

New thiourea organocatalysts and their application for the synthesis of 5-(1*H*-indol-3-yl)methyl-2,2-dimethyl-1,3-dioxane-4,6-diones a source of chiral 3-indoymethyl ketenes

Ewelina Najda-Mocarska¹, Anna Zakaszewska¹, Karolina Janikowska¹ Sławomir Makowiec¹

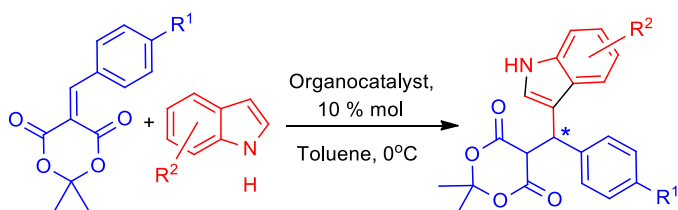
¹Department of Organic Chemistry, Gdansk University of Technology, Narutowicza 11/12, 80-233, Gdańsk, Poland

Corresponding author Sławomir Makowiec E-mail: mak@pg.edu.pl

Abstract

The stereoselective properties of modified thiourea organocatalysts were tested in the Friedel–Crafts alkylation of indole with 5-arylidene-2,2-dimethyl-1,3-dioxane-4,6-diones, which produces chiral 5-((1*H*-indol-3-yl)(aryl)methyl)-2,2-dimethyl-1,3-dioxane-4,6-diones. Based on a tentative reaction mechanism for ((*S*)-*N*-benzyl-2-(3-(3,5-bis(trifluoromethyl)phenyl)thioureido)-*N*,3,3-trimethylbutanamide organocatalysts, modifications were applied in four selected regions. Systematic structure–stereoselectivity relationship study allowed designing the best efficient organocatalyst for the investigated Friedel–Crafts alkylation of indole with 5-arylidene-2,2-dimethyl-1,3-dioxane-4,6-diones.

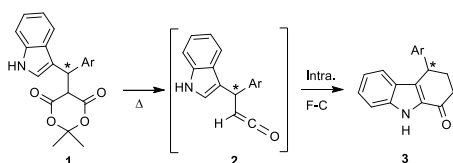
Graphical Abstract



KEYWORDS: 1,3-dioxane-4,6-dione, heteroaromatic, thiourea organocatalyst, alkylation, Meldrum's acid

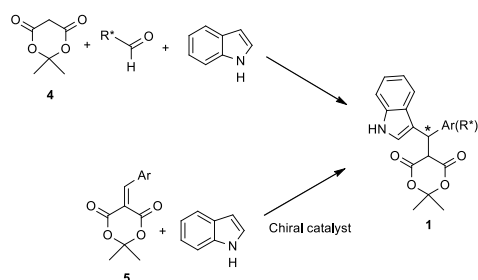
INTRODUCTION

Indole derivatives are biologically active compounds. The structural pattern of indole can be found in an impressive variety of molecules, such as: phytohormones^[1], neurotransmitters^[2], anti-inflammatory agents^[3], and anticancer medicine^[4]. From the perspective of modern pharmacology, manipulation with serotonin and 5-HT receptors by stimulating with indole derivatives could be a key in solving problems related to mood, depression, and anxiety disorders. Therefore, synthesis of serotonin agonists, particularly targeted as selective serotonin reuptake inhibitors (SSRI), can be the center of interest in medicinal chemistry. The derivatives of homotryptamine^[5] and tetrahydrocarbazoles^[6] are an interesting group of SSRIs with indole moiety in molecules. Tetrahydrocarbazole derivatives are also useful for the treatment of human papillomaviruses (HPV)^[7]. The aforementioned tetrahydrocarbazole derivatives can be easily accessible by thermal decomposition of 5-((1H-indol-3-yl)(aryl)methyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (Meldrum's acid derivative) (**1**) to ketene (**2**) and by subsequent intramolecular Friedel–Crafts acylation, which lead to the production of 2,3,4,9-tetrahydro-1H-carbazol-1-ones (**3**). Fillion and co-workers have published a series of research works, which describes transformation of 2,2-dimethyl-5-benzyl-1,3-dioxane-4,6-diones to useful bioactive 1-indanones through intramolecular Friedel–Crafts acylation^[8].



Scheme 1. Synthetic application of chiral 5-((1H-indol-3-yl)(aryl)methyl)-2,2-dimethyl-1,3-dioxane-4,6-diones.

We took a challenge to introduce indole moiety into a derivative of Meldrum's acid with simultaneous chiral creation. One of the easiest synthetic method to obtain such a group of compounds is through the condensation of three components: Meldrum's acid (**4**), aldehyde, and indole^[9]. Such an approach allows for subsequent stereoselective course of reaction if an aldehyde contained a chiral auxiliary^[10]. (Scheme 2) But, induction of chirality center is a problem for aldehydes that cannot be functionalized with a chiral auxiliary moiety. We have also experienced such a problem, therefore we decided to apply chiral organocatalysts. Since we learned that thiourea organocatalysts are not effective in the three components reaction, we followed a different approach for the synthesis by using a stereocontrolled reaction between the indole and the electrophile reagent 5-arylidene-2,2-dimethyl-1,3-dioxane-4,6-dione (**5**)^[11].



