Dynamic Catalytic Highly Enantioselective 1,3-Dipolar Cycloadditions

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Abstract: In dynamic covalent chemistry, reactions follow a thermodynamically controlled pathway through equilibria. Reversible covalent-bond formation and breaking in a dynamic process enables the interconversion of products formed under kinetic control to thermodynamically more stable isomers. Notably, enantioselective catalysis of dynamic transformations has not been reported and applied in complex molecule synthesis. We describe the discovery of dynamic catalytic enantioselective metal-complex-catalyzed 1,3-dipolar cycloaddition reactions. We have developed a stereodivergent tandem synthesis of structurally and stereochemically complex molecules that generates eight stereocenters with high diastereo- and enantioselectivity through asymmetric reversible bond formation in a dynamic process in two consecutive Ag-catalyzed 1,3-dipolar cycloadditions of azomethine ylides with electron-poor olefins. Time-dependent reversible dynamic covalent-bond formation gives enantiodivergent and diastereodivergent access to structurally complex double cycloadducts with high selectivity from a common set of reagents.

Introduction

The synthesis of organic compounds is dominated by kinetically controlled reactions, which enables irreversible formation of strong covalent bonds.[1–2] The irreversible nature of the reaction guarantees that, once the particular product is formed, it is stable and will not be reformed or converted into another product.[3]

As an alternative to selective product formation, Rowan et al. introduced the concept of dynamic covalent chemistry (DCC).[2] In DCC covalent bonds can be formed and broken reversibly in a fast equilibrium and under conditions in which equilibrium control leads to efficient formation of products under thermodynamic control.[3] DCC has been proposed primarily in the context of supramolecular chemistry including applications in combinatorial chemistry.[3,4] The reversible nature of reactions permits “error checking” and “proof reading” for interconverting components to access the thermodynamically most stable adduct.[4–7] However, while in supramolecular chemistry weak noncovalent interactions dominate, for DCC more robust covalent bonds are relevant with slower kinetics of bond cleavage and formation. In DCC the relative stability of the products (i.e., thermodynamic parameters) determines the product distribution rather than the relative magnitudes of energy barriers of each pathway (i.e., kinetic parameters) (Scheme 1a). Since both the thermodynamic and the kinetic parameters are functions of reaction parameters, the outcome is highly dependent on reaction conditions such as temperature, catalyst and reaction time required to reach an equilibrium.[7,8] Turner et al. employed DCC in enzyme catalysis. They used an aldolase for preparation of a dynamic combinatorial library through stereoselective carbon-carbon bond formation and enabled change in equilibrium in product distribution in presence of a thermodynamic trap.[9]

DCC was also observed for non-enzymatic aldol/retro-aldol reactions,[5,10] for Diels–Alder cycloadditions at higher temperature,[11] and for additional transformations including Michael additions,[2] alkene cross-metathesis,[13] and [2+2] cycloaddition.[14] However, non-enzymatic enantioselective catalysis of DCC has not been reported and DCC has not been observed for dipolar cycloadditions yet. Herein we describe the discovery of catalytic and highly enantioselective dynamic covalent chemistry in metal complex-catalyzed 1,3-dipolar cycloaddition reactions, that is, a reaction type which belongs to the most important and widely used transformation in organic synthesis.

In the course of a program aimed at the synthesis of pseudo-natural products,[15–21] which contain two or more natural product (NP) derived fragments in novel and structurally complex arrangements, we intended to combine two pyrrolidone fragments in an unprecedented manner. To this end, it was envisaged to subject cyclopentenones containing both an endocyclic and an exocyclic conjugated...
double bond (Scheme 1b), to a sequence of two subsequent enantioselectively catalyzed 1,3-dipolar cycloadditions with azomethine ylides generated in situ from imines.\[21–26\]

