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Programmable enantioselective one-pot synthesis of molecules with eight stereocenters

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We developed an enantioselectively catalyzed tandem synthesis of structurally and stereochemically complex molecules that forms four carbon-carbon bonds and sets eight stereocenters with high regio-, diastereo- and enantioselectivity. It can be programmed to yield different stereoisomers by varying only the order of combination of a common set of reagents and catalysts. We report what is to our knowledge the first synthesis of both enantiomers of a chiral compound using the same chiral catalyst.

The synthesis of structurally and stereochemically complex molecular architectures is at the heart of chemical biology research. In particular, there is a high demand for methods that give efficient regio-, diastereo- and enantioselective access to natural product–inspired compound collections with scaffolds composed of two to four rings and with multiple stereocenters[1]. In addition, synthetic methods that allow the construction of compound collections with high structural and stereochemical diversity from a limited set of starting materials and catalysts are of particular value[2]. High levels of synthetic efficiency can be reached in one-pot, multistep sequences that selectively form one or several stereocenters out of a much greater number of theoretically possible isomers[3–5].

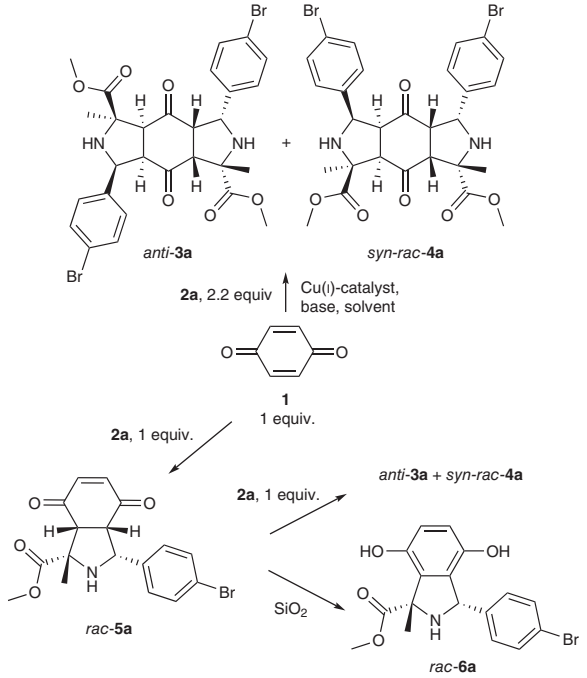
Here we describe the development of an asymmetric one-pot tandem synthesis of structurally complex molecular architectures by two consecutive cycloadditions of azomethine ylides to *p*-benzoquinone. In the tandem sequence, four new carbon-carbon bonds and eight stereocenters are formed with very high regio-, diastereo- and enantioselectivity, allowing the highly selective formation of one stereoisomer from 512 possible isomers. The sequence can readily be programmed; that is, it is possible to start from a common set of reagents and steer all levels of selectivity by varying only the order of reagents and/or the catalyst used. We describe what is to our knowledge the first highly enantioselective separate synthesis of both enantiomers of a chiral compound using, in both cases, identical reagents and the same chiral catalyst.

For the development of an efficient programmable synthesis, we used the enantioselectively catalyzed dipolar cycloaddition of azomethine ylides to electron-deficient olefins because it allows the formation of up to four stereocenters in one step and has found widespread application in the synthesis of bioactive compounds, natural products and materials[6–11]. We chose to use *p*-benzoquinone (**1**) as a dipolarophile that could react twice with the 1,3-dipoles to raise the number of simultaneously formed stereocenters to eight and the number of possible isomers of the product to 512. *p*-Benzoquinone has been used in tandem cycloadditions before, but enantioselective diannulations have not been explored yet[12–16].

Initially, alanine methyl ester imine **2a** was treated with the quinone in CH_2Cl_2 in the presence of base (**Scheme 1**). In the ensuing stepwise double cycloaddition, only isomers *anti*-**3a** and *syn-rac*-**4a** were formed, and in a 1:1 ratio; that is, the reaction proceeded with high diastereocontrol but low regiocontrol, which could be improved by varying the reaction conditions (**Supplementary Results**, **Supplementary Table 1**). The relative configuration of the *anti*-isomer **3a** was determined by means of crystal-structure analysis (**Supplementary Fig. 1** and **Supplementary Data Set 1**), which revealed that the central 1,4-cyclohexadione ring adopts a chair conformation such that cycloadduct **3a** has an inversion center and is achiral.

