysts, the ones incorporating a squaramide moiety were the most efficient and the use of catalyst **6** afforded the desired *trans*-dihydrofuran **3a** in 92% yield and 95% ee.[17] Oxidative conditions to form chiral furan **4a** were studied, and we found that the use of hypervalent iodine reagents under basic conditions[18] allowed to reach best efficiencies in the central-to-axial chirality conversion process. (Diacetoxyiodo)-benzene [$PhI(OAc)_2$] was the most efficient and we noticed an important effect of the base (see Supporting Information). Hence, compared to classical organic bases (Et_3N, DMAP), inorganic base cesium carbonate gave the best results both in terms of yield and conversion percentage (cp) up to 94% for **4a**, which displays a very good stability with a barrier to rotation

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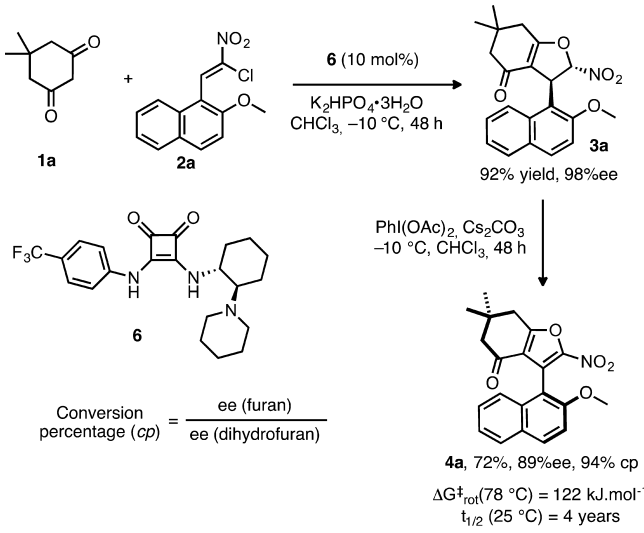
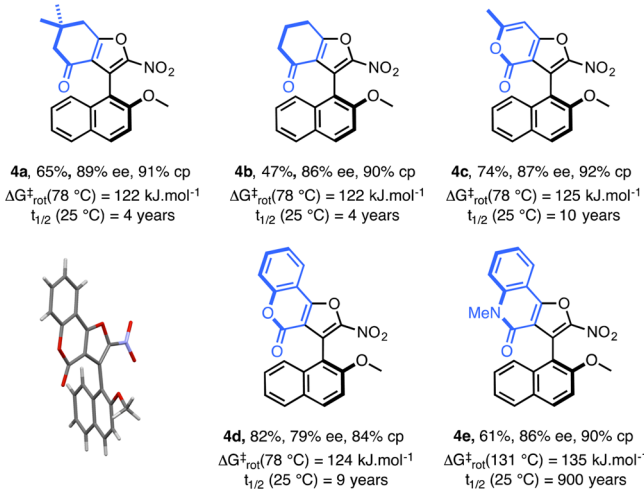
Scheme 2. Optimization of the Reaction Conditions



of 122 kJ mol^{-1}. The use of other oxidizing agents gave inferior results. For example, manganese dioxide afforded **4a** in only 32% yield with 15% cp.

We next assessed the scope of this transformation by varying the nature of the 1,3-diketone partner (Scheme 3). Starting

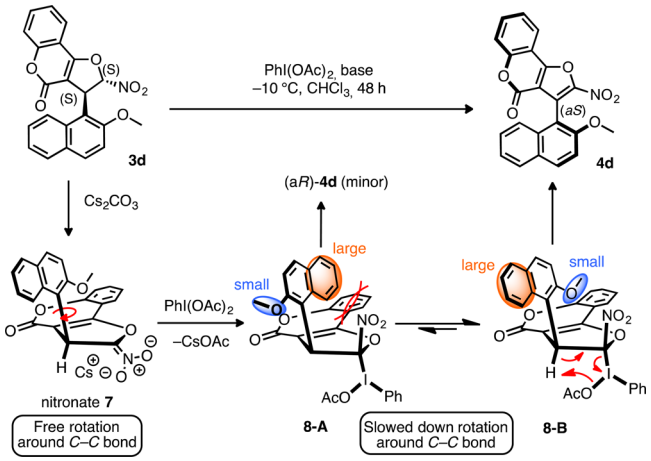
Scheme 3. Reaction Scope[a]