**Results and Discussion**

To establish the reaction sequence initial screening studies were conducted with cyclic enone (R = H) and glycine methyl ester imine 2a in dichloromethane in the presence of base (Scheme 1b, Supplementary Table 1). We found that the double 1,3-dipolar cycloaddition can be catalyzed efficiently with AgOAc to yield cycloadduct rac-3a with 82% yield and high diastereoselectivity (d.r. > 20:1). The regioselectivity of the first addition was investigated by treating cyclic enone (R = H) with 1.1 equiv of imine 2a under the same reaction conditions which resulted in the regioselective formation of rac-4a with high diastereoselectivity (> 20:1) in 72% yield (Scheme 1b). A change in regioselectivity was observed when a methyl substituent was introduced at the endocyclic double bond of the dipolarophile (R = CH₃). Monocycloaddition of cyclic enone and the ylide derived from glycine methyl ester imine 2a resulted in formation of spirocycle rac-4b in 57% yield and with good diastereoselectivity (10:1). The product rac-4a reacts with glycine methyl ester imine 2a to form rac-3a with high diastereoselectivity (> 20:1) and 75% yield under the same reaction conditions.

In order to explore the enantioselective synthesis of tricyclic compound 3a, different chiral ligands, metal catalysts, bases and solvents were investigated (Supplementary Table 2). Optimization experiments indicated that the best result could be obtained using AgOAc (6 mol %) as a Lewis acid in combination with the S,P-ferrocenyl ligand (R)-Fesulphos, (L1 6.5 mol %) in dichloromethane using cesium carbonate (Cs₂CO₃ 40 mol %) as a base at room temperature after 24 h. Under these conditions, tricyclic compound 3a was obtained in 81% yield with high diastereoselectivity (d.r. > 20:1) and excellent enantioselectivity (99% ee; Table 1).
Results of the enantioselective synthesis of the chiral compounds 3.

Table 1: Results of the enantioselective synthesis of the chiral compounds 3.

| Product | R¹ | R² | R³ | Yield [%][b] | ee [%][b] |
|---------|----|----|----|-------------|-----------|
| 3a      | H  | 4-Br-C₆H₄ | 4-Br-C₆H₄ | 81          | 99        |
| 3b      | H  | 4-Br-C₆H₄ | 3-Br-C₆H₄ | 72          | 91        |
| 3c      | H  | 4-Br-C₆H₄ | 2-Br-C₆H₄ | 65          | 96        |
| 3d      | H  | 4-Br-C₆H₄ | 4-Cl-C₆H₄ | 81          | 98        |
| 3e      | H  | 4-Br-C₆H₄ | 4-MeO-C₆H₄ | 60          | 98        |
| 3f      | H  | 4-Br-C₆H₄ | 4-F-C₆H₄  | 75          | 98        |
| 3g      | H  | 4-Br-C₆H₄ | 4-Me-C₆H₄ | 63          | 93        |
| 3h      | H  | 4-Br-C₆H₄ | 2-naphthyl | 66          | 97        |
| 3i      | H  | 4-Br-C₆H₄ | 3-furyl   | 40          | 95        |
| 3j      | H  | 4-Br-C₆H₄ | 2-furyl   | 45          | 95        |
| 3k      | H  | 4-Br-C₆H₄ | 4-Br-C₆H₄ | 21          | 91        |
| 3l      | H  | 4-NO₂-C₆H₄ | 4-F-C₆H₄ | 80          | 95        |
| 3m      | H  | 4-NO₂-C₆H₄ | 3-Br-C₆H₄ | 72          | 91        |
| 3n      | H  | 4-MeO-C₆H₄ | 4-F-C₆H₄ | 65          | 98        |
| 3o      | H  | 4-Me-C₆H₄ | 4-F-C₆H₄  | 60          | 98        |
| 3p      | H  | 2-naphthyl | 4-F-C₆H₄ | 65          | 95        |
| 3q      | H  | 3-Br-C₆H₄ | 4-Br-C₆H₄ | 81          | 91        |
| 3r      | H  | 3-Br-C₆H₄ | 2-Br-C₆H₄ | 60          | 91        |
| 3s      | H  | 2-Br-C₆H₄ | 4-Br-C₆H₄ | 80          | 95        |
| 3t      | H  | 3-Br-C₆H₄ | 4-MeO-C₆H₄ | 55         | 91        |
| 3u      | H  | 4-Cl-C₆H₄ | 4-Cl-C₆H₄ | 80          | 95        |
| 3υ      | H⁻¹Butyl | 4-Br-C₆H₄ | 21          | 93        |
| 3W      | H  | 3-Br-C₆H₄ | 4-F-C₆H₄  | 75          | 95        |
| 3x      | Me  | 4-Br-C₆H₄ | 4-Br-C₆H₄ | 40          | 93        |
| 3y      | H  | 4-Br-C₆H₄ | [Fe(n⁻¹-C₆H₄)(n⁻¹-C₆H₄)] | 48          | 94        |

[a] For General Procedure A, see Supplementary Methods. [b] Isolated yields of the pure major enantiomer after column chromatography. Diastereomeric ratio for all products is >20:1. [c] Determined by HPLC analysis using a chiral stationary phase. Me, methyl; Ph, phenyl.

