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Synthesis of Functionalized Cyclobutenes and Spirocycles *via* Asymmetric P(III)/P(V) Redox Catalysis

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Abstract. An enantioselective phosphine-catalyzed transformation has been developed for the synthesis of chiral cyclobutene triesters and fluorinated spirocyclic compounds. The strategy involved a P(III)/P(V) redox cycling process, *via in situ* reduction of phosphine oxide with phenylsilane. This catalytic methodology has enabled the enantioselective synthesis of functionalized cyclobutenes (24 examples, up to

94% ee). On the occasion of the extension of this study to α -ketoester indenone substrates, a surprising reactivity has been discovered for the synthesis of spiro-indenone products.

Keywords: Organocatalysis; Phosphine; Chirality; Cyclobutenes; Spiro compounds

Cyclobutanes and cyclobutenes are important structural units found in many natural products and pharmaceutical active compounds.^[1] Some representative natural cyclobutenes such as cyclomegistine or β -lumicolchicine are depicted in Scheme 1a. Due to the highly rigid backbone and the well-defined three-dimensional rearrangement of the substituents, these scaffolds are privileged in medicinal chemistry.^[1f] They can also be considered as key building blocks for the synthesis of highly substituted cyclic, heterocyclic or acyclic derivatives, *via* ring expansion, ring contraction or rearrangements.^[2] The asymmetric synthesis of substituted four-membered rings remains very challenging and a hot topic in organic synthesis, notably due to the difficulty to build highly-strained ring system in an efficient and stereoselective way.

Though the development of catalytic methodologies for the synthesis of chiral cyclobutanes is well documented,^[3] enantioselective syntheses of chiral cyclobutenes are relatively scarce (Scheme 1b). Various metal-catalyzed [2+2] cycloaddition reactions were developed between olefins and alkynyl sulfides,^[4a-b] ynamides,^[4c-e] electron-poor^[4f-h] or electron-rich^[4i-j] alkynes. Other strategies for the synthesis of cyclobutenes include a copper-catalyzed 1,4-addition/trapping reaction of cyclobutenones^[5a] and an intermolecular Heck annulation with propargylic acetates.^[5b] Besides these metal-catalyzed methodologies, some enantioselective organocatalyzed processes appeared recently. Bach described an impressive enantioselective [2+2] photocycloaddition of dialkyl acetylenedicarboxylate with 2-pyridones,^[6a] while Zheng reported a chiral phosphoric acid-catalyzed enantioselective desymmetrization reaction allowing the formation of chiral 3-aminocyclobut-2-en-1-ones.^[6b]

a. Representative cyclobutene-containing natural products^[1]

b. Enantioselective catalytic strategies

Organometallic catalysis

Lewis acid catalyzed [2+2] cycloaddition of alkenes and alkynes^[4]
1,4-Addition/trapping reaction of cyclobutenone^[5a]
Heck annulation^[5b]

Organocatalysis

[2+2] Photocycloaddition^[6a]
Desymmetrization of cyclobutane-1,3-diones^[6b]

c. Enantioselective P^{III}/P^V redox catalysis^[8]

d. Extension of the methodology (this work)

Scheme 1. (a) Representative natural products containing cyclobutenes, (b) and (c) known catalytic and asymmetric methodologies and (d) proposed work.

This sole couple of organocatalyzed examples led us to imagine and develop a new organocatalytic methodology. The proposed Michael addition/intramolecular Wittig reaction already proved its robustness, with the use of stoichiometric amounts

of phosphine.^[7] Aiming at developing the first enantioselective phosphine-catalyzed formation of substituted cyclobutenes and exploring an underdeveloped disconnection strategy, we established in 2019 a catalytic and asymmetric P^{III}/P^V redox cycling process (Scheme 1c).^[8] In order to develop catalytic and asymmetric transformations, phosphine oxide formed during the reaction was *in situ* reduced in the presence of phenylsilane. This strategy has been efficiently illustrated in many transformations over the past decade.^[9] Herein, we propose to fully explore the scope of enantioselective phosphine-catalyzed Michael addition/intramolecular Wittig reactions between dialkyl acetylenedicarboxylates (DAAD) and different 2,4-dioxo-4-arylbutanoates or fluorinated 2,3-dihydro-1*H*-inden-1-ones (Scheme 1d). Interestingly, the use of α -ketoester indenone substrates allowed us to discover a new reactivity and the formation of unknown spirocyclic compounds.^[10]