[a]Yields are for two steps.

with cyclohexan-1,3-dione led to the formation of the corresponding furan **4b** with similar efficiency even if the yield during the oxidation step slightly decreased. Cyclic ketoesters or ketoamides could also be employed as starting materials leading to the desired furans **4c**−**e** in good yields and good enantiopurity, with barriers to rotation from 122 to 135 kJ mol^{-1}. Concerning the stereochemical assignment, **4d** as well as its dihydrofuran precursor **3d** were crystallized and absolute configurations of these molecules were unambiguously identified by X-ray diffraction as (2*S*,3*S*)-**3d** and (a*S*)-**4d**.[19] Scheme 4 shows our current understanding of the reaction pathway and its stereochemical outcome. From (*S*,*S*)-**3d**, proton abstraction by Cs_2CO_3 would give the chiral nitronate anion **7**, in which the fast rotation of the methoxynaphthyl group around the *Csp2*−*Csp3* bond shields significantly the *β*-

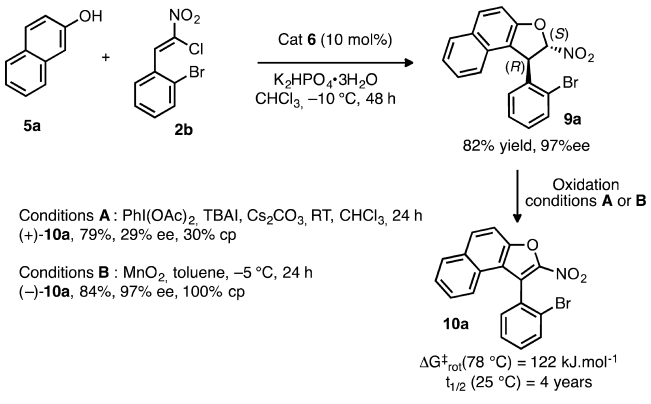
Scheme 4. PhI(OAc)$_2$ Oxidation Mechanism



face. Therefore, we can assume that the approach of PhI(OAc)$_2$ occurs preferentially from the *α*-face delivering two rotamers **8-A** and **8-B** with a transient restricted rotation of the methoxynaphthyl group because of the resulting cis relationship with the nitro group. Finally, the minimum steric congestion developed in **8-B** accounts for an efficient central-to-axial chirality conversion resulting in the highly selective formation of optically active furan (a*S*)-**4d**. This constitutes the first efficient enantioselective approach to furan atropisomers. However, the use of a naphthyl substituent at the 3 position of the furan ring is mandatory to reach high enough barriers to rotation, and only the methoxy function provides isolable compounds after oxidation.[20]

To overcome this limitation, and expand the range of applications of our strategy, we focused on related 3-phenylnaphtho[2,1-*b*]furan atropisomers **10a** potentially accessible from *β*-naphthol (**5a**) as pro-nucleophile and *o*-bromo-3-phenyl nitroolefin **2b** (Scheme 5). Gratifyingly, using the same

Scheme 5. Reaction Conditions Optimization



catalytic system as before, a smooth *O*-cycloalkylation occurred at −10 °C and dihydrofuran **9a** was isolated in 82% yield and an excellent 97% ee. However, the oxidation step using hypervalent iodine (condition A) was less efficient in this series. The corresponding naphthofuran **10a** was produced in a satisfying 79% yield but only 29% ee (30% cp). However, the barrier to rotation of **10a** (122 kJ mol^{-1}) was in agreement with our expectations and this molecule nicely complements with the previous family of furan atropisomers **4**. The screening of other oxidizing agents was carried out and to our delight, the

