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**Binap-silver-catalyzed enantioselective multicomponent 1,3-dipolar cycloaddition of azomethines ylides derived from ethyl glyoxylate**

J. Mancebo-Aracil, C. Nájera,* J. M. Sansano.*

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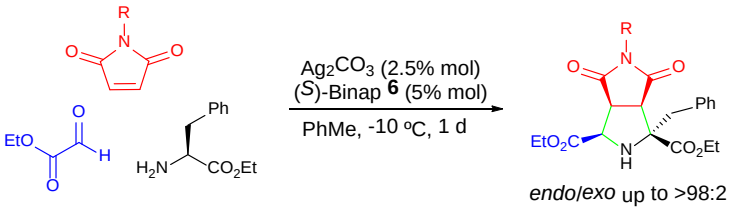


*endo*/*exo* up to >98:2
$ee_{endo}$ up to 92%

## Stereochemistry Abstract

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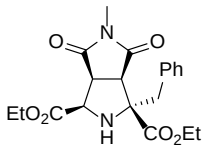


Ee = 90%
$[a]_D$ = - 23.8 (*c* 1, $CHCl_3$, 90% *ee* from HPLC)
Source of chirality: ($S_a$)-Binap

$C_{20}H_{24}N_2O_6$

Diethyl (1*S*,3*R*,3a*S*,6a*R*)-1-benzyl-5-methyl-4,6-dioxooctahydropyrrolo[3,4-*c*]pyrrole-1,3-dicarboxylate

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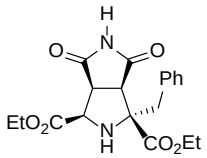


Ee = 30%
$[a]_D$ = - 12.8 (*c* 1, $CHCl_3$, 30% *ee* from HPLC)
Source of chirality: ($S_a$)-Binap

$C_{19}H_{22}N_2O_6$

Diethyl (1*S*,3*R*,3a*S*,6a*R*)-1-benzyl-4,6-dioxooctahydropyrrolo[3,4-*c*]pyrrole-1,3-dicarboxylate

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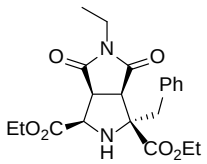


Ee = 88%
$[a]_D$ = - 17.7 (*c* 1, $CHCl_3$, 88% *ee* from HPLC)
Source of chirality: ($S_a$)-Binap

$C_{21}H_{26}N_2O_6$

Diethyl (1*S*,3*R*,3a*S*,6a*R*)-1-benzyl-5-ethyl-4,6-dioxooctahydropyrrolo[3,4-*c*]pyrrole-1,3-dicarboxylate

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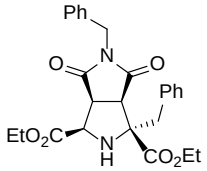


Ee = 80%
$[a]_D$ = - 36.9 (*c* 1, $CHCl_3$, 80% *ee* from HPLC)
Source of chirality: ($S_a$)-Binap

$C_{26}H_{28}N_2O_6$

Diethyl (1*S*,3*R*,3a*S*,6a*R*)-1,5-dibenzyl-4,6-dioxooctahydropyrrolo[3,4-*c*]pyrrole-1,3-dicarboxylate

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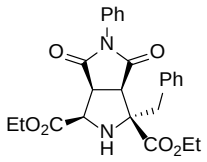


Ee = 90%
$[a]_D$ = - 28.0 (*c* 1, $CHCl_3$, 90% *ee* from HPLC)
Source of chirality: ($S_a$)-Binap

$C_{25}H_{26}N_2O_6$

Diethyl (1*S*,3*R*,3a*S*,6a*R*)-1-benzyl-4,6-dioxo-5-phenyl octahydropyrrolo[3,4-*c*]pyrrole-1,3-dicarboxylate

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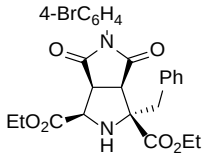


Ee = 92%
$[a]_D$ = - 32.6 (*c* 1, $CHCl_3$, 92% *ee* from HPLC)
Source of chirality: ($S_a$)-Binap

$C_{25}H_{25}BrN_2O_6$

Diethyl (1*S*,3*R*,3a*S*,6a*R*)-1-benzyl-5-(4-bromophenyl)-4,6-dioxooctahydropyrrolo[3,4-*c*]pyrrole-1,3-dicarboxylate

# Binap-silver-catalyzed enantioselective multicomponent 1,3-dipolar cycloaddition of azomethines ylides derived from ethyl glyoxylate

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***Abstract***: The enantioselective binap-silver catalyzed multicomponent 1,3-dipolar cycloaddition using ethyl glyoxylate, phenylalanine ethyl ester and maleimides is described. The employment of the basic silver carbonate allows the reaction in the absence of an extra base giving high yields and *ee*. In addition, a low-level calculations regarding the importance of the benzyl substituent at the α-position of the amino ester justify the expected absolute configuration of final cycloadducts and the observed high enantiodiscrimination.

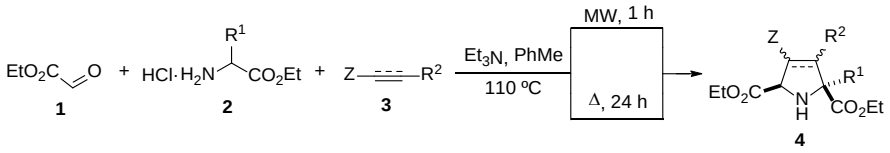
**Keywords**: Cycloaddition · binap · silver(I) · enantioselective · multicomponent

## 1. Introduction

Since Huisgen´s seminal work[1] 1,3-dipolar cycloadditions (1,3-DC) emerged as a potent and useful tool in organic synthesis.[2] Modern chemistry focused on asymmetric synthesis increased the interest of the organic chemists by these transformations in which it is possible to achieve just in one step up to four stereogenic centres in multiple series of heterocycles or cyclopentanes. Concerning the reaction involving azomethine ylides and alkenes, very efficient chiral organocatalyst- or chiral Lewis acid-mediated processes have been published since 2002.[3] In all of them, the reaction occurred starting from the freshly prepared imino ester which is the direct precursor of the azomethine ylide. However, it is noteworthy that the multicomponent[4] version of this 1,3-DC[5] is not frequently found in the literature. A few examples have been recently recorded in cycloadditions promoted by organocatalysts, for example, chiral prolinol derivatives,[6] chiral phosphoric acids,[7] chiral thioureas,[8] and chiral squaramides.[9] However, the multicomponent asymmetric 1,3-DC of azomethine ylides employing chiral metal complexes has been seldom achieved.[10]