Table 2: Results of the enantioselective synthesis of the tandem cycloadditions with two different imines.

| Product | R¹ | R² | R³ | Yield [%][b] | ee [%][b] |
|---------|----|----|----|-------------|-----------|
| 5a      | 4-Cl-C₆H₄ | 4-Cl-C₆H₄ | 4-Br-C₆H₄ | 77          | 85        |
| 5b      | 4-Cl-C₆H₄ | 4-Cl-C₆H₄ | 4-Me-C₆H₄ | 65          | 82        |
| 5c      | 4-Cl-C₆H₄ | 4-Cl-C₆H₄ | 4-MeO-C₆H₄ | 56         | 84        |
| 5d      | 4-Br-C₆H₄ | 4-Me-C₆H₄ | 2-naphthyl | 75          | 89        |
| 5e      | 4-Cl-C₆H₄ | 4-Me-C₆H₄ | 4-MeO-C₆H₄ | 70          | 85        |
| 5f      | 4-Cl-C₆H₄ | 4-Me-C₆H₄ | 4-Br-C₆H₄ | 65          | 90        |
| 5g      | 4-Br-C₆H₄ | 4-Me-C₆H₄ | 2-Br-C₆H₄ | 56          | 90        |
| 5h      | 4-Br-C₆H₄ | 4-Me-C₆H₄ | 4-MeO-C₆H₄ | 69         | 89        |
| 5i      | 4-Br-C₆H₄ | 4-Me-C₆H₄ | 4-F-C₆H₄  | 78          | 90        |
| 5j      | 4-Br-C₆H₄ | 4-Me-C₆H₄ | 4-Br-C₆H₄ | 72          | 87        |

[a] General procedure B can be found in Supplementary Methods. [b] Isolated yields of the pure major enantiomer after column chromatography. Diastereomeric ratio for all products is >20:1. [c] Determined by HPLC analysis using a chiral stationary phase. Me, methyl; Ph, phenyl.

Notably, this reaction created eight stereocenters including one quaternary center in a one-pot transformation. The absolute configuration of product 3a was determined by crystal structure analysis (Supporting Information, Crystal Data), which revealed that product 3a is formed by double endo-selective cycloaddition.

The scope of the tandem reaction is wide. Regardless of the substitution pattern of the aromatic ring, enones 1 react with various azomethine ylides derived from imines 2 with moderate to good yields of 40–81% with high diastereoreg- (20:1) and enantioselectivity (91–99% ee). 3a–3y in Table 1. In the presence of electron-donating substituents such as methyl- or methoxy groups (3e and 3g, respectively), the yield was reduced to 60–63% whereas electron-neutral or withdrawing substituents such as bromine or fluorine (3a and 3f) led to higher yields. Heterocycle-containing azomethine ylides reacted to provide products (3i and 3j) in moderate yield and with high enantioselectivity (95% ee). In general, the enantioselectivity of the double cycloaddition remained consistent regardless of substitution pattern. When an enone with a sterically hindering tert-butyl substituent on the exocyclic olefin was employed, the double cycloaddition product (3v) was obtained in 21% yield, and high enantioselectivity was still observed (93% ee). Furthermore, introduction of a methyl substituent to the endocyclic double bond of the enone yielded 3x with two quaternary centers with high enantioselectivity (93% ee).

A more hindered o-phenyl substituted ylide, afforded product 3k in 21% yield but with high enantioselectivity (91% ee), thereby inducing formation of three quaternary centers. For all of examples shown in Table 1, the products were formed as single diastereomers (d.r. >20:1) after 24 h.