Although the azomethine ylides derived from aliphatic aldehydes did not react, the cycloaddition has considerable scope, producing the products from imines obtained from aromatic aldehydes with electron-donating or electron-accepting substituents in different positions (**Supplementary Table 2**). Attempts to isolate monocycloadduct **5a** resulted in formation of hydroquinone **6a** (**Scheme 1**).

Given that *syn*-isomer **4a** does not have a center of symmetry (discussed below; **Supplementary Fig. 2**), we explored its enantioselective synthesis by varying the chiral ligands for the metal catalyst. Exploration of a variety of copper catalysts and chiral ligands in different solvents and in the presence of different bases revealed



Scheme 1 | Tandem 1,3-dipolar cycloaddition. Catalytic, double 1,3-dipolar cycloaddition of 1,4-benzoquinone **1** and azomethine ylide **2a** in the presence of catalytic amounts of Cu(I) salt.

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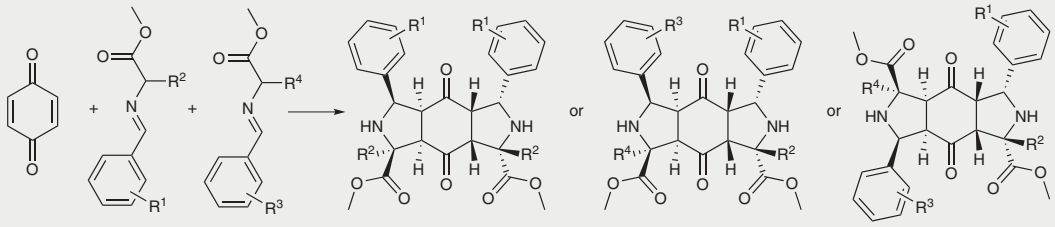
Table 1 | Results of the enantioselective synthesis of the chiral compounds bearing eight stereocenters



Product	R^1	R^2	R^3	R^4	Procedure[a]	Yield (%)[b]	e.e. (%)[c]
4a	4-Br-C_6H_4	Me			A	65	98
4b	4-Me-C_6H_4	Me			A	54	97
4c	4-MeO-C_6H_4	Me			A	42	98
4d	4-F-C_6H_4	Me			A	65	98
4e	3-F-C_6H_4	Me			A	65	97
4f	2-F-C_6H_4	Me			A	73	98
4g	Ph	Me			A	79	98
4h	2-Naphthyl	Me			A	84	98
4i	2-Cl-6-F-C_6H_3	Me			A	41	96
4j	4-CF_3-C_6H_4	Me			A	66	99
4k	4-Br-C_6H_4	H			A	38	98
4l	4-Br-C_6H_4	Ph			A	54	98
8a	4-F-C_6H_4	Me	4-MeO-C_6H_4	Me	B	51	98
8b	4-Br-C_6H_4	Me	4-F-C_6H_4	Me	B	56	98
8c	4-Br-C_6H_4	Me	3-F-C_6H_4	Me	B	34	98
8d	4-Br-C_6H_4	Ph	2-Naphthyl	Me	B	70	98
8e	4-Br-C_6H_4	Ph	4-MeO-C_6H_4	Me	B	64	98
8f	4-Br-C_6H_4	Ph	4-F-C_6H_4	Me	B	72	98
8g	4-Br-C_6H_4	Ph	4-Me-C_6H_4	Me	B	64	98
8h	4-Br-C_6H_4	Ph	2-Cl-6-F-C_6H_3	Me	B	57	98
8i	4-Br-C_6H_4	Ph	2-Me-C_6H_4	Me	B	70	98
9a	4-F-C_6H_4	Ph	4-Br-C_6H_4	Me	C	50	98
9b	4-Br-C_6H_4	Ph	4-Br-C_6H_4	Me	C	49	98
9c	4-Me-C_6H_4	Ph	4-Br-C_6H_4	Me	C	44	98
9d	4-MeO-C_6H_4	Ph	4-Br-C_6H_4	Me	C	46	98
9e	2-Naphthyl	Ph	4-Br-C_6H_4	Me	C	54	98
9f	4-Br-C_6H_4	Ph	Ph	Me	C	44	98
9g	4-Br-C_6H_4	Ph	3-F-C_6H_4	Me	C	49	99
9h	4-Br-C_6H_4	Ph	4-F-C_6H_4	Me	C	50	99
9i	4-Br-C_6H_4	Ph	4-Me-C_6H_4	Me	C	49	98
9j	4-Br-C_6H_4	Ph	2-Naphthyl	Me	C	44	98
9k	2-Naphthyl	Me	4-Br-C_6H_4	Ph	C	40	95
9l	4-Me-C_6H_4	Me	4-Br-C_6H_4	Ph	C	42	94