Scheme 2. Routes to synthesis of chiral 5-((1H-indol-3-yl)(aryl)methyl)-2,2-dimethyl-1,3-dioxane-4,6-diones (**1**).

Over the last few decades, organocatalysis has become an indispensable tool in asymmetric synthesis^[12]. One of the most applicable groups of organocatalysts are compounds containing chiral moiety attached to the thiourea system the Bronsted acid catalyst. From our point of view, the most interesting application of thiourea organocatalyst is Friedel–Crafts reaction^[13] which has been thoroughly studied on many levels^[14]. We have focused our research on the stereocontrolled Friedel-Crafts

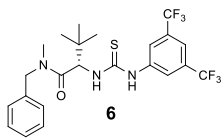
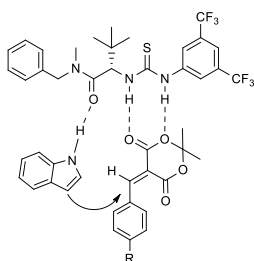


Figure 1. (S)-N-benzyl-2-(3-(3,5-bis(trifluoromethyl)phenyl)thioureido)-N,3,3-trimethylbutanamide (**6**)

alkylation of indoles with 5-arylidene-2,2-dimethyl-1,3-dioxane-4,6-diones (**5**)^[15]. As a result of such a process, 5-(aryl(1H-indol-3-yl)methyl)-2,2-dimethyl-1,3-dioxane-4,6-diones (**1**), a product with new chiral center can be obtained. The thermally labile 1,3-dioxane-4,6-dione fragment is a convenient source of ketene, which might be used for intramolecular acylation leading to the desired derivative of chiral 2,3,4,9-tetrahydro-1H-carbazol-1-ones (**3**).

DISCUSSION

In the present study, we have focused our research efforts on the modifications of (S)-N-benzyl-2-(3-(3,5-bis(trifluoromethyl)phenyl)thioureido)-N,3,3-trimethylbutanamide organocatalyst (**6**) (Figure 1) and on their synthetic application for the preparation of our target chiral 2,2-dimethyl-5-(aryl(1H-indol-3-yl)methyl)-1,3-dioxane-4,6-diones (**1**). The parent structure of the organocatalyst (**6**) was chosen during the previous study, from among a number of commercially available catalysts.



Scheme 3. Plausible transition state with action of (S)-N-benzyl-2-(3-(3,5-bis(trifluoromethyl)phenyl)thioureido)-N,3,3-trimethyl butanamide (**6**)

To describe the role of catalyst as a working hypothesis, we have assumed the following reaction mechanism for the stereoselective catalysis that is presented on (Scheme 3). Our hypothesis is supported by the following facts: application of N-methylindole instead of indole caused decrease of stereoselectivity in preliminary experiments; and the use of organocatalyst (**6**) with tertiary amide in the amidic fragment implies only one possible combination of reagents.

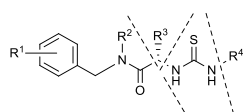
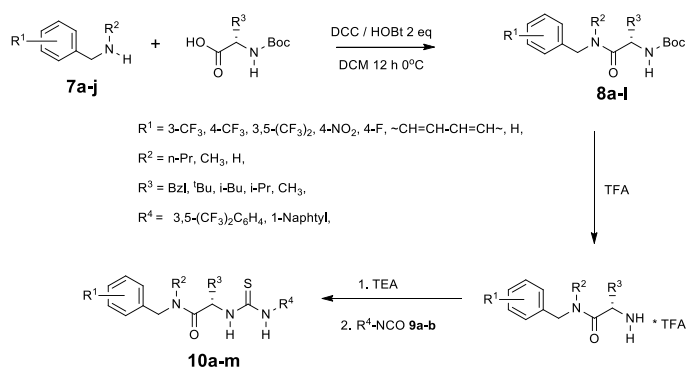


Figure 2. Regions of thiourea organocatalyst

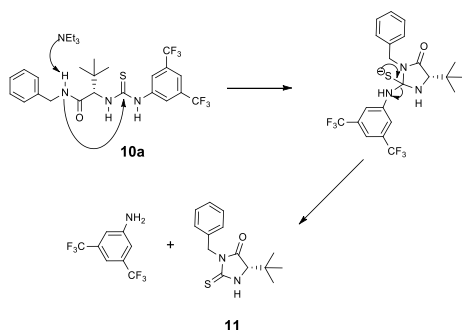
For systematic study of the relationship between structure and stereoselectivity of designed organocatalysts, we have specified four regions in the molecule (Figure 2). 1. The amidic part with the possibility to tune electron density in the phenyl ring R^1 and N-substitution with different R^2 . 2. The side chain of aminoacid R^3 , where the size of the group can be changed. 3. The inviolable thiourea system. 4. The R^4 aromatic ring with the electron withdrawing group (EWG), which is also responsible for the acidity of thiourea protons. Most of our modification took place in the first and second fragment of the molecule. For thiourea moiety, only reasonable modifications should lead to the increase of acidity and hence we tried S-alkylation to achieve more acidic species, but it was unsuccessful. In the last region of molecule, we tried to make just one modification by replacing the 3,5-bis(trifluoromethyl)phenyl with 1-naphthyl aromatic system to make a possible stronger π - π interaction.