In previous contributions, our group pioneered the development of these multicomponent 1,3-DCs by using binap·$AgSbF_6$ complex in the transformation involving imino esters and maleimides or 1,2-bis(phenylsulfonyl)ethylene.[11] We have recently reported that ethyl glyoxylate **1** can be used as aldehyde in a multicomponent diastereoselective 1,3-DC with α-amino esters **2** (derived from glycine, alanine, phenylalanine, and phenylglycine) and different dipolarophiles **3** (Scheme 1).[12] Microwave-assisted heating processes gave better results than conventional heating ones, affording *endo*-cycloadducts as major stereoisomers with a 2,5-*cis*-relative arrangement through the W-shaped dipole. We describe here the binap·silver(I) catalyzed enantioselective

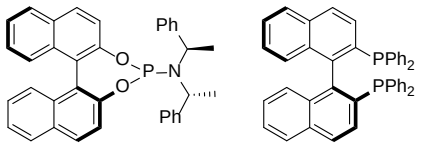
multicomponent 1,3-DC using ethyl glyoxylate for the preparation of enantiomerically enriched pyrrolidines **4**.




**Scheme 1.** Multicomponent diastereoselective 1,3-dipolar cycloaddition of ethyl glyoxylate derived azomethine ylides.

## 2. Results and discussion

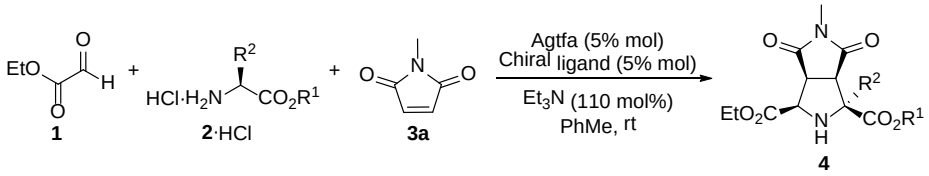
Privileged chiral ligands[13] selected for this survey, such as phosphoramidite **5** and binap **6**, were successfully employed in precedent multicomponent or two-component1,3-DC[14] reported by our group (Figure 1). The starting model reaction for the study of this enantioselective 1,3-DC process involved ethyl glyoxylate **1**, amino ester hydrochloride **2** and *N*-methylmaleimide **3a** (NMM) using 5 mol% of both chiral ligand and silver trifluoroacetate (Agtfa) in toluene at room temperature for 18 h (Scheme 2 and Table 1).




(*Sa*,*R*,*R*)-**5** (*S*)-Binap **6**

**Figure 1.** Chiral privileged ligands employed in this work.

Preliminary results demonstrated that phosphoramidite ligand **5** was not appropriate for this transformation (Table 1, entries 1, 3, 5, 7 and 9). Glycine, alanine, and phenylglycine derivatives **2** gave good yields but low enantioselectivities (Table 1, entries 2, 4, and 8). Only phenylalanine ethyl ester hydrochloride **2c**·HCl reacted in the presence of binap affording the corresponding cycloadduct **4** with a modest 30% *ee* (Table 1, entry 6) in 10 h. Low enantioselection was again detected in the presence of the chiral phosphoramidite **5**·Agtfa complex when the free phenylalanine ethyl ester was employed, but the enantioselection was improved in the binap **6**·AgTfa-catalyzed process to 70% *ee* (Table 1, entries 9 and 10). In this last example exclusively one 2,5-*cis*-*endo*-diastereoisomer **4ca** was identified.



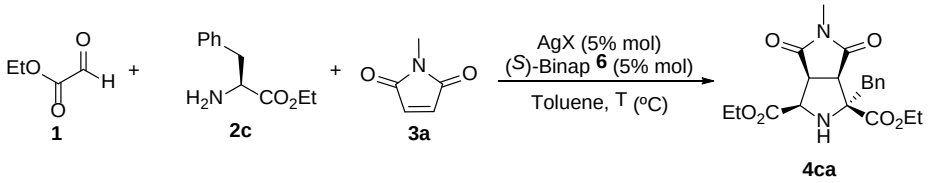

**Scheme 2.** Optimization reaction conditions modifying the amino ester hydrochloride **2** and the chiral ligand.

**Table 1.** Study of the reaction conditions.

| Ent. | **2**·HCl | $R^1$ | $R^2$ | Ligand | Product **4** | Conv.[a] | *ee*[b] |
|---|---|---|---|---|---|---|---|
| 1 | **2a**·HCl | Et | H | **5** | **4aa** | 100 | 0 |
| 2 | **2a**·HCl | Et | H | **6** | **4aa** | 100 | 0 |
| 3 | **2b**·HCl | Me | Me | **5** | **4ba** | 20 | 0 |
| 4 | **2b**·HCl | Me | Me | **6** | **4ba** | 60 | 6 |
| 5 | **2c**·HCl | Et | Bn | **5** | **4ca** | 90 | 0 |
| 6 | **2c**·HCl | Et | Bn | **6** | **4ca** | 95 | 30 |
| 7 | **2d**·HCl | Me | Ph | **5** | **4da** | 67 | 0 |
| 8 | **2d**·HCl | Me | Ph | **6** | **4da** | 85 | 7 |
| 9 | **2c**[c] | Et | Bn | **5** | **4ca** | 100 | 15 |
| 10 | **2c**[c] | Et | Bn | **6** | **4ca** | 100 | 70 |

[a] Determined by $^1$H NMR of the crude reaction mixture. 10 h Reaction time.
[b] Determined by HPLC using chiral columns.
[c] Free amino ester was used.