To rapidly expand the chemical space accessible via the double cycloaddition, we explored whether a sequential multicomponent transformation could give access to cycloadducts formed from two different imines. Following optimization, a sequence was established in which cyclic...
enones 1 were treated with 1.1 equiv of an iminoester 2 in the presence of \((R)-\text{Fesulphos} \) \((L1, 6.5 \text{ mol }\%\), AgOAc (6 mol \%) and \(\text{Cs}_2\text{CO}_3\) (40 mol \%) in dichloromethane for 3 h (Supplementary Methods, procedure B) followed by treatment with a second, different iminoester 2' for 24 h. Based on the different reactivity of the double bonds, the first cycloaddition occurs with the endocyclic double and the second cycloaddition targets the exocyclic double bond, which results in selective formation of mixed double cycloaddition products 5 by means of a sequential one-pot, three-component reaction (5a–5j in Table 2). The mixed double cycloaddition products 5 were obtained at high diastereoselectivity but, unexpectedly, with lower enantioselectivity (82–91 \% ee) relative to the two-component double-cycloaddition products 3, for which the products were formed with up to 99 \% ee.

To explain the findings we hypothesized that both cycloadditions, that is, formation of 3 and 4, may be the result of an enantioselectively catalyzed dynamic covalent process. In this process the double cycloaddition first proceeds reversibly through a kinetically controlled path due to the lower energy barrier of the transition state followed by an interconversion to the thermodynamically more stable product by a fast equilibrium process. To validate this mechanistic hypothesis changes in enantioselectivity of the double cycloaddition were investigated stepwise (Table 3, Table 5). Upon

| Table 3: Results of the time dependent enantioselective synthesis of chiral mono-adducts (1e–4). |
|------------------------------------------------|
| Entry | \( t [\text{h}] \) | Yield [\%] | ee\(^{[a]}\) |
|---|---|---|---|
| 1 | 3 | 59 | 95 |
| 2 | 12 | 59 | 87 |
| 3 | 29 | 59 | 84 |
| 4\(^{[b]}\) | 16 | 58 | 80 |
| 5\(^{[b]}\) | 24 | 57 | 70 |

\(^{[a]}\) \(12 \text{ mol of } (R)-\text{Fesulphos was used.}^{[a]}\) Determined by HPLC analysis using a chiral stationary phase.

This suggests that monoadduct 1a with 1.1 equiv of iminoester 2a in the presence of \((R)-\text{Fesulphos} \) \((L1, 6.5 \text{ mol }\%\), AgOAc (6 mol \%) and \(\text{Cs}_2\text{CO}_3\) (40 mol \%) in DCM, leads to formation of monoadduct 4a with 90–95 \% ee after 3 h but with only 80 \% ee after 16 h (Table 3, Supporting Information, Experimental studies).

Cycloaddition product 3a is formed with 99 \% ee regardless of the AgOAc/(\(R)-\text{Fesulphos ratio. These results indicate that one enantiomer of monoadduct 4a is involved in a retrocycloaddition as it matches with the chiral environment of the Ag/(\(R)-\text{Fesulphos complex in a selective manner. In order to confirm that retrocycloaddition is an enantioselective process, enantiomer enriched mono adduct 4a (81 \% ee) was subjected to reaction with \((R)-\text{Fesulphos} \) \((L1, 12 \text{ mol }\%\), AgOAc (6 mol \%) and \(\text{Cs}_2\text{CO}_3\) (40 mol \%) in DCM and a decrease of enantiomeric excess for the recovered monoadduct 4a was observed (74 \% ee) (Table 4, Supporting Information, Experimental studies). Furthermore, racemic mono adduct 4a was treated under identical conditions and was recovered with –10 \% ee (Table 4, Scheme 2).

| Table 4: Treatment of mono-adduct 4 using chiral catalyst. |
|------------------------------------------------|
| Entry | \( ee \) of 4a before reaction | \( t [\text{h}] \) | Yield [\%] | \( ee \) of 4a after reaction |
|---|---|---|---|---|
| 1 | 81 | 24 | 94 | 74 |
| 2 | 0 (rac) | 24 | 95 | –10 |

\(^{[a]}\) Determined by HPLC analysis using a chiral stationary phase.

These results indicate that the mono addition reaction in the presence of Ag/(\(R)-\text{Fesulphos is a reversible process in which the forward cycloaddition is enantioselective whereas the retrocycloaddition undergoes kinetic resolution. Similarly investigations with enone 1a and imine 2g further confirmed a dynamic covalent mono cycloaddition (Supporting Information, Experimental studies).