The approach for the preparation of modified thiourea organocatalysts consisted of a three-step synthetic path, starting from Boc-protected aminoacid. (Scheme 4) In the first step Boc-AA was activated in the usual manner and coupled with benzyl amines (**7a-j**).



Scheme 4. Synthetic strategy for preparation of modified thiourea organocatalysts

In the aforementioned step, reduction of racemization is a crucial issue. We tested racemization level for several approaches suggested in chemical literature for similar synthesis^[16]. Mostly, O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HBTU), O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate (TBTU) uronium salts, or the combination of ethyl-(N',N'-dimethylamino)propylcarbodiimide hydrochloride (EDC) and 1-hydroxybenzotriazole (HOBT) are used for the low racemization procedures. However, we applied our own modification with the use of N,N'-dicyclohexylcarbodiimide (DCC) in the presence of 1.1 eq. of HOBT hydrate where we observed the lowest level of racemization on the stage formation (**8a-l**). After deprotection, the resulting amino amide was treated with chloroform solution of isothiocyanate (**9a-b**) to yield final organocatalysts (**10a-m**). In most cases, the synthesis had



Scheme 5. Proposed reaction mechanism for the formation of side product (S)-3-benzyl-5-(tert-butyl)-2-thioxoimidazolidin-4-one (**11**).

good yields and any significant byproducts, except for the model with secondary amidic system. In the last step of synthesis of organocatalyst (**10a**), we observed a drastic drop in the yield, with simultaneous formation of a significant amount of byproduct. Analysis of the NMR spectra allows us to propose the structure of byproduct as (S)-3-benzyl-5-(tert-butyl)-2-thioxoimidazolidin-4-one (**11**). We have proposed possible mechanism for the formation of the byproduct (Scheme 5). In the basic condition previously formed organocatalyst undergoes an intramolecular cyclization with the departure of 3,5-bistrifluoroaniline as a leaving group. A similar process was observed by Walter and co-workers,^[17] but with a nucleophilic attack of thioureido nitrogen of amide carbonyl and with the loss of dimethylamine. The structures and yields of all prepared organocatalysts are presented in Figure 3.

The stereocatalytic effectiveness of the prepared organocatalysts we tested in the reaction of 5-arylidene-2,2-dimethyl-1,3-dioxane-4,6-diones with indole in the optimal conditions. We determined these conditions during our previous researches and hence the process has to be performed in toluene at 0°C through 168 h, with 10% mol of

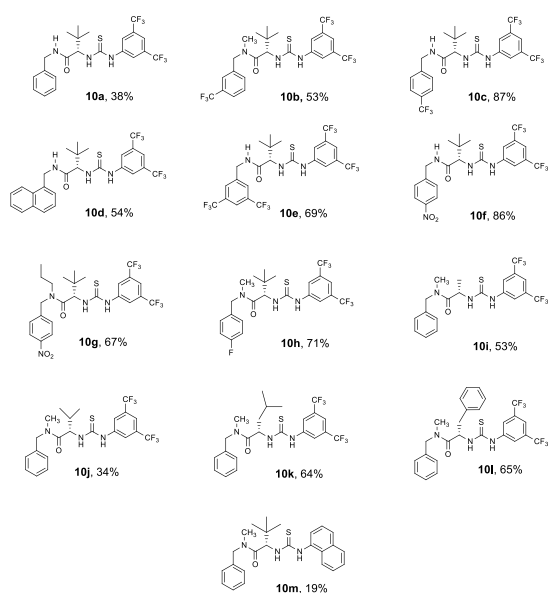


Figure 3. Structures and yields of organocatalyst **10a-m**

catalyst and 0.04 M concentration of reagent. For the ee determination of the products, we used previously developed method based on the formation of diastereoisomeric salts of Meldrum's acid with (*R*)-1-phenylethylamine and measurement of methine proton signals intensity with NMR technique. As testing models, we chose three representative type of arylidene Meldrum's acids basic 5-(phenyl)methylene-2,2-dimethyl-1,3-dioxane-4,6-dione (**5a**) (*Z* = H), 4-chlorophenyl (**5b**) (*Z* = Cl), and 4-nitrophenyl substituent (**5c**) (*Z* = NO₂). In the beginning, we decided to check influence of size substituent in the side chain of aminoacid R³ (second region). We prepared four different organocatalyst substituted with methyl, isopropyl, iso-butyl and benzyl substituents (**10i,j,k,l**). We tested their organocatalytic properties with the use of the standard method. The results are presented in Table 1. (Entries 10-13). We also have included data for commercially available catalyst that possess tert-butyl substituent in the second region and was previously tested. The best ee was obtained for bulky side chain; however, the effectiveness of the catalyst is strongly dependent on the type of reacting molecules. The most universal substituent appears to be tert-butyl which allow to obtain high ee independent of the reacting system, however comparable ee could be achieved in some cases with R³ = isobutyl (Entry 12, *Z* = H). For further experiments, we decided to use tert-butyl derivatives as they were more predictable and trustworthy. Later, we decided to check the influence of the substituent in the phenyl ring of the first amidic part of catalyst. We expected stronger π–π interaction between indole ring and EWG -substituted benzyl moiety. Thus we prepared a series of organocatalysts with CF₃ and NO₂ groups in the benzylic ring. Eventually, we made modification in the nitrogen of the amide moiety; we prepared a series of organocatalysts with secondary amide to compare their stereospecific properties with N-alkyl type of catalysts, for instance pairs of catalysts **10a – 6** and