After developing the enantioselective synthesis of (trifluoromethyl)cyclobutenes in excellent yields and enantioselectivities,^[8] we propose in the framework of this study to first expand the reactivity to 2,4-dioxo-4-arylbutanoate substrates (Scheme 2). Reaction conditions were optimized by using ethyl 2-hydroxy-4-oxo-4-phenylbut-2-enoate **1a** and diethyl acetylenedicarboxylate **2** as model substrates. The initial catalytic system employs 10 mol% of chiral phosphine, phenylsilane (2.0 equivalents) as reducing agent and a catalytic amount of *bis*(4-nitrophenyl)phosphate, at 40 °C in toluene. Chiral HypPhos phosphines^[11] were first tested to find the right balance between reactivity and enantioselectivity. Screening of nine *P*-stereogenic phosphines, substituted with *endo* (I–IV) or *exo* (V–IX) aromatic ring possessing different electronic and steric properties gave the desired cyclobutene product **3a** in up to 75% yield and 85% ee with phosphine IX.

Scheme 2. Optimization of the catalytic and asymmetric tandem reaction.

In the development of P^{III}/P^V redox processes, our group and others have repeatedly demonstrated the benefit of adding Brønsted acid in the reaction

mixture.^[9, 12] Here again, the presence of phosphoric acid proved to be essential, since it greatly facilitated the reduction of phosphine oxide. The best enantioselectivity was obtained with toluene as solvent at 40 °C. A higher temperature (60–80 °C) allows a faster reaction, but to the detriment of the enantiometric excess. Conversely, the reaction is slower at room temperature.

These optimal reaction conditions were then applied to the enantioselective formation of diversely substituted cyclobutenes (Scheme 3). The presence of electron-donating substituents such as methyl or benzyloxy groups, in different positions on the aromatic ring has low effect on both yields and enantiomeric excesses (compounds **3a–g**, up to 98% yield, 81–89% ee). Absolute configuration of products was tentatively assigned to be (3*R*,4*R*)-**3**, by analogy with our previous work.^[8] When the substituent on the aromatic ring was replaced by an electron-withdrawing group, such as chloride, bromide or trifluoromethyl, in *ortho*-, *meta*- or *para*-position, overall results remained very good (compounds **3h–n**, 50–90% yield, 86–94% ee). Substrates substituted with heteroaryls such as furan and thiophene also furnished efficiently the corresponding products **3o–3p**.

Scheme 3. Enantioselective phosphine-catalyzed synthesis of cyclobut-1-ene-1,2,3-tricarboxylates.

Finally, alkyl 5,5-dimethyl-2,4-dioxohexanoate substrates **1q-r** properly reacted to give products **3q-r** in 68-85% yields and 84% ee. The major diastereoisomer of all the products depicted in Scheme 3 was assigned to the *trans*-isomer, notably thanks to the two cyclobutanic proton $J_{\text{H-H}}$ couplings in ^1H NMR ($\delta \approx 3.85$ and 4.75 ppm, doublet, $J \approx 2.0$ Hz). As a general trend, such compounds show typical J constants of 3.0-5.0 Hz for the *cis*-isomer and 0.5-2.0 Hz for the *trans*-isomer.^[7] Highly hindered substrates such as **1s**, substituted with a 1,3,5-trimethylphenyl substituent did not react, highlighting one of the limitations of this reaction. No conversion was observed in this case, even by increased heating of the reaction mixture.