For examination of the second cycloaddition in the sequence from 4a to 3a enantiomer enriched mono addition product 4a (70 \% ee) was treated with 1 equiv of iminoester 2a under racemic conditions. No change in enantioselectivity was observed for the double cycloaddition product 3a (70 \% ee Table 5, Supporting Information, Experimental studies), thereby confirming that the stereochemistry is already set in the first step of the reaction sequence. However, employing enantiomer enriched 4a (70 \% ee) in the presence of a chiral catalyst led to a decrease in enantioselectivity for the double cycloaddition product 3a (60 \% ee, Table 5; Supporting Information, Experimental studies).

Furthermore, when racemic mono addition product \(\text{rac-4a} \) was subjected to the cycloaddition in the presence of \((R)-\text{FeSulphos and AgOAc with 1 equiv of iminoester 2a, double cycloaddition product 3a was obtained as an opposite alternative.} \)
enantiomer (−)3a with 20% ee (Table 5, Scheme 2) and was confirmed by crystal structure analysis (Supporting Information, Experimental studies, Crystal Data). The decreased enantioslectivity observed for 3a employing a chiral catalyst may be due to the enantioselective retrocycloaddition of 4a as discussed above (Table 5).

To further elucidate the reaction pathway, we performed a kinetic experiment by reacting rac-4a with imine 2a employing chiral catalyst (Supporting Information, Experimental studies, Supplementary Table 3). In the early stages of the reaction, 4a is rapidly converted into the endo, endo-product (−)3a and an endo, exo-diastereomer (+)6a (Scheme 3a, Supporting Information, Experimental studies, Supplementary Table 3). X-Ray analysis of the stereoisomeric endo, exo-product (+)6a revealed that it is formed through an exo-selective cycloaddition of iminoester 2a to the endo monoadduct product (+)4a (Supporting Information, Crystal Data). After three minutes, (−)3a and (+)6a are formed with noticeable ee (40% and 37% ee, respectively) (Supporting Information, Experimental studies, Supplementary Table 3). Over the course of the reaction, the ee of both products (−)3a and (+)6a decreases to 13% and −13% ee, respectively. Furthermore, the product ratio changes throughout the course of the reaction with more endo, endo-product 3a being formed over time while the yield of the endo, exo-product 6a decreases over time (Supporting Information, Experimental studies, Supplementary Table 3). A similar trend was observed by performing the kinetic experiment by subjecting racemic mono adduct rac-4a to cycloaddition with iminoester 2g under chiral conditions (Supporting Information, Experimental studies, Supplementary Table 4).

Since rac-4a is converted into two stereoisomers (−)3a and (+)6a with varying ratios and ee’s over time, it implies the formation of kinetically and thermodynamically controlled products during an enantioselective dynamic covalent process resulting in interconversion of those stereoisomers. (Scheme 3a, Supporting Information Figure 1). The endo, exo-stereoisomer (+)6a is the kinetically favored product and is formed faster than the thermodynamically more stable product (−)3a.

To explain the decrease in enantioselectivity and the change in product ratio over time, in accordance to the observation in Scheme 2, we investigated the stability of (+)6a. Compound (+)6a (37% ee) was subjected to AgOAc (6 mol%), (R)-Fesulphos (6.5 mol%) and Cs2CO3 (40 mol%) and was partially converted to the more stable and thermodynamically favored endo, endo-product (−)3a with 59% ee (37% yield) while (+)6a was recovered with a lower ee of 20% (51% yield) (Scheme 3a, Supporting Information, Experimental studies). This result provides further evidence that (+)6a is labile under the reaction conditions and that the change of enantioselectivity is due to an enantioselective dynamic process in which the main enantiomer of the kinetically favored product (+(+)6a) is converted to the minor enantiomer ((−)3a) of the thermodynamically stable product (Scheme 3a/b). Furthermore, highly enantiopure endo, exo-product (+)6a (95% ee) was treated under identical conditions and was converted to the stable thermodynamically favored endo, endo-product (+)3a (95% ee, 92% yield) with retention of enantioselectivity (Scheme 3a).