Table 1. Stereoselective Friedel-Crafts alkylation of indole with catalyst **10a-m**

Entry	R ¹	R ²	R ³	R ⁴	Cat.	Solv. = Toluene; T = 0°C						Solv. = Hexane T = 7°C	
						Z = H		Z = Cl		Z = NO ₂		Z = Cl	
						Yield [%]	Ratio ^a 1a:1'a	Yield [%]	Ratio ^a 1b:1'b	Yield [%]	Ratio ^a 1c:1'c	Yield [%]	Ratio ^a 1b:1'b
1	H	H	t-Bu	3,5-(CF ₃) ₂ C ₆ H ₄	10a	89	63:37	54	63:37	40	61:39	89	77:23
2 ^b	H	CH ₃	t-Bu	3,5-(CF ₃) ₂ C ₆ H ₄	6	84	68:32	99	69:31	81	68:32	76	78:22
3	3-CF ₃	CH ₃	t-Bu	3,5-(CF ₃) ₂ C ₆ H ₄	10b	75	56:44	31	68:32	67	71:29	92	72:28
4	4-CF ₃	H	t-Bu	3,5-(CF ₃) ₂ C ₆ H ₄	10c	82	59:41	87	70:30	61	72:28	94	57:43
5	CH ₂ =CHCH=CH ₂	H	t-Bu	3,5-(CF ₃) ₂ C ₆ H ₄	10d	64	65:35	100	72:28	93	74:26	47	67:33
6	3,5-bisCF ₃	H	t-Bu	3,5-(CF ₃) ₂ C ₆ H ₄	10e	86	51:49	87	63:37	71	73:27	37	64:36
7	4-NO ₂	H	t-Bu	3,5-(CF ₃) ₂ C ₆ H ₄	10f	52	60:40	79	67:33	25	70:30	81	64:36
8	4-NO ₂	n-Pr	t-Bu	3,5-(CF ₃) ₂ C ₆ H ₄	10g	61	61:39	92	66:34	10	68:32	99	74:26
9	4-F	CH ₃	t-Bu	3,5-(CF ₃) ₂ C ₆ H ₄	10h	76	64:36	73	67:33	67	68:32	68	75:25
10	H	CH ₃	CH ₃	3,5-(CF ₃) ₂ C ₆ H ₄	10i	77	57:43	83	56:44	40	52:48	86	57:43
11	H	CH ₃	i-Pr	3,5-(CF ₃) ₂ C ₆ H ₄	10j	75	58:42	79	57:43	40	57:43	58	67:33
12	H	CH ₃	i-Bu	3,5-(CF ₃) ₂ C ₆ H ₄	10k	70	61:39	70	61:39	20	52:48	92	59:41
13	H	CH ₃	Bzl	3,5-(CF ₃) ₂ C ₆ H ₄	10l	52	60:40	87	52:48	20	51:49	99	56:44
14	H	CH ₃	t-Bu	1-Naphthyl	10m	43	51:49	100	53:47	21	45:55	89	53:47

^a Determined by ¹H NMR spectra of **1** with (*R*)-1-phenylethylamine - arbitrarily assigned configuration., ^b data for reference catalyst.

10f-g. In two cases we decided to introduce extended aromatic system to the molecule, instead of benzylic moiety we introduced 1-naphthyl – catalysts **10d** and we also replaced 3,5-bis(trifluoromethyl)phenyl with 1-naphthyl - catalyst **10m** (Entry 14). We tested organocatalytic properties of the prepared organocatalyst with the use of the standard method. The results are presented in the Table 1. We did not observe simply correlation between EWG in benzylic ring and stereoselective properties of catalyst. Thus, secondary amide catalysts with EWG groups were found to exhibit better properties than the unsubstituted one (Entries 1 ver 4, 6, 7) but for tertiary amides substitution with EWG) leads to catalysts with worse or comparable properties (Entries 2 ver 3, 8). Surprisingly, organocatalyst **10d** with 1-naphthyl, instead of benzyl moiety, proved to be even better and was more independent to the catalyzed system than the commercially available (**6**) (Entry 5). Whereas, the replacement of 3,5-

bis(trifluoromethyl)phenyl with 1-naphthyl caused a dramatic drop in the stereoselectivity of the catalysts, demonstrating that EWG 3,5-bis(trifluoromethyl)phenyl is necessary to ensure enough acidity of thiourea protons for binding to substrates. Surprisingly, application of hexane as a solvent allowed to obtain even higher ee (Entries 1, 2, 3, 8, 9), unfortunately this solvent cannot be applied for all spectrum of substrates due to poor solubility.

In summary, a series of new thiourea organocatalysts were prepared and their stereoselectivity was tested in the Friedel–Crafts alkylation of indole. Modifications comprised of selected, four most promising sites in the catalyst molecule. Structure and stereoselectivity studies allowed elucidating structure factors to design the most effective organocatalysts. The best properties were obtained for (S)-2-(3-(3,5-bis(trifluoromethyl)phenyl)thioureido)-3,3-dimethyl-N-(naphthalen-1-ylmethyl)butanamide **10d** with secondary 1-naphthyl amide moiety and bulky tert-butyl side chain on the central aminoacid.