We then extended the reaction scope to the synthesis of fluorinated cyclobutenes (Scheme 4). The potential formation of new perfluoroethyl- and difluoropropyl-substituted products is of great interest given the large number of applications of fluorinated molecules as active pharmaceutical ingredients (APIs) and agrochemicals.^[13] The use of a stoichiometric amount of triphenylphosphine gave the racemic products **5a-b** in 62-95% yields. After some optimization and screening of chiral phosphines **I-IX**, we were able to obtain at best the fluorinated compound **5a** and **5b** with good isolated yields and moderate enantioselectivities (71-72% ee).

Scheme 4. Synthesis of chiral perfluoroethyl- and 1,1-difluoropropyl-cyclobutene derivatives.

To further increase the substrate scope of this study, we envisaged its application in the synthesis of fluorinated spiro(cyclobutane)indenones **7** (Scheme 5). Whether with the use of 1.2 equivalents of PPh_3 (*Condition A*) or 10 mol% of chiral phosphine **IX** (*Condition B*), yields were lower than in the case of the synthesis of cyclobutenes **3** or **5**. This lesser reactivity could be explained by the highly-strained spirocyclic ring system of **7a-g** and the inherent difficulty in the formation of such scaffolds. Fortunately, the enantiomeric excesses reached 86-90% for compounds **7a-c**. However, it was not possible to isolate enantioenriched products **7d-f**, even by using harsher reaction conditions or changing the chiral organocatalyst. Some modest preliminary results were

obtained in the synthesis of CF_3 -substituted spiro[3.5]non-1-en-5-one **7g** (up to 42% ee).

Scheme 5. Synthesis of spirocyclic-cyclobutene compounds.

To ascertain the relative configuration of the spirocyclic compounds, **7c** was derivatized in the presence of (3,4-dinitrophenyl)hydrazine (Scheme 6). X-ray diffraction studies of compound **8** allowed us to assign for the first time the *trans*-configuration of compound **7c**.

Scheme 6. Derivatization of **7c** and ORTEP view of **8**. Ellipsoids are drawn at the 50% probability level.

We then wanted to explore the reactivity of 1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate substrates **9a-b** (Scheme 7). Surprisingly, the NMR analysis of **10a-b** revealed the presence of two esters and two ketones, instead of the expected three esters and one ketone. The structural assignment of this new spirocyclic backbone was then confirmed by X-ray diffraction study on a single crystal of **10b**. With the use of stoichiometric amount of PPh₃ (*Condition A*), spiro(cyclopentane)indenones **10a** and **10b** were isolated in 57-68% yield. In the presence of 10 mol% of HypPhos phosphine **VII**, phenylsilane (2.0 equivalents) and a catalytic amount of *bis*(4-nitrophenyl)phosphate (*Condition B*), products **10a,b** were synthesized in decent yields, with 72% ee. This methodology could be extended to the isolation of spiro[4.4]non-2-ene-1,6-dione **10c**. For this substrate, the right balance between reactivity and selectivity was difficult to achieve (27% yield/66% ee at 40 °C or 61% yield/62% ee at 60 °C). Finally, when a less constrained 6-membered ring was used, such as the ethyl 2-oxo-2-(2-oxocyclohexyl)acetate substrate, cyclobutene triester **11** was isolated.^[7c] Unfortunately, none of the tested chiral phosphines gave satisfactory results with this substrate.

Scheme 7. Synthesis of new spirocyclic compounds **10a-c** and 5-oxospiro[3.5]non-1-ene derivative **11**.