### Table 5: Catalytic 1,3-dipolar cycloaddition of enantioenriched/racemic mono-adduct 4.

| Entry | Ligand        | ee of 4a | Yield [%] | ee of 3a |
|-------|---------------|----------|-----------|----------|
| 1     | (R)-Fesulphos | 70       | 71        | 60       |
| 2     | PPh3          | 70       | 75        | 70       |
| 3     | (R)-Fesulphos | 0 (rac)  | 72        | −20      |

[a] Determined by HPLC analysis using a chiral stationary phase.
To clarify through which intermediate the stereoisomeric endo, exo-product (+)-6a is converted to product (+)-3a, compound (+)-6a (37% ee) was treated with iminoester 2g (2 equiv) in the presence of AgOAc (6 mol%), (R)-Fesulphos (6.5 mol%), and Cs₂CO₃ (40 mol%) in DCM. An imine exchange reaction was observed on the spirocycle affording product 5k in moderate yield (65%) and 33% ee (Scheme 3a, Supporting Information, Experimental studies). The imine exchange on the spirocycle indicates that the transformation of endo, exo-product (+)-6a to 5k proceeds through mono-

Scheme 3. a) Establishment of the stereodivergent catalyzed, double 1,3-dipolar cycloaddition of enone 1a and selected azomethine ylides and control of enantioselectivity. b) Proposed mechanism and intermediates for the AgOAc/(R)-Fesulphos mediated retrocycloaddition and interconversion.
addition product (±)-4a as an intermediate. Therefore, the thermodynamically less stable endo, exo-product 6a is converted to mono addition product 4a through a retro cycloaddition followed by an endo-selective cycloaddition with iminoester 2g to regenerate the spirocycle (Scheme 3a, Supporting Information, Experimental studies). A chiral (Ag-/(R)-Fesulphos) mediated dynamic covalent process is occurring in which covalent bonds are cleaved through a retro cycloaddition and reformed again by cycloaddition.

We also investigated whether endo, endo-product 3a can be converted to its stereoisomer endo, exo-product 6a. Racemic endo, endo 3a was treated with AgOAc (6 mol %), (R)-Fesulphos (6.5 mol %) and Cs₂CO₃ (40 mol %) with and without iminoester 2a. Compound 3a was not converted to product 6a which confirms the stability of endo, endo-product 3a compared to its stereoisomeric endo, exo-analog 6a under the reaction conditions (Supporting Information, Experimental studies).

These findings suggest that the double cycloaddition of enone 1 with imine 2 is in general a dynamic covalent process which can be divided in two cycles (Supporting Information, Figure 2). First, a Ag-/(R)-Fesulphos-catalyzed mono addition occurs to generate the chiral mono addition product 4 in which the chirality is set. The initial enantioselectivity of the mono addition is > 95% ee. Over time, a selective retro-cycloaddition for the major enantiomer of mono adduct 4 is catalyzed by Ag-/(R)-Fesulphos which induces its decomposition and results in a decreased ee of monoaddition product 4 from > 95% ee to 70–80% ee (Table 3, Supporting Information, Figure 2). The main enantiomer of mono adduct 4 matches with the chiral environment of the Ag-/(R)-Fesulphos complex as its decomposition is faster compared to its enantiomer, resulting in decrease of ee for mono adduct. In a second cycle starting from the enantioenriched mono addition product 4, a second cycloaddition takes place to generate a double cycloaddition product. Here, two diastereomers are formed, the kinetically favored non-stable endo, exo product 6 and the thermodynamically controlled stable endo, endo product 3 (Scheme 3a). Through a dynamic covalent process, enantioselective retro-cycloaddition of non-stable kinetic product endo, exo-6a occurs generating mono addition product 4, which is then converted to the thermodynamically favored and stable endo, endo product 3 (Scheme 3b, Supporting Information, Figure 2).

Finally we investigated whether changes in reaction conditions would enable a selective synthesis of kinetic diastereomer 6. To this end, a solvent screen revealed that in the aqueous system THF:H₂O (4:1) a switch in diastereoelectivity occurs. Treatment of enone 1a with 2.2 equiv of iminoester 2a in the presence of (R)-Fesulphos L1 (6.5 mol %) AgOAc (6 mol %) and Cs₂CO₃ (40 mol %) in this aqueous solvent system yields the endo, exo-product 6a (95% ee, 60% yield) as the main diastereomer relative to endo, endo product (+)-3a (d.r. 4:1) (Table 6).