EXPERIMENTAL

Commercially available reagents were purchased from Sigma-Aldrich or Acros. Toluene and cyclohexane were distilled from potassium under argon and stored over molecular sieves. DCM, CCl₄, and hexafluorobenzene were distilled over P₄O₁₀ and stored over molecular sieves. Commercially unavailable reagents 2,2-dimethyl-5-arylidene-1,3-dioxane-4,6-diones **2a-f** were prepared according to literature procedures^[11]. Analytical TLC was performed on aluminum sheets of silica gel UV-254 Merck. Flash chromatography was performed using 40-63 microns of Zeochem silica gel. The ¹H, ¹³C were recorded on Varian Gemini 200 and Varian Unity Plus 500, chemical shifts (δ) in ppm rel. to internal Me₄Si; coupling constants *J* in Hz. High-resolution (HRMS) was recorded on *MicroMas Quattro LCT* mass spectrometer.



Melting points were determined with *Warsztat Elektromechaniczny W-wa* apparatus and are not corrected.

General procedure for the synthesis of thiourea organocatalysts.

To a ice cooled solution of N-Boc-aminoacid (L-tert-leucine, L-Leu, L-Val, L-Phe, L-Ala) 1mmol in DCM 10 ml, HOBt hydrate (0.153 g, 1 mmol) and DCC (0.205 g, 1 mmol) was added. Reaction mixture was stirred at 0°C through 30 minutes, and amine **7a-j** (2 mmol) was added. Resulting reaction mixture was stirred for 12 h and allowed to warm to room temperature. Then a few drops of acetic acid was added, solvents was removed under reduced pressure. Residue was dissolved in AcOEt and cooled to 4°C, precipitate of urea was removed by filtration. Organic phase was washed with aqueous solution of KHSO₄ (10%, 20ml) followed by aqueous solution of NaHCO₃ (5%, 20ml) and dried with MgSO₄. Solvents were removed under reduced pressure and residue was dissolved in 10ml mixture of TFA:DCM (1:1). Progress of N-deprotection was monitored with TLC. Then mixture of TFA:DCM was evaporated and trifluoroacetate salt was dissolved in DCM 10 ml. To a resulted mixture NET₃ (0.303 g, 3 mmol) and chloroform solution of isothiocyanate **9a,b**^[18] was added dropwise. After completion of the reaction, the solvent was removed under vacuum, and the residue was purified with flash column chromatography.

(S)-N-benzyl-2-(3-(3,5-bis(trifluoromethyl)phenyl)thioureido)-3,3-dimethylbutanamide (10a)

Purification by flash column chromatography, (EtOAc/Hex, gradient elution 1:5 to 1:3), (187 mg, 38 % over two steps). white solid; mp 149-151 °C; $[\alpha]_D^{26} = -12.5^\circ$ (c = 0.4, CHCl₃); ¹H NMR (500 MHz, C₆D₆) δ 8.60 (s, 1H), 8.06 (d, *J* = 9.2 Hz, 1H), 7.99 (s, 2H), 7.42 (s, 1H), 6.96-6.90 (m, 4H), 6.89-6.84 (m, 1H), 5.51 (s, 1H), 5.02 (d, *J* = 9.2 Hz, 1H), 4.08 (dd, *J*² =



14.7 Hz, $J^3 = 6.4$ Hz, 1H), 3.88 (dd, $J^2 = 14.7$ Hz, $J^3 = 5.3$ Hz, 1H), 0.97 (s, 9H); ^{13}C NMR (CDCl₃, 100 MHz): $\delta = 181.9, 172.1, 139.9, 136.2, 131.7$ (q, $J^{\text{C-F}}=33.3$ Hz), 128.8, 127.9, 127.6, 124.2 (m), 123.0 (q, $J^{\text{C-F}}=271.1$ Hz), 118.5 (m), 66.4, 44.2, 35.1, 27.2; HRMS (ESI+): m/z [M + Na]⁺ calcd for C₂₂H₂₃F₆N₃OSNa: 514.1364; found: 514.1368

General Procedure for stereoselective preparation of 2,2-dimethyl-5-(aryl(heteroaryl)methyl)-1,3-dioxane-4,6-diones (1a-c, 1a'-c').

To a solution of 2,2-dimethyl-5-arylidene-1,3-dioxane-4,6-dione 5a-c (0.2 mmol) in anhydrous solvent (5ml) (DCM (A), toluene (B), toluene : cyclohexane 1:1 (C), Cyclohexane (D), CCl₄ (E), hexafluorobenzene (F)), at temperature specified in the Table 1, 2 and 3, catalyst 5-15 10% mol was added followed by heteroaromatic compound 2a-f (0.2 mmol). The resulting mixture was stirred for the time specified in the Table 1, 2 and 3. After completion of the reaction, the solvent was removed under vacuum, and the residue was purified as specified below.