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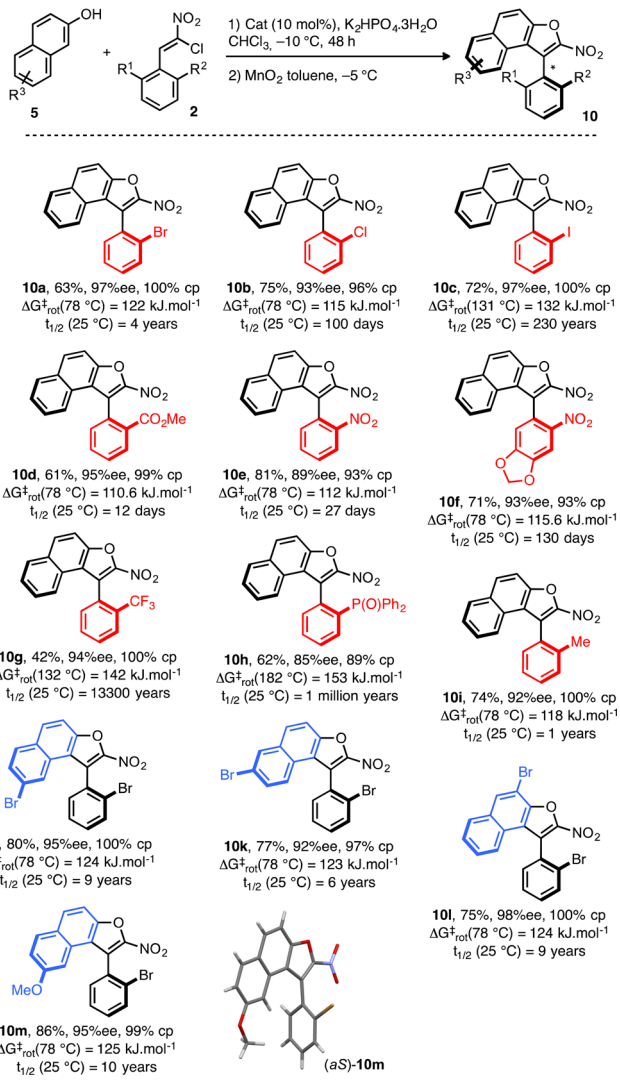
use of manganese dioxide (MnO_2, conditions B) in toluene at −5 °C promoted the oxidation of **9a** to 3-phenyl-naphthofuran atropisomer **10a** with total chirality conversion (84% yield, 97% ee, 100% *cp*). Interestingly, these two oxidizing systems [$PhI(OAc)_2$ under basic conditions and MnO_2] afforded opposite enantiomers (+)-**10a** and (−)-**10a**, respectively pointing out two different mechanisms with opposite stereochemical outcomes.[12d]

With the optimized conditions in hand, we next examined the scope of the nitroalkene partner (Scheme 6). Other

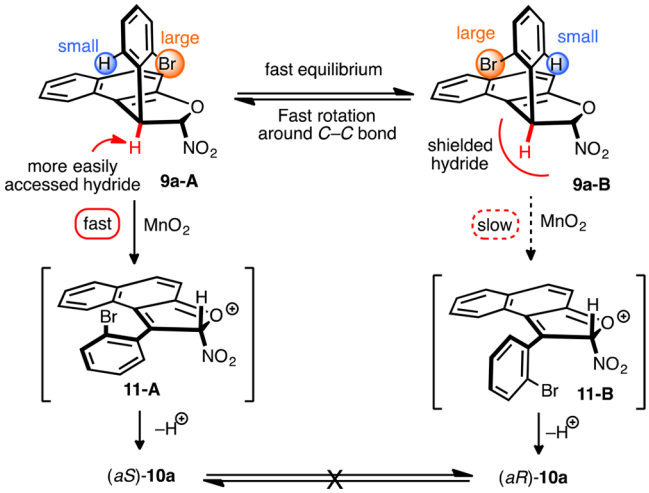
Scheme 6. Reaction Scope[a]