In contrast, in DCM the endo, endo-product 3a is selectively obtained. The inversion in diastereoselectivity may be due to a more favorable exo-selective transition state in the aqueous environment. Alternatively interconversion of 6a to 3a is much slower in the aqueous solvent system relative to DCM. The interconversion of the less stable kinetically favored endo, exo product 6 to the thermodynamically controlled product 3 might be a slow equilibrium process which results in the kinetically controlled endo, exo product as major diastereomer in THF:H₂O (Scheme 4). Thus the speed of isomerization of the stereoisomers is decreased. In DCM the interconversion to reach the thermodynamically controlled equilibrium may proceed faster, since the retro cycloaddition from kinetically favored endo, exo product 6 to mono adduct 4 is more accelerated (Scheme 4). This was confirmed by analysis of the interconversion of the non-stable kinetic product endo, exo-6a to its thermodynamically more stable endo, endo product 3a in both solvent systems. Subjecting Compound (±)-6a (95% ee) to AgOAc (6 mol %), (R)-Fesulphos (6.5 mol %) and Cs₂CO₃ (40 mol %) in DCM afforded (±)-3a with 37% yield after 1 h, while only traces were observed in aqueous conditions after 1 h (Table 7). Expansion of the substrate scope confirmed the diastereoselectivity trend favoring 6 over its thermodynamically more stable stereoisomer 3 when an aqueous solvent system (THF:H₂O) was employed (Table 6).

**Table 6: Results of the enantioselective synthesis of the chiral endo-exo adducts 6.\[^a\]**

| Product | R² | R³ | Yield [%] \[^b\] | ee [%] \[^c\] | d.r. |
|---------|----|----|----------------|-----------|-----|
| 6a      | 4-Br-C₆H₄ | 4-Br-C₆H₄ | 65 | 95 | 4:1 |
| 6b      | 4-Br-C₆H₄ | 4-MeO-C₆H₄ | 60 | 93 | 7:1 |
| 6c      | 4-Br-C₆H₄ | 4-F-C₆H₄ | 51 | 97 | 4:1 |
| 6d      | 4-Br-C₆H₄ | 2-furyl | 49 | 95 | 7:1 |
| 6e      | 4-Br-C₆H₄ | 3-furyl | 48 | 95 | 7:1 |
| 6f      | 4-Br-C₆H₄ | 3-Me-C₆H₄ | 46 | 89 | 3:1 |
| 6g      | 4-Br-C₆H₄ | 3-furyl | 52 | 95 | 6:1 |

\[^a\] For General Procedure A, see Supplementary Methods. \[^b\] Isolated yields of the pure major enantiomer after column chromatography. \[^c\] Determined by HPLC analysis using a chiral stationary phase.

**Conclusion**

In summary, we have discovered an enantioselectively catalyzed dynamic covalent one-pot-tandem cycloaddition of azomethine ylides to α-alkyldiene-2-cyclopentenones. High diastereo- and enantioselectivity was obtained for the formation of the double cycloaddition products in a thermodynamically controlled equilibrium process. A stereodivergent synthesis was achieved since a switch in diastereoselectivity is observed in aqueous solvent system (THF:H₂O) and an enantiodivergent selectivity is recorded for reactions starting from racemic intermediate. Owing to differences in the reactivity of the endo- and exocyclic double bonds of the α-
alkylidene-2-cyclopentenones, two different dipoles could be successfully used in a one-pot process, yielding structurally complex molecular frameworks with up to 8 stereocenters.

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Conflict of Interest

The authors declare no conflict of interest.

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Table 7: Results of the time dependent enantioselective interconversion of enantioenriched endo, exo (±)6a to endo, endo (±)3a.

| Entry | t [h] | Solvent     | Yield [%] | ee[a]  |
|-------|-------|-------------|-----------|--------|
| 1     | 0.5   | DCM         | 13        | 95     |
| 2     | 1     | DCM         | 37        | 95     |
| 3     | 0.5   | THF: H₂O   | no conversion | n.d.  |
| 4     | 1     | THF: H₂O   | traces    | n.d.   |

[a] Determined by HPLC analysis using a chiral stationary phase. n.d. = not detected.
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