The 1,3-DC of **1** with phenylalanine ethyl ester (**2c**) and NMM (**3a**) was performed in the presence of binap (5 mol%) and different silver salts (5 mol%) in toluene (Scheme 2 and Figure 2). The modification of the stoichiometry binap:silver cation or the loading of the catalyst did not improve the previous results (Table 1, entry 10). The analysis of the solvent effect was also evaluated (toluene, THF, diethyl ether, dichloromethane, water, methanol, and acetonitrile were tested) and, as conclusion, toluene was the most appropriate giving pure crude reaction product **4ca**. Due to the formation of three different silver aggregates of binap·AgOTf at different temperatures,[15] we decided to carry out a study at different temperatures (Figure 2). At room temperature the reaction took place in 10 h and AgOAc gave the highest 79% *ee*. When the reaction was performed at -20 ºC Agtfa gave the highest 90% *ee*, which could also obtained employing $Ag_2CO_3$ at -10 ºC, being necessary 24 h for the reaction completion in both examples.




**Scheme 3.** Optimization reaction of (*S*)-binap **6**·silver salt-temperature-solvent parameter in the synthesis of adduct **4ca**.

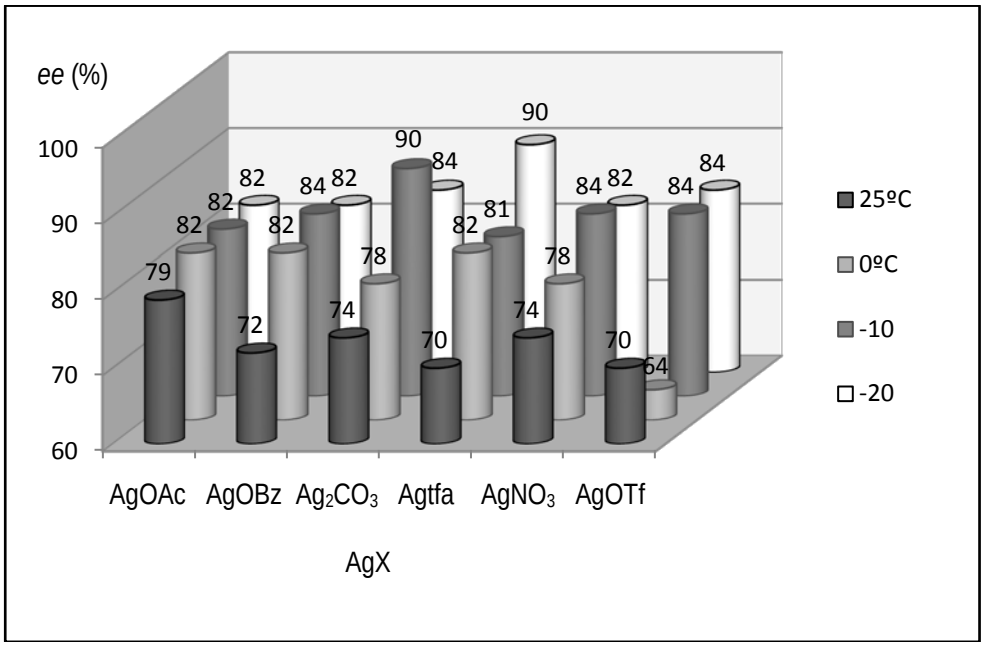
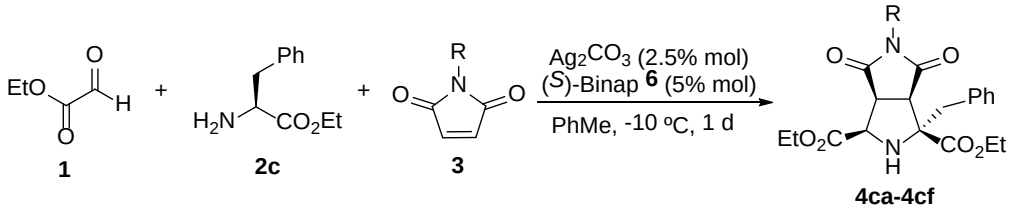



**Figure 2.** Effect of (*S*)-binap **6**·silver salt-temperature-toluene in the enantiomeric excess of cycloadduct **4ca**.

Then, the scope of this multicomponent reaction between ethyl glyoxylate **1**, ethyl phenylalaninate **2c** and different maleimides **3** was next studied in toluene at -10 ºC with $Ag_2CO_3$ as silver salt (Scheme 4). Maleimide **3b** afforded the lowest enantioselectivity of this series (Table 2, entry 1). *N*-Alkyl maleimides **3a**, **3c**, and **3d** afforded good yields and high enantioselections for cycloadducts **4** (Table 2, entries 1, 3, and 4). *N*-Arylmaleimides such as *N*-phenylmaleimide (NPM) and *N*-(4-bromophenyl)maleimide offered 90 and 92% *ee*, respectively (Table 2, entries 5 and 6).




**Scheme 4.** Multicomponent 1,3-DC of ethyl glyoxylate **1**, phenylalanine ethyl ester **5**, and maleimides **3**.

**Table 2.** Multicomponent 1,3-DC of ethyl glyoxylate **1**, phenylalanine ethyl ester **2**, and maleimides **3**.

| Ent. | **3** | R | Product **4** | Yield (%)[a] | *ee* (%)[b] |
|---|---|---|---|---|---|
| 1 | **3a** | Me | **4ca** | 94 | 90 (90) |
| 2 | **3b** | H | **4cb** | 65 | 30 (30) |
| 3 | **3c** | Et | **4cc** | 96 | 85 (88) |
| 4 | **3d** | $PhCH_2$ | **4cd** | 95 | 77 (80) |
| 5 | **3e** | Ph | **4ce** | 95 | 88 (90) |
| 6 | **3f** | 4-Br-$C_6H_4$ | **4cf** | 98 | 92 (92) |

[a] Isolated chemical yield obtained after column chromatography (silica gel).
[b] Determined by HPLC using chiral columns of crude cycloadduct. In parentheses the *ee* values of the purified cycloadduct **4**.

The general scope of this reaction was restricted to maleimides because the reaction depicted in Scheme 4 with other electrophilic alkenes gave low enantioselectivities. Thus, methyl and *tert*-butyl acrylates gave good conversions (83, and 75% respectively) of the corresponding racemic cycloadduct. Methyl fumarate (70% conversion), and (*E*)-1,2-bis(phenylsulfonyl)ethylene (90% conversion) gave very low enantioselectivities (<10% *ee*), and β-nitrostyrene did not react at all.