[a]General procedures A, B and C are in **Supplementary Methods**. [b]Isolated yields of the pure major regioisomer after column chromatography. Diastereomer ratio for all products is >95:5. Regioisomer ratio for products **4** and **8** is >94:6, and for products **9** it is 75:25, on the basis of ^{1}H-NMR analysis. [c]Determined by HPLC analysis using a chiral stationary phase. Me, methyl; Ph, phenyl.

that the best result could be obtained using $Cu(CH_3CN)_4BF_4$ (3 mol%) as a Lewis acid in combination with the *S*,*P*-ferrocenyl ligand (*R*)-Fesulphos[17–19] (**7g**; 3 mol%) in toluene in the presence of *N*,*N*-diisopropylethylamine (DIPEA; 20 mol%) at 18–25 °C (**4a**–**4l** in **Table 1** and **Supplementary Table 3**). Under these conditions, *syn*-regioisomer **4a** was obtained with high regioselectivity (94:6) and diastereoselectivity (>95:5) in 65% yield and with very high enantioselectivity (98% enantiomeric excess (e.e.)). Notably, this reaction created eight stereocenters in a one-pot transformation. The absolute configuration of *syn*-product **4a** was determined by crystal-structure analysis (**Supplementary Fig. 2** and **Supplementary Data Set 2**), which revealed that in *syn*-regioisomer **4a** the cyclohexa-1,4-dione adopts a twist-boat conformation.

Regardless of the substitution pattern of the aromatic ring, the asymmetric reactions of 1,4-benzoquinone **1** with various azomethine ylides proceeded with moderate to good yields of 41–84% and high regioselectivity (94:6), diastereoselectivity (>95:5) and enantioselectivity (96–99% e.e.) (**4a**–**4l** in **Table 1**). Depending on the electronic properties of the substituents of the aromatic ring, slight differences in yield were observed. In the presence of electron-donating substituents such as methyl or methoxy groups (**4b** and **4c**, respectively), the yield was reduced to 42–54%, whereas electron-withdrawing substituents such as bromine or fluorine (**4a** and **4d**, respectively) led to higher yields. Enantioselectivity was consistently high (97–98% e.e.) and was not affected by position (**4d**–**4f**) or number (**4g**–**4h**) of substituents. An exception was **4i**, which

was formed in only 41% yield but had high regio-, diastereo- and enantioselectivity. In addition, cycloadditions with other amino acid ester imines (**4k** and **4l**) showed excellent selectivity.

To expand the chemical space accessible via the double cycloaddition, we explored whether the transformation could give access to cycloadducts formed from two different dipoles. In the presence of the chiral catalyst **7g** carrying a bulky ligand, the second cyclization step proceeds with a lower reaction rate than the first reaction. Thus, a sequence was established in which 1,4-benzoquinone **1** was treated with 1 equiv. of an α-iminoester **2** in the presence of (*R*)-Fesulphos **7g** (3 mol%), $Cu(CH_3CN)_4BF_4$ (3 mol%) and DIPEA (20 mol%) in toluene for 1 h (**Supplementary Table 4**), followed by treatment with a second α-iminoester **2** for 15 h to selectively yield the mixed double-cycloaddition products *syn*-**8** by means of a one-pot tandem reaction (**8a**–**8i** in **Table 1**) with high regio-, diastereo- and enantioselectivity. Analogous reactions with various α-iminoesters **2** proceeded with very high enantioselectivity (98% e.e.) to form eight stereocenters in a one-pot tandem reaction with high stereocontrol. We note that, independently of the order of addition of the 1,3-dipoles, the absolute configuration of all stereocenters in the cycloadducts is the same.