2,2-dimethyl-5-(phenyl(1*H*-indol-3-yl)methyl)-1,3-dioxane-4,6-dione (1a, 1a')^[9]

Purification by flash column chromatography, (EtOAc/Hex, 1:2), yellow oil; ^1H NMR (CDCl₃, 500 MHz): $\delta = 8.18$ (s, 1 H), 7.44-7.35 (m, 5 H), 7.30-7.17 (m, 4 H), 7.08-7.05 (m, 1 H), 5.65 (d, $J = 2.0$ Hz, 1 H), 4.31 (d, $J = 2.4$ Hz, 1 H), 1.71 (s, 3 H), 1.42 (s, 3 H). ^{13}C NMR (CDCl₃, 125 MHz): $\delta = 165.8, 164.9, 140.0, 136.0, 129.3, 128.6, 127.4, 127.2, 124.4, 122.5, 119.9, 119.3, 115.2, 111.4, 105.4, 52.1, 41.9, 28.3, 28.2$.

General procedure for enantiomeric excess determination of 2,2-dimethyl-5-(aryl(heteroaryl)methyl)-1,3-dioxane-4,6-diones (1a-c, 1a'-c').

To a solution 2,2-dimethyl-5-(aryl(heteroaryl)methyl)-1,3-dioxane-4,6-diones (3aa-fe) 10 mg in CDCl₃ (0,7ml) in 5mm NMR tube, 20 eq of (R)-1-phenylethylamine was added. The spectrum was acquired through 20 min (with 40s relaxation time). Ratio of enantiomers was determined based on integration of methine protons region.

FUNDING

The project was carried-out within the PARENT-BRIDGE programme of the Foundation for Polish Science (POMOST/2013-8/6), co-financed from the European Union under the European Regional Development Fund.

REFERENCES

- [1] (a) Affonso, V.; Bizzo, H.; Lage, C.; Sato, A.; Influence of Growth Regulators in Biomass Production and Volatile Profile of in Vitro Plantlets of *Thymus vulgaris* L. *J Agric. Food Chem.* **2009**, *57*, 6392–6395. (b) Abel, S. Auxin Is Surfacing. *ACS Chem. Biol.* **2007**, *2*, 380–384.
- [2] (a) Kochanowska-Karamyan, A. J.; Hamann, M. T. Marine Indole Alkaloids: Potential New Drug Leads for the Control of Depression and Anxiety. *Chem. Rev.* **2010**, *110*, 4489–4497. (b) Baganz, N. L.; Blakely, R. D. A Dialogue between the Immune System and Brain, Spoken in the Language of Serotonin. *ACS Chem. Neurosci.* **2013**, *4*, 48–63. (c) Angoa-Pérez, M.; Kane, M. J.; Briggs, D. I.; Herrera-Mundo, N.; Sykes, C. E.; Francescutti, D. M.; Kuhn, D. M. Mice Genetically Depleted of Brain Serotonin Do Not Display a Depression-like Behavioral Phenotype. *ACS Chem. Neurosci.* **2014**, *5*, 908–919.
- [3] (a) Humber, L. G.; Ferdinandi, E.; Demerson, C. A.; Ahmed, S.; Shah, U.; Mobilio, D.; Sabatucci, J.; De Lange, B.; Labbadia, F. Etodolac, a novel



antiinflammatory agent. The syntheses and biological evaluation of its metabolites. *J. Med. Chem.* **1988**, *31*, 1712–1719. (b) Dejaco, Ch.; Duftner, Ch.; Schirmer, M. Lack of influence of body mass index on efficacy and tolerance of acemetacin in short-term treatment of musculoskeletal diseases. *Rheumatol. Int.* **2007**, *27*, 351-355. (c) Hughes, P.; DeVirgilio, J.; Humber, L. G.; Weichman, B.; Neuman, G. Synthesis and biological evaluation of 4,6-diethyl-1,3,4,5-tetrahydropyrano[4,3-b]indole-4-acetic acid, an isomer of etodolac. *J. Med. Chem.* **1989**, *32*, 2134–2137. (d) Lione, A.; Scialli, A. R. The developmental toxicity of indomethacin and sulindac. *Reprod. Toxicol.* **1995**, *9*, 7-20. (e) Bellamy, N. Etodolac in the management of pain: A clinical review of a multipurpose analgesic. *Inflammopharmacology* **1997**, *5*, 139-152.

[4] (a) Michnovicz, J. J. Altered estrogen metabolism and excretion in humans following consumption of indole-3-carbinol. *Nutr. Cancer* **1991**, *16*, 59-66. (b) Michnovicz, J. J. Changes in levels of urinary estrogen metabolites after oral indole-3-carbinol treatment in humans. *Natl. Cancer Inst.* **1997**, *89*, 718-724. (c) Holt, D. A.; Yamashita, D. S.; Konialian-Beck, A. L.; Luengo, J. I.; Abel, A. D.; Bergsma, D. J.; Brandt, S. M.; Levy, M. A. Benzophenone- and Indolecarboxylic Acids: Potent Type-2 Specific Inhibitors of Human Steroid 5 α -Reductase. *J. Med. Chem.* **1995**, *38*, 13-15.

[5] (a) Mattson, R. J.; Catt, J. D.; Denhart, D. J.; Deskus, J. A.; Ditta, J. L.; Higgins, M. A.; Marcin, L. R.; Sloan, C. P.; Beno, B. R.; Gao, Q.; Cunningham, M. A.; Mattson, G. K.; Molski, T. F.; Taber, M. T.; Lodge, N. J. Conformationally Restricted Homotryptamines. Indole Cyclopropylmethylamines as Selective Serotonin Reuptake Inhibitors. *J. Med. Chem.* **2005**, *48*, 6023–6034. (b) Anthes, R.; Benoit, S.; Chen, C.; Corbett, E. A.; Corbett, R. M.; DelMonte, A. J.; Gingras, S.; Livingston, R. C.; Pendri, Y.; Sausker, J.; Soumeillant, M. An Improved Synthesis of a Selective Serotonin Reuptake Inhibitor. *Org. Process. Res. Dev.* **2008**, *12*, 178–182.