According to the physical and spectroscopic data reported for the racemic 1,3-DC we confirm that compounds **4** were isolated as only one diastereoisomer, derived from the generation of a W-dipole shape **I** (Figure 4) affording 2,5-*cis*-arrangement of both ester groups in **4**. The absolute configuration of the final products was established following the usual trend of binap-promoted enantioselective cycloadditions. (*S*)-Binap·AgX complexes induce 2*S*,3*R*,4*S*,5*R* absolute configuration in maleimide derived cycloadducts.[11,14]

Based on our experience in this type of asynchronous concerted cycloaddition with maleimides employing stabilized 1,3-dipoles derived from arylideneglycinates or alaninates and considering the absence of non-linear effects, we performed a simple study of the lowest energy arrangement of chiral intermediate **I**.[16] The presence of a monomeric (ligand-metal) structure **A**/**B** during computing series with a minimal energy value (108.3403 kcal/mol) was very satisfactory. From this saddle point intermediate, where the anion effect was not considered, it was possible to justify several experimental results. First, the high enantioselectivity observed just with the phenylalanine derivative can be originated, presumably, by a possible favorable π-stacking interaction between the phenyl ring of the amino ester and the phenyl group of a phosphorous atom.[17] Distance of both aromatic rings (3.5-3.8 Å, better observed in view **B**) forces the chiral ligand to block one of the two faces of the dipole living accessible the opposite face. Second, the *endo*-approach of the maleimide by this face afforded the predicted the absolute configuration of compounds **4**.

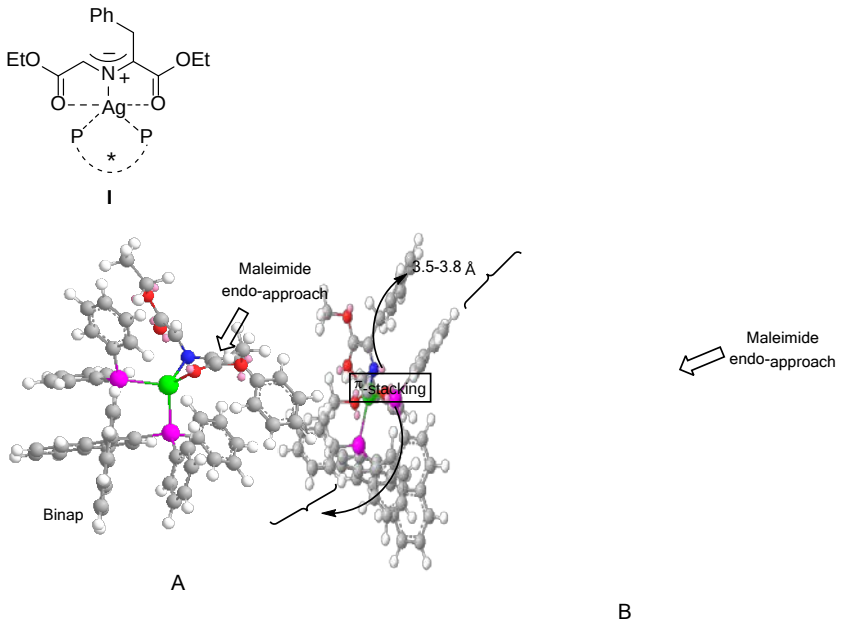



**Figure 4**. Proposed W-dipole shape **I** for the initial study. A and B are two different views of the most stable intermediate chiral dipole **I** running basic MM2 energy calculations.

## 3. Conclusions

A 1:1 mixture of (*S*)-binap and $Ag_2CO_3$ is the suitable catalyst (prepared *in situ*) for the multicomponent enantioselective 1,3-DC between the azomethine ylide, generated by ethyl glyoxylate and ethyl phenylalaninate, and maleimides. (*S*)-Binap·AgX complexes efficiency depends on the temperature due to the presence of several aggregates, which operate following different enantiodiscrimination patterns. The absence of an extra base and the highest enantioselections observed with a more basic counteranion of the silver salt suggest that this multicomponent sequence operates in the presence of a bifuntional catalyst activating and controlling the cycloaddition and promoting the deprotonation. The scope of the process is limited to ethyl phenylalaninate and maleimides. The origin of the high enantioselection resides in a π-stacking interaction between the phenyl ring of the amino ester and the phenyl group of the phosphorous atom.

## 4. Experimental Part

### 4.1. General information

Melting points were determined with a Reichert Thermowar hot plate apparatus and are uncorrected. Only the structurally most important peaks of the IR spectra (recorded whit a FT-IR 4100LE (JASCO) (PIKE MIRacle ATR) are listed. $^1$H NMR (300 MHz) and $^{13}$C NMR (75 MHz) spectra were obtained with a Bruker AC-300 by using $CDCl_3$ as solvent and TMS as the internal standard, unless otherwise stated. Optical rotations were measured with a Perkin-Elmer 341polarimeter. HPLC analyses were performed with a JASCO-2000 series equipped with a chiral column (detailed for each compound in the main text) by using mixtures of *n*-hexane/isopropyl alcohol as the mobile phase at 25 ºC. Low-resolution electron impact (EI) mass spectra were obtained with a Shimadzu QP-5000 by injection or DIP, and high-resolution mass spectra

were obtained with a Finnigan VG Platform or a Finnigan MAT 95S. Analytical TLC was performed on Schleicher & Schuell F1400/LS 254 silica gel plates and the spots were visualized under UV light (λ = 254 nm). Merck silica gel 60 (0.040-0.063 mm) was used for flash chromatography.

**4.2. General procedure for the enantioselective 1,3-DC.**

In a 10 ml vial covered by aluminum foil, $Ag_2CO_3$ (6.9 mg, 0.025 mmol), (*S*)-binap **6** (31 mg, 0.050 mmol) and toluene (3 mL) were added and the resulting mixture was stirred at room temperature for 1 h. The mixture was cooled at -10 ºC and the amino ester **2c** (193 mg, 1 mmol), the corresponding maleimide **3** (1 mmol), and ethyl glyoxylate **1** (*ca*.50% solution in toluene, 102 μL, 1.2 mmol) were slowly added in this order. The reaction was stirred 1 d at -10 ºC and the crude was analyzed by $^1$H NMR spectroscopy to determine the conversion, and then purified by flash chromatography (*n*-hexane:EtOAc), affording cycloadducts **4**.