To further explore the stereochemical space defined by the scaffold of the double cycloadducts, we exploited the findings that regioselectivity can be changed by switching from the chiral to an achiral catalyst (**Scheme 1** versus **4a**–**4l** in **Table 1**) and that in the presence of the chiral catalyst with bulky ligands the velocity of the second reaction is low, but in the presence of a ligand-free catalyst (**Scheme 1** and **Supplementary Table 2**) it is high. Thus, we hypothesized that the first and faster dipolar cycloaddition is the enantioselectivity-determining step and is steered by the chirality of the ligands, whereas in the second, much slower step, the type of the metal complex only serves to determine the regioselectivity. The configuration of the four newly formed stereocenters is directed by the stereogenic centers established in the first step.

Accordingly, 1,4-benzoquinone **1** was initially treated with 1 equiv. of an α-iminoester **2** in the presence of (*R*)-Fesulphos **7g** (3 mol%), $Cu(CH_3CN)_4BF_4$ (3 mol%) and DIPEA (20 mol%) in toluene. After completion of this initial cycloaddition, a solution of a second α-iminoester **2**, $Cu(CH_3CN)_4PF_6$ (30 mol%) and triethylamine (30 mol%) in tetrahydrofuran was added (**9a**–**9l** in **Table 1**). In the presence of a ten-fold excess of achiral copper complex relative to the amount of the chiral complex, regioselectivity was shifted to a ratio of 75:25 in favor of the mixed *anti*-regioisomer **9**. Regardless of the electronic properties and positions of the imine substituents, the reactions proceeded with high enantioselectivity (98–99% e.e.) and with viable yields (43–54%) to give various mixed *anti*-cycloadducts.

As the direction of enantioselectivity is exclusively determined in the first step of this reaction sequence, reversing the order of imine addition should give the opposite enantiomer. Indeed, **9i** and **9l**, which were formed by using a toluyl-imine in the first step and a bromophenyl-imine in the second step (**9i**) and by reversing this order (**9l**), are enantiomers (**9i** and **9l** in **Table 1** and **Supplementary Results**). By analogy, **9j** and **9k** are also enantiomers (**9j** and **9k** in **Table 1** and **Supplementary Fig. 3**).

Notably, both pairs of enantiomers were obtained under identical conditions, including the use of the same chiral catalyst in both tandem transformations, and the different enantiomers were produced only by switching the order of imine addition.

The enantioselectively catalyzed one-pot tandem cycloaddition of azomethine ylides to *p*-benzoquinone proceeds with very high regio-, diastereo- and enantioselectivity and can readily be reprogrammed to access different *anti*- or *syn*-cycloadducts by only varying the order of combination of a given set of reagents and catalysts. Varying reaction conditions and the catalyst used gave access to either achiral *anti*- or chiral *syn*-cycloadducts. By means of a chiral catalyst, the *syn*-isomers were synthesized with very high diastereo- and enantioselectivity. Owing to differences in reaction rates of the stepwise tandem process, two different dipoles could successfully be used in the one-pot process. The knowledge gleaned in the *syn*-selective and the nonasymmetric cycloadditions further allowed us to extend the scope of the synthesis to mixed *anti*-products. To our knowledge, it was the first time that it was possible to synthesize both enantiomers of a chiral compound using identical reagents and the same chiral catalyst simply by changing the order of addition of the starting chemicals.

The tandem dipolar cycloaddition is of considerable scope and promises to efficiently give access to great structural and chemical diversity. Thus, for instance, a 240,600-member compound library that would encompass more than 1.9 million stereocenters could, in principle, be selectively prepared by the described one-pot reactions using only 20 amino acids, 20 aldehydes, 1,4-benzoquinone and one chiral ligand. In a sense, such a synthetic methodology can be compared with the biosynthesis of small molecules in nature, which also requires only variation in the combination of relatively few building blocks under the influence of different biocatalysts.

Accession codes. Small-molecule crystal structures are deposited in the Cambridge Crystallographic Data Centre under accession codes 834647 and 834648.

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Author contributions

A.P.A. and H.W. designed experiments and supervised the project. M.P. performed experiments. M.S. and H.P. carried out the X-ray crystallographic analysis. All authors discussed the results, commented and wrote the manuscript.

Competing financial interests

The authors declare no competing financial interests.

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