[a]Yields are for two steps.

synthetically valuable halogens could be incorporated in the final furan structures with preserved high barriers to rotation and excellent cp as in the cases of chloro- and iodo-derivatives **10b,c**, respectively.[21] Other electron-withdrawing substituents such as an ester in **10d**, a nitro in **10e−f**, a trifluoromethyl **10g** or a phosphine oxide **10h** also behave with comparable efficiency and good to excellent cp from 89% to 100%. Alternatively, a 2-tolyl substituent as in **10i** is compatible with the sequence. Concerning the variation of the pronuceophile partner, we can notice that the overall process nicely tolerates the use of functionalized 2-naphthol derivatives bearing either methoxy or bromo substituents at various positions allowing the isolation of **10j−m** with very good yields, >91% ee and >96% cp. In this series also, X-ray diffraction analysis allowed to attribute the (1*R*,2*S*) and (*aS*) absolute configurations to dihydrofuran **9m** and furan **10m**,[19] respectively and to propose a mechanistic rationale (Scheme 7). In the case of dihydrofuran

Scheme 7. MnO_2-Promoted Oxidation Mechanism



9a, because no atropodiastereomers can be visualized by ^1H NMR (see Supporting Information) we can argue for a fast equilibrium between the two rotamers **9a-A** and **9a-B**. In the presence of manganese dioxide, hydride transfer could potentially afford two possible oxonium ion intermediates **11-A** and **11-B**. We can reasonably expect that the hydride transfer would preferentially occur from conformation **9a-A** in which the hydride is more easily accessed by the oxidant compared to the conformation **9a-B**. Subsequent fast deprotonation of the acidic hydrogen atom in **11-A** would then lead to the expected enantioenriched (*aS*)-**10a** with efficient central-to-axial chirality conversion.

In summary, we have developed an enantioselective synthesis of hitherto unknown furan atropisomers using a central-to-axial chirality conversion strategy based on the formation of the furan heterocycle, from acyclic precursors, and with the concomitant creation of the chiral axis. Two structurally different optically active heteroatropisomeric families displaying a five-membered heterocycle could be obtained with great efficiency from readily available substrates. The crucial central chirality in the dihydrofuran precursor is mastered by an enantioselective organocatalyzed *C*−*O*-heterocyclization sequence, and the chiral axis is revealed with good to excellent cp by an oxidative dehydrogenation with either $PhI(OAc)_2$ or MnO_2.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b11079.

Experimental details (PDF)
Data for **9m** ($C_{19}H_{14}BrNO_4$) (CIF)
Data for **3a** $C_{22}H_{15}NO_6$, C_2H_3N (CIF)
Data for **10m** $C_{19}H_{12}BrNO_4$ (CIF)
Data for **4a** $C_{22}H_{13}NO_6$, C_2H_3N (CIF)

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Notes

The authors declare no competing financial interest.

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(19) (2*S*,3*S*)-**3d**, (a*S*)-**4d**, (1*R*,2*S*)-**9m** and (a*S*)-**10m** refer to CCDC 1505555, CCDC 1505557, CCDC 1505556, CCDC 1505558 respectively, which contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk.

(20) With other hindered aryl groups (e.g., 2-methylnaphthyl, 2-bromo-6-methylphenyl, 2-methyl-6-nitrophenyl), the corresponding furans proved unstable during the oxidation step.

(21) With fluorine atom, the barrier to rotation was only of 85 kJ mol^{-1} preventing the isolation of a stable atropisomer of the corresponding furan.

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