**4.3. Diethyl (1*S*,3*R*,3a*S*,6a*R*)-1-benzyl-5-methyl-4,6-dioxooctahydropyrrolo[3,4-*c*]pyrrole-1,3-dicarboxylate (4ca).**

$[\alpha]_{D20}$= -23.8 (*c* 1, $CHCl_3$), 90% *ee* from HPLC (Chiralpak AD-H, 90:10, *n*-hexane:isopropyl alcohol, 1 mL/min, $t_{min}$ 46.5 min, $t_{maj}$ 50.0 min); IR (neat) $\nu_{max}$ 3030, 2982, 2936, 1779, 1734, 1699 cm$^{-1}$; $^1$H NMR $\delta_H$: 1.32, 1.34 (2t, *J* = 7.2 Hz, 3H, $CO_2CH_2CH_3$), 2.88, 3.30 (2d, *J* = 13.8 Hz, 2H, $CH_2$Ph), 2.92 (s, 3H, $NCH_3$), 3.38 [d, *J* = 8.0 Hz, 1H, C*H*C(CO$_2$Et)Bn], 3.55 [deform. dd, *J* = 8.4, 8.0 Hz, 1H, C*H*CH(CO$_2$Et)NH], 4.09 [d, *J* = 8.4, Hz, 1H, C*H*(CO$_2$Et)NH], 4.24 (q, *J* = 7.2 Hz, 2H, $CO_2CH_2CH_3$ ), 4.26 (q, *J* = 7.2 Hz, 2H, $CO_2CH_2CH_3$), 7.23-7.27 (m, 5H, Ar*H*), N*H* nd; $^{13}$C NMR $\delta_C$: 14.0 (2x$CO_2CH_2CH_3$), 25.4 ($NCH_3$), 42.2 ($CH_2$Ar), 50.4 [*C*HCH(CO$_2$Et)NH], 56.6 [*C*HC(CO$_2$Et)Bn], 62.0 [*C*H(CO$_2$Et)NH], 62.1, 62.3 (2x$CO_2CH_2CH_3$), 73.6 [*C*(CO$_2$Et)Bn], 127.2, 128.3, 130.4, 135.7 (Ar*C*), 169.6, 170.1 (2x*C*O$_2$), 175.0, 175.1 (2xCON); MS (EI-GC) *m/z*: 388 ($M^+$+1, <1%), 315 (13), 298 (14), 297 (100), 223 (11), 166 (45), 94 (11), 91 (17); HRMS calculated for $C_{20}H_{24}N_2O_6$: 388.1634, found: 388.1631.

**4.4. Diethyl (1*S*,3*R*,3a*S*,6a*R*)-1-benzyl-4,6-dioxooctahydropyrrolo[3,4-*c*]pyrrole-1,3-dicarboxylate (4cb).**

$[\alpha]_{D20}$= -12.8 (*c* 1, $CHCl_3$), 30% *ee* from HPLC (Chiralpak OD-H, 90:10, *n*-hexane:isopropyl alcohol, 1 mL/min, , $t_{maj}$ 36.7 min, $t_{min}$ 73.5 min); IR (neat) $\nu_{max}$ 3220, 1731, 1700 cm$^{-1}$; $^1$H NMR $\delta_H$: 1.28–1.34 (m, 6H, 2x$CO_2CH_2CH_3$), 2.88, 3.33 (2xd, *J* = 13.8 Hz, 2H, $CH_2$Ph), 3.50 (br. s, 1H, N*H*), 3.42 [d, *J* = 7.8 Hz, 1H, C*H*C(CO$_2$Et)Bn], 3.58 [deform. dd, *J* = 8.0, 7.8 Hz, 1H, C*H*CH(CO$_2$Et)NH], 4.11–4.18 [m, 1H, C*H*(CO$_2$Et)NH], 4.20–4.28 [m, 4H, 2x$CO_2CH_2CH_3$], 7.27–7.29 (m, 6H, Ar*H* and NH); $^{13}$C NMR $\delta_C$: 14.1, 14.2 (2x$CO_2CH_2CH_3$), 42.2 ($CH_2$Ph), 51.5 [*C*HCH(CO$_2$Et)NH], 57.7 [*C*HCH(CO$_2$Et)NH], 62.2, 62.4 (2x$CO_2CH_2CH_3$), 62.5 [*C*H(CO$_2$Et)NH], 73.7 [*C*Bn(CO$_2$Et)NH], 123.0, 128.5, 130.5, 135.7 (ArC), 169.6, 170.1 (2x*C*O$_2$), 175.0, 174.9 (2xCON); MS (EI-GC) *m/z*: 374 ($M^+$, 11%), 155 (15), 94 (13), 91 (100); HRMS calculated for $C_{19}H_{22}N_2O_6$: 374.1478, found: 374.1489.

**4.5. Diethyl (1*S*,3*R*,3a*S*,6a*R*)-1-benzyl-5-ethyl-4,6-dioxooctahydropyrrolo[3,4-*c*]pyrrole-1,3-dicarboxylate (4cc).**