- [6] King, F. D.; Gaster, L. M.; Kaumann, A. J.; Young, R. C. Medicaments 1,2,3,4-tetrahydrocarbazoles and 5-HT₁ Agonist use thereof. 27 Oct **1998** US 5,827,871.
- [7] Boggs, S. D.; Catalano, J. G.; Gudmundsson, K. S.; Richardson, L. D.; Sebahar, P. R. Novel cycloalkyl condensed Indoles. 17 Dec **2006** US2006/0281804 A1.
- [8] (a) Fillion, E.; Fishlock, D.; Wilsily, A.; Goll, J. M. Meldrum's Acids as Acylating Agents in the Catalytic Intramolecular Friedel–Crafts Reaction. *J. Org. Chem.* **2005**, *70*, 1316-1327. (b) Fillion, E.; Dumas, A. M.; Hogg, S. A. Modular Synthesis of Tetrahydrofluorenones from 5-Alkylidene Meldrum's Acids. *J. Org. Chem.* **2006**, *71*, 9899-9902. (c) Fillion, E.; Fishlock, D. Convenient Access to Polysubstituted 1-Indanones by Sc(OTf)₃-Catalyzed Intramolecular Friedel–Crafts Acylation of Benzyl Meldrum's Acid Derivatives. *Org. Lett.* **2003**, *5*, 4653-4656.
- [9] Oikawa, Y.; Hirasawa, H.; Yonemitsu, O. Meldrum's acid in organic synthesis. 1. A convenient one-pot synthesis of ethyl indole propionates. *Tetrahedron Lett.* **1978**, *20*, 1759-1762.
- [10] (a) Dardennes, E.; Gerard, S.; Petermann, C.; Sapi, J. Diastereoselective trimolecular condensation between indole, Meldrum's acid and chiral sugar-derivatived aldehydes. *Tetrahedron: Asymmetry* **2010**, *21*, 208-215. (b) Dardennes, E.; Kovacs-Kulyassa, A.; Boisbrun, M.; Petermann, C.; Laronze, J. Y.; Sapi, J. Diastereocontrolled multicomponent pathway to 3,4-heterocycle-annulated tetrahydro-β-carbolines *Tetrahedron: Asymmetry* **2005**, *16*, 1329–1339.
- [11] Dumas, A. M.; Seed, A.; Zorzitto, A. K.; Fillion, E. A general and practical preparation of alkylidene Meldrum's acids *Tetrahedron Lett.* **2007**, *48*, 7072-7074.
- [12] (a) Pellissier, H. Asymmetric organocatalysis. *Tetrahedron* **2007**, *63*, 9267-9331. (b) Marcelli, T.; Hiemstra, H. Cinchona Alkaloids in Asymmetric Organocatalysis. *Synthesis* **2010**, *8*, 1229-1279. (c) Melchiorre, P.; Marigo, M.; Carlone, A.; Bartoli, G.



Asymmetric aminocatalysis-gold rush in organic chemistry. *Angew. Chem. Int. Ed.* **2008**, *47*, 6138-6171. (d) Vilavan, T.; Bhanthumnavin, W. Organocatalyzed Asymmetric α -Oxidation, α -Aminoxylation and α -Amination of Carbonyl Compounds. *Molecules* **2010**, *15*, 917-958. (e) Desimoni, G.; Faita, G.; Quadrelli, P. Substituted (E)-2-Oxo-3-butenates: Reagents for Every Enantioselectively-Catalyzed Reaction. *Chem. Rev.* **2013**, *113*, 5924-5988.

[13] (a) Terrasson, V.; Figueiredo, R. M.; Campagne, J. M. Organocatalyzed Asymmetric Friedel-Crafts Reactions. *Eur. J. Org. Chem.* **2010**, *14*, 2635-2655. (b) Lu, H. H.; Tan, F.; Xiao, W. J. Enantioselective Organocatalytic Friedel-Crafts Alkylations. *Curr. Org. Chem.* **2011**, *15*, 4022-4045. (c) Marques-Lopez, E.; Diez-Martinez, A.; Merino, P.; Herrera, R. P. The Role of the Indole in Important Organocatalytic Enantioselective Friedel-Crafts Alkylation Reactions. *Curr. Org. Chem.* **2009**, *13*, 1585-1609. (d) Herrera, R. P.; Sgarzani, V.; Bernardi, V.; Ricci, A. Catalytic enantioselective Friedel-Crafts alkylation of indoles with nitroalkenes by using a simple thiourea organocatalyst. *Angew. Chem. Int. Ed.* **2005**, *44*, 6576-6579. (e) Scettri, A.; Villano, R.; Acocella, M. R.; Asymmetric Friedel-Crafts Alkylation of Indole with Chalcones Catalyzed by Chiral Phosphoric Acids. *Molecules* **2009**, *14*, 3030-3036. (f) Wang, X.; Zheng, C.; Zhao, S.; Chai, Z.; Zhao, G.; Yang, G. Organocatalyzed Friedel-Craft-type reaction of 2-naphthol with β,γ -unsaturated α -keto ester to form novel optically active naphthopyran derivatives. *Tetrahedron: Asymmetry*. **2008**, *19*, 2699-2704.