The preferential formation of either cyclopentenone- or cyclobutene-fused spirocycles may be tentatively explained by mechanistic considerations (Scheme 8). The tandem reaction starts with the addition of the phosphine to DAAD substrate, to form the zwitterionic species (I). This intermediate

subsequently deprotonates the substrates **6** (EWG = CF₃) or **9** (EWG = CO₂Et), to give the vinylphosphonium salt (II). Addition of the enolate (III) to (II) generates *in situ* a phosphorus ylide (IV) or (V), which undergoes an intramolecular Wittig olefination to form the final spiro-butenes **7a-g** or the spiro-cyclopentenones **10a-c** and phosphine oxide. The reduction of phosphine oxide with phenylsilane closes the catalytic cycle. If the formation of the CF₃-cyclobutene product **7** was expected, with the intermediate (V) two Wittig reaction are possible, with the two carbonyl functions. In the case of synthesis of extremely strained spirocyclic compounds, the formation of compound **10** is favoured. As soon as the cycle strain is decreased, as in the case of the cyclohexanone product **11**, the expected four-membered ring was found again.

Scheme 8. Mechanistic proposal for the formation of compounds **7/11** and **10**.

In conclusion, we have synthesized benzoylcyclobutene triester derivatives *via* a P(III)/P(V) redox catalysis strategy. Products were isolated in good yields and enantioselectivities (18 examples, up to 94% ee). The synthesis of chiral perfluoroethyl- and 1,1-difluoropropyl-cyclobutenes was also developed. Extension of this methodology to spirocyclic compounds gave us the opportunity to discover significant divergence in reactivity between α -substituted trifluoroacetyl- and ketoester-indenone substrates. Six spirocyclic compounds were isolated in moderate yields and good enantioselectivities (70-90% ee). Further studies on the development of new catalytic and asymmetric tandem reactions *via* redox catalysis are ongoing.

Experimental Section

The crystallographic data of **8** (CCDC 1983080) and **10b** (CCDC 2077651) can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. Ellipsoids are drawn

at the 50% probability level and H atoms are shown as spheres of arbitrary radius.

General procedure for the synthesis of substrates 1a-s. Diethyl oxalate (5.5 mmol, 1.1 equiv.) was added to a suspension of sodium hydride (7.5 mmol, 1.5 equiv.) in distilled THF (5 mL) at 0 °C. After 15 minutes, a solution of aryl methyl ketones (5.0 mmol, 1.0 equiv.) in distilled THF (5 mL) was then added dropwise for 5 minutes at the same temperature. The reaction was then stirred at 70 °C for 2 hours before to be quenched by addition of a solution of HCl (1 M) and extracted twice with EtOAc. The combined organic layers were washed with water, dried over MgSO₄ and concentrated *in vacuo*. The crude mixture was then purified by automatic flash chromatography using silica gel pre-packed column and EtOAc/heptane as eluent (40-60% EtOAc/heptane).

General procedures for the synthesis of products 3a-s and 7a-g. Synthesis of racemic products: Substrates **1a-s** or **6a-g** (0.075 mmol, 1.0 equiv.) and triphenylphosphine (0.09 mmol, 1.2 equiv.) in anhydrous toluene (0.75 mL) were placed under argon into a Schlenk tube. Then diethyl but-2-ynedioate **2** (0.15 mmol, 2.0 equiv.) was added and the solution was heated at 40 °C for 40 h. The crude mixture was concentrated *in vacuo* before to be purified by column chromatography on silica gel (10-20% heptane/EtOAc).

Synthesis of enantioenriched products: Substrates **1a-s** or **6a-g** (0.075 mmol, 1.0 equiv.), (1*S*,4*S*,5*R*)-5-(naphthalen-1-yl)-2-tosyl-2-aza-5-phosphabicyclo[2.2.1]heptane **IX** (0.0075 mmol, 10 mol%) and *bis*(4-nitrophenyl) phosphate (0.0075 mmol, 10 mol%) were placed under argon into a Schlenk tube and diluted with anhydrous toluene (0.75 mL). Diethyl but-2-ynedioate **2** (0.15 mmol, 2.0 equiv) and phenylsilane (0.15 mmol, 2.0 equiv.) were then added using microsyringes. The solution was heated at 40 °C for 40 h. After which it was concentrated *in vacuo*, the crude mixture was purified by column chromatography on silica gel (10-20% heptane/EtOAc).

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