$[\alpha]_{D20}$= -17.7 (*c* 1, $CHCl_3$), 88% *ee* from HPLC (Chiralpak OD-H, 90:10, *n*-hexane:isopropyl alcohol, 1 mL/min, $t_{min}$ 14.7 min, $t_{maj}$ 33.4 min); IR (neat) $\nu_{max}$ 3002, 2985, 2930, 1725, 1715, 1700 cm$^{-1}$; $^1$H NMR $\delta_H$: 1.12 (t, *J* = 7.2 Hz, 3H, $NCH_2CH_3$), 1.35, 1.37 (2t, *J* = 7.2 Hz, 6H, 2x$CO_2CH_2CH_3$), 2.92, 3.34 (2d, *J* = 13.9 Hz, 2H, $CH_2$Ph), 3.39 [d, *J* = 7.7 Hz, 1H, C*H*C(CO$_2$Et)Bn], 3.40 (q, *J* = 7.2 Hz, 2H, $NCH_2CH_3$), 3.55 [deform. dd, *J* = 8.6, 7.7 Hz, 1H, C*H*CH(CO$_2$Et)NH], 4.10 [d, *J* = 8.6, Hz, 1H, C*H*(CO$_2$Et)NH], 4.24-4.32 (m, 4H, 2x$CO_2CH_2CH_3$), 7.23-7.27 (m, 5H, Ar*H*), N*H* nd; $^{13}$C NMR $\delta_C$: 13.1, 14.1, 14.2 (3x$CO_2CH_2CH_3$), 34.4 ($NCH_2CH_3$), 42.3 ($CH_2$Ar), 50.3 [*C*HCH(CO$_2$Et)NH], 56.6 [*C*HC(CO$_2$Et)Bn], 62.0 [*C*H(CO$_2$Et)NH], 62.2, 62.4 (2x$CO_2CH_2CH_3$), 73.8 [*C*(CO$_2$Et)Bn], 127.3, 128.3, 130.5, 135.8 (Ar*C*), 169.6, 170.1 (2x*C*O$_2$), 174.8, 174.9 (2xCON); MS (EI-GC) *m/z*: 402 ($M^+$+1, <1%), 329 (10), 315 (10), 298 (15), 297 (100), 222 (10), 166 (50), 94 (11), 91 (18); HRMS calculated for $C_{21}H_{26}N_2O_6$: 402.1791, found: 402.1789.

### 4.6. Diethyl (1*S*,3*R*,3a*S*,6a*R*)-1,5-dibenzyl-4,6-dioxooctahydropyrrolo[3,4-c]pyrrole-1,3-dicarboxylate (4cd).

[α]D20= -36.9 (*c* 1, $CHCl_3$), 80% *ee* from HPLC (Chiralpak AD-H, 90:10, *n*-hexane:isopropyl alcohol, 1 mL/min, $t_{maj}$ 23.9 min, $t_{min}$ 42.7 min); IR (neat) $\nu_{max}$ 3030, 2989, 1741, 1719, 1699 $cm^{-1}$; $^1H$ NMR $\delta_H$: 1.23 (t, *J* = 7.2 Hz, 3H, $CO_2CH_2CH_3$), 1.28 (t, *J* = 7.2 Hz, 3H, $CO_2CH_2CH_3$), 2.89, 3.31 (2d, *J* = 13.9 Hz, 2H, $CH_2Ph$), 3.38 [d, *J* = 7.8 Hz, 1H, C*H*C($CO_2$Et)Bn], 3.55 [deform. dd, *J* = 7.8, 7.8 Hz, 1H, C*H*CH($CO_2$Et)NH], 4.03–4.27 (m, 5H, 2x$CO_2CH_2CH_3$ and C*H*($CO_2$Et)NH], 4.54, 4.60 (d, *J* = 14.3 Hz, 2H, $CH_2Ph$), 7.20–7.35 (m, 10H, Ar*H*), N*H* nd; $^{13}C$ NMR $\delta_C$: 14.0, 14.1 (2x$CO_2CH_2CH_3$), 42.2, 43.0 (2x$CH_2Ph$), 50.4 [*C*HCH($CO_2$Et)NH], 56.6 [*C*HCH($CO_2$Et)NH], 61.9, 62.1 (2x$CO_2CH_2CH_3$), 62.3 [*C*H($CO_2$Et)NH], 73.7 [*C*Bn($CO_2$Et)NH], 127.2, 128.0, 128.3, 128.6, 128.7, 130.5, 135.2, 135.8 (ArC), 169.4, 169.9 (2x$CO_2CH_2CH_3$), 174.6, 174.7 (2xCON); MS (EI-GC) *m/z*: 464 ($M^+$+1, <1%), 391 (14), 374 (22), 373 (100), 166 (22), 91 (73); HRMS calculated for $C_{26}H_{28}N_2O_6 - C_7H_7$: 373.1400, found: 373.1401.

### 4.7. Diethyl (1*S*,3*R*,3a*S*,6a*R*)-1-benzyl-4,6-dioxo-5-phenyloctahydropyrrolo[3,4-*c*]pyrrole-1,3-dicarboxylate (4cd).

[α]D20= -28.0 (*c* 1, $CHCl_3$), 90% *ee* from HPLC (Chiralpak AD-H, 90:10, *n*-hexane:isopropyl alcohol, 1 mL/min, $t_{maj}$ 42.0 min, $t_{min}$ 51.1 min); IR (neat) $\nu_{max}$ 2979, 2937, 1729, 1714 $cm^{-1}$; $^1H$ NMR $\delta_H$: 1.25–1.30 (m, 6H, 2x$CO_2CH_2CH_3$), 2.96, 3.36 (2xd, *J* = 13.9 Hz, 2H, $CH_2Ph$), 3.51 (s, 1H, N*H*), 3.55 [d, *J* = 7.8 Hz, 1H, C*H*C($CO_2$Et)Bn], 3.73 [deform. dd, *J* = 7.8, 7.8 Hz, 1H, C*H*CH($CO_2$Et)NH], 4.15–4.30 [m, 5H, 2x$CO_2CH_2CH_3$ and C*H*($CO_2$Et)NH], 7.15–7.49 (m, 10H, Ar*H*); $^{13}C$ NMR $\delta_C$: 13.9, 14.0 (2x$CO_2CH_2CH_3$), 42.3 ($CH_2Ph$), 50.4 [*C*HCH($CO_2$Et)NH], 56.6 [*C*HCH($CO_2$Et)NH], 62.1, 62.2 (2x$CO_2CH_2CH_3$), 62.3 [*C*H($CO_2$Et)NH], 74.1 [*C*Bn($CO_2$Et)NH], 126.6, 127.2, 128.0, 128.2, 128.9, 129.2, 130.4, 135.6 (ArC), 169.7, 170.1 (2x$CO_2$), 174.0, 174.2 (2xCON); MS (EI-GC) *m/z*: 450 ($M^+$+1, <1%), 377 (14), 360 (22), 359 (100), 207 (44), 166 (40), 156 (10), 119 (10), 94 (13), 91 (45); HRMS calculated for $C_{25}H_{26}N_2O_6$: 450.1791, found: 450.1801.

### 4.8. Diethyl (1*S*,3*R*,3a*S*,6a*R*)-1-benzyl-5-(4-bromophenyl)-4,6-dioxooctahydropyrrolo[3,4-*c*]pyrrole-1,3-dicarboxylate (4cf).