[14] (a) Łyżwa, D.; Dudziński, K.; Kwiatkowski, P. High-Pressure Accelerated Asymmetric Organocatalytic Friedel-Crafts Alkylation of Indoles with Enones: Application to Quaternary Stereogenic Centers Construction. *Org. Lett.* **2012**, *3*, 1540-1543. (b) Li, J.; Yue, C.; Chen, P.; Xiao, Y.; Chen, Y. Remote enantioselective Friedel-Crafts alkylations of furans through HOMO activation. *Angew. Chem. Int. Ed.* **2014**, *53*,



5449-5452. (c) Zhou, C. Y.; Sun, X.; Tang, Y. Cu(OTf)₂/trioxazoline catalyzed asymmetric Friedel–Crafts reaction of pyrroles with alkylidene malonates *Tetrahedron* **2008**, *64*, 10676-10680. (d) Siau, W. Y.; Wang, J. Asymmetric organocatalytic reactions by bifunctional amine-thioureas. *Catal. Sci. Technol.* **2011**, *1*, 1298-1310.

[15] (a) Dumas, A. M.; Fillion, E. Meldrum's Acids and 5-Alkylidene Meldrum's Acids in Catalytic Carbon–Carbon Bond-Forming Processes. *Acc. Chem. Res.* **2010**, *43*, 440-454. (b) Ivanov, A. S. Meldrum's acid and related compounds in the synthesis of natural products and analogs. *Chem. Soc. Rev.* **2008**, *37*, 789-811. (c) Lipson, V.V.; Gorobets, N. Y. One hundred years of Meldrum's acid: advances in the synthesis of pyridine and pyrimidine derivatives. *Mol. Divers.* **2009**, *13*, 399-419. (d) Gaber, A. A. M.; McNab, H. Synthetic Applications of the Pyrolysis of Meldrum's Acid Derivatives. *Synthesis* **2001**, *14*, 2059-2074. (e) Janikowska, K.; Rachon, J.; Makowiec, S. Acyl Meldrum's acid derivatives: application in organic synthesis. *Russ. Chem. Rev.* **2014**, *83*, 620-637. (f) Mahoney, S. J.; Dumas, A. M.; Fillion, E. Asymmetric Addition of Alkenylstannanes to Alkylidene Meldrum's Acids. *Org. Lett.* **2009**, *11*, 5346-5349. (g) Watanabe, T.; Knopfel, T. F.; Carreira, E. M. Asymmetric Conjugate Addition Reactions of Meldrum's Acid Derived Acceptors Employing Chiral Phosphoramidite Ligands. *Org. Lett.* **2003**, *5*, 4557-4558. (h) Wilsily, A.; Fillion, E. Asymmetric Synthesis of All-Carbon Benzylic Quaternary Stereocenters via Conjugate Addition to Alkylidene and Indenylidene Meldrum's Acids. *J. Org. Chem.* **2009**, *74*, 8583-8594. (i) Fillion, E.; Zorzitto, A. K. Enantioselective Rhodium-Catalyzed Conjugate Alkynylation of 5-Benzylidene Meldrum's Acids with TMS-acetylene. *J. Am. Chem. Soc.* **2009**, *131*, 14608-14609. (j) Riguet, E. Enantioselective Organocatalytic Friedel–Crafts Alkylation Reaction of Indoles with 5-Hydroxyfuran-2(5H)-one: Access to Chiral γ -Lactones and γ -Lactams via a Ugi 4-Center 3-Component Reaction. *J. Org. Chem.* **2011**, *76*, 8143-8150.



- [16] (a) Reisman, S. E.; Doyle, A. G.; Jacobsen, E. N. Enantioselective Thiourea-Catalyzed Additions to Oxocarbenium Ions. *J. Am. Chem. Soc.* **2008**, *130*, 7198–7199.
- (b) Martin, N. J. A.; Ozores, L.; List, B. Organocatalytic Asymmetric Transfer Hydrogenation of Nitroolefins. *J. Am. Chem. Soc.* **2007**, *129*, 8976–8977. (c) Zuend, S. J.; Jacobsen, E. N. Mechanism of Amido-Thiourea Catalyzed Enantioselective Imine Hydrocyanation: Transition State Stabilization via Multiple Non-Covalent Interactions. *J. Am. Chem. Soc.* **2009**, *131*, 15358–15374.
- [17] Schaumann, E.; Kausch, E.; Walter, W. 1:1, 2:1 und 3:1-Addukte aus der Umsetzung von Isothiocyanaten mit 3-Dimethylamino-2,2dimethyl-2H-azirin. *Chem. Ber.* **1977**, *10*, 820-832.
- [18] Tarkanyi, G.; Kiraly, P.; Varga, Sz.; Vakulya, B.; Soos, T. Edge-to-Face CH/ π Aromatic Interaction and Molecular Self-Recognition in epi-Cinchona-Based Bifunctional Thiourea Organocatalysis. *Chem. Eur. J.* **2008**, *14*, 6078-6086.