[α]D20= -32.6 (*c* 1, $CHCl_3$), 92% *ee* from HPLC (Chiralpak OD-H, 80:20, *n*-hexane:isopropyl alcohol, 1 mL/min, $t_{maj}$ 25.3 min, $t_{min}$ 30.0 min); IR (neat) $\nu_{max}$ 2979, 1731, 1700 $cm^{-1}$; $^1H$ NMR $\delta_H$: 1.27–1.33 (m, 6H, 2x$CO_2CH_2CH_3$), 2.96, 3.35 (2xd, *J* = 13.9 Hz, 2H, $CH_2Ph$), 3.51 (br. s, 1H, N*H*), 3.56 [d, *J* = 7.8 Hz, 1H, C*H*C($CO_2$Et)Bn], 3.67 [deform. dd, *J* = 8.0, 7.8 Hz, 1H, C*H*CH($CO_2$Et)NH], 4.11–4.18 [m, 1H, C*H*($CO_2$Et)NH], 4.20–4.28 [m, 4H, 2x$CO_2CH_2CH_3$], 7.09 (d, *J* = 8.6 Hz, 2H, Ar*H*), 7.27–7.29 (m, 5H, Ar*H*), 7.55 (d, *J* = 8.6 Hz, 2H, Ar*H*); $^{13}C$ NMR $\delta_C$: 14.1, 14.2 (2x$CO_2CH_2CH_3$), 42.5 ($CH_2Ph$), 50.6 [*C*HCH($CO_2$Et)NH], 56.7 [*C*HCH($CO_2$Et)NH], 62.4, 62.5 (2x$CO_2CH_2CH_3$), 62.6 [*C*H($CO_2$Et)NH], 74.4 [*C*Bn($CO_2$Et)NH], 123.0, 127.4, 128.3, 128.4, 128.5, 130.5, 132.6, 135.7 (ArC), 169.9, 170.3 (2x$CO_2$), 173.9, 174.0 (2xCON); MS (EI-GC) *m/z*: 528, 530 ($M^+$+2, <1%), 451 (10), 374 (15), 361 (21), 360 (10), 359 (100), 207 (48), 166 (31), 155 (10), 119 (10), 94 (13), 91 (45); HRMS calculated for $C_{25}H_{25}BrN_2O_6$: 528.0896, found: 528.0891.

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## References

1. Clovis J. S.; Eckell A.; Huisgen R.; Sustmann, R. *Chem. Ber.* **1967**, *100*, 60-70.
2. a) *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products*, Padwa, A.; Pearson, W. H. Eds., John Wiley & Sons: New Jersey, **2003**; b) Nájera, C.; Sansano, J. M. *Curr. Org. Chem.* **2003**, *7*, 1105-1150; c) Eberbach, W. In *Sci. Synth., Houben-Weyl Methods of Molecular Transformations*;

Padwa, A., Bellus, D., Eds.; Thieme Verlag: Stuttgart, 2004; Vol. 27, chp. 11, pp 441-498; d) Coldham, I.; Hufton, R. *Chem. Rev.* **2005**, *105*, 2765-2810; e) Nair, V.; Suja, T. D. *Tetrahedron* **2007**, *63*, 12247-12275; f) Padwa, A.; Bur, S. K. *Tetrahedron* **2007**, *63*, 5341-5378; g) Hashimoto, T.; Maruoka, K. *Handbook of Cyclization Reactions*, Ma, S. Ed. Wiley-VCH: Weinheim, 2010; h) Kanemasa, S. *Heterocycles* **2010**, *82*, 87-200; i) Han, M.-Y.; Jia, J.-Y.; Wang, W. *Tetrahedron Lett.* **2014**, *55*, 784-794; j) Suga, H.; Itoh, K. in *Methods and Applications of Cycloaddition Reactions in Organic Syntheses*, Nishiwaki, N. Ed., Wiley: Weinheim, 2014, pp. 175-204.

3. For recent reviews of asymmetric 1,3-DC, see: a) Pellissier, H. *Tetrahedron* **2007**, *63*, 3235-3285; b) Nájera, C.; Sansano J. M. in *Topics in Heterocyclic Chemistry*, Hassner, A. Ed., Springer-Verlag: Berlin-Heidelberg, 2008, vol. 12, pp. 117-145; c) Stanley, L. M.; Sibi, M. P. *Chem. Rev.* **2008**, *108*, 2887-2902; d) Álvarez-Corral, M.; Muñoz-Dorado, M.; Rodríguez-García, I. *Chem. Rev*. **2008**, *108*, 3174-3198; e) Naodovic, M.; Yamamoto, H. *Chem. Rev*. **2008**, *108*, 3132-3148; f) Nájera, C.; Sansano, J. M.; Yus, M. *J. Braz. Chem. Soc*. **2010**, *21*, 377-412; g) Kissane, M.; Maguire, A. R. *Chem. Soc. Rev*. **2010**, *39*, 845-883; h) Adrio, J.; Carretero, J. C. *Chem. Commun.* **2011**, *47*, 6784-6794; i) Adrio, J.; Carretero, J. C. *Chem. Commun.*, **2014**, *50*, 12434-12446; j) Nájera, C.; Sansano, J. M. *J. Organomet. Chem*. **2014**, *771*, 78-92.
4. a) *Multicomponent Reactions in Organic Synthesis*, Zhu J.; Wang, M.; Wang, Q. (Eds.), Wiley-VCH, Weinheim, 2014; b) *Multicomponent Reactions: Concepts and Applications for Design and Synthesis*, Herrera, R. P., Marqués-López, E. (Eds.) Wiley-VCH, Weinheim, 2015.
5. For recent applied MCRs using azomethine ylides, see: Craven P.; Aimon, A.; Dow, M.; Fleury-Bregeot, N.; Guilleux, R.; Morgentin, R.; Roche, D.; Kalliokoski, T.; Foster, R.; Marsden, S. P.; Nelson, A. *Bioorg. Med. Chem.* **2015**, http://dx.doi.org/10.1016/j.bmc.2014.12.048.
6. a) Ibrahem, I.; Ríos, R.; Vesely, J.; Córdova, A. *Tetrahedron Lett.* **2007**, *48*, 6252-6257; b) Lin, S.; Deiana, L.; Zhao, G.-L.; Sun, J.; Córdova, A. *Angew. Chem. Int. Ed.* **2011**, *50*, 7624-7630.
7. a) Chen, X-.H.; Zhang, W.-Q.; Gong, L.-Z. *J. Am. Chem. Soc.* **2008**, *130*, 5652-5653; b) Liu, W.-J.; Chen, X-.H.; Gong, L.-Z. *Org. Lett.* **2008**, *10*, 5357-5360; c) Chen, X-.H.; Wei, Q.; Luo, S.-W.; Xiao, H.; Gong, L.-Z. *J. Am. Chem. Soc.* **2009**, *131*, 13819-13825; d) Wang, C.; Chen, X-.H.; Zhou, S.-M.; Gong, L.-Z. *J. Chem. Commun.* **2010**, *46*, 1275-1277; e) Li, N.; Song, J.; Tu, X.-F.; Liu, B.; Chen, X.-H.; Gong, L.-Z. *Chem. Commun.* **2010**, *46*, 2016-2019, f) Cheng, M.-N.; Wang, H.; Gong, L.-Z. *Org. Lett.* **2011**, *13*, 2418-2421; g) Shi, F.; Tao, Z.-L.; Yu, J.; Tu, S.-J. *Tetrahedron: Asymmetry* **2011**, *22*, 2056-2064; h) Shi, F.; Luo, S.-W.; Tao, Z.-L.; He, L.; Yu, J.; Tu, S.-J.; Gong, L.-Z. *Org. Lett.* **2011**, *13*, 4680-4683; i) He, L.; Chen, X.-H.; Wang, D.-N.; Luo, S.-W.; Zhang, W.-Q.; Yu, J.; Ren, L.; Gong, L.-Z. *J. Am. Chem. Soc.* **2011**, *133*, 13504-13518; j) Shi, F.; Tao, Z.-L.; Luo, S.-W.; Tu, S.-J.; Gong, L.-Z. *Chem. Eur. J.* **2012**, *18*, 6885-6894; k) Shi, F.; Tao, Guo, Chang; Song, Jin; Gong, Liu-Zhu *Org. Lett.* **2013**, *15*, 2676-2679; l) Shi, F.; Xing, G.-J.; Tan, W.; Zu, R.-Y.; Tu, S.-J. *Org. Biomol. Chem*. **2013**, *11*, 1482-1489; m) Zhu, R-Y.; Wang, C.-S.; Jiang, F.; Shi, F.; Tu, S. J. *Tetrahedron: Asymmetry* **2014**, *25*, 617-624.
8. a) Liu, Y.-K.; Liu, H.; Du, W.; Yue, L.; Chen, Y.-C. *Chem. Eur. J.* **2008**, *14*, 9873-9877; b) Wang, L.-L.; Bai, J.-F.; Peng, L.; Qi, L.-W.; Jia, L.-N.; Guo, Y.-L.; Luo, X.-Y.; Xu, X.-Y.; Wang, L.-X. *Chem. Commun* **2012**, *48*, 5175-5177.
9. Tian, L.; Hu, X.-Q.; Li, Y.-H.; Xu, P.-F. *Chem. Commun* **2013**, *49*, 7213-7215.
10. a) Chaulagain, M. R.; Felten, A. E.; Gilbert, K.; Aron Z. D. *J. Org. Chem.* **2013**, *78*, 9471–9476; b) Potowski, M.; Merten, C.; Antonchick, A. P.; Waldmann, H. *Chem. Eur J*. **2015**, DOI: 10.1002/chem.201500125.
11. a) Martín-Rodríguez, M.; Nájera, C.; Sansano, J. M.; Costa, P. R. R.; Crizanto de Lima, E.; Dias, A. G. *Synlett* **2010**, 962-966; b) Mancebo-Aracil, J.; Martín-Rodríguez, M.; Nájera, C.; Sansano, J. M.; Costa, P. R. R.; Crizanto de Lima, E.; Dias, A. G. *Tetrahedron: Asymmetry* **2012**, *23*, 1596-1606.
12. Mancebo-Aracil, J.; Nájera, C.; Sansano, J. M. *Org. Biomol. Chem*. **2013**, *11*, 662-675.
13. a) *Privileged Chiral Ligands and Catalysts*, Qi-Lin Zhou, Ed.; Wiley-VCH: New York, 2011; b) Teichert, J. F.; Feringa, B. L. *Angew. Chem. Int. Ed*. **2010**, *49*, 2486–2528.
14. a) Nájera, C.; Retamosa, M. G.; Sansano, J. M. *Org. Lett.* **2007**, *9*, 4025–4028; b) Nájera, C.; Retamosa, M. G.; Sansano, J. M.; de Cózar, A.; Cossío, F. P. *Tetrahedron*: *Asymmetry* **2008**, *19*, 2913-2923; c) Nájera, C.; Retamosa, M. G.; Sansano, J. M. *Angew. Chem. Int. Ed.* **2008**, *47*, 6055-6058; d) Nájera, C.; Retamosa, M. G.; Martín-Rodríguez, M.; Sansano, J. M.; de Cózar, A.; Cossío, F. P. *Eur. J. Org. Chem.* **2009**, 5622-5634; e) Castelló, L. M.; Nájera, C.; Sansano, J. M.; Larrañaga, O.; de Cózar, A.; Cossío, F. P. *Org. Lett.* **2013**, *15*, 2902–2905; f) Castelló, L. M.; Nájera, C.; Sansano, J. M.; Larrañaga, O.; de Cózar, A.; Cossío, F. P. *Adv. Synth. Catal.* **2014**, *356*, 3861-3870; g) Castelló, L. M.; Nájera, C.; Sansano, J. M.; Larrañaga, O.; de Cózar, A.; Cossío, F. P. *Synthesis* **2015**, *47*, 934-943.
15. Momiyama, N.; Yamamoto, H. *J. Am. Chem. Soc.* **2004**, *126*, 5360-5361.
16. *ChemBio3D Ultra 14*, CambridgeSoft Corp. 2014.
17. This π-stacking effect was not observed when phenylglycine derivative was modeled under the same computing program.