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Stereoselective Alkylation of Indole with 5-Arylidene-Meldrum's Acids in the presence of Organocatalysts

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Abstract:

Background: **I**ndole motif is frequently present in biologically active compounds. Enantiomerically pure or enriched 2,2-dimethyl-5-(aryl(1*H*-indol-3-yl)methyl)-1,3-dioxane-4,6-diones can be considered as a convenient starting point for the synthesis of a indole ring fused with cyclic ketones with biological activity. Preparation of chiral 2,2-dimethyl-5-(aryl(1*H*-indol-3-yl)methyl)-1,3-dioxane-4,6-diones requires reaction of indole with 2,2-dimethyl-5-arylidene-1,3-dioxane-4,6-diones in the presence of chiral catalysts or other source of chiral induction.

Methods: Enantioselective Friedel-Crafts alkylation of indole has been performed with 2,2-dimethyl-5-arylidene-1,3-dioxane-4,6-diones in the presence of organocatalysts to give 5-((1*H*-indol-3-yl)(aryl)methyl)-2,2-dimethyl-1,3-dioxane-4,6-diones. Broad scope of organocatalysts as well as various temperatures and solvents used for the reaction were tested.

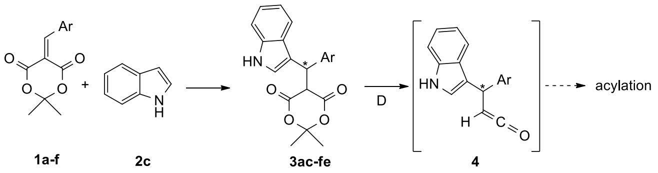
Results: 2,2-Dimethyl-5-(aryl(1*H*-indol-3-yl)methyl)-1,3-dioxane-4,6-diones were obtained with quantitative yield and enantiomeric ratio 1:3 using thiourea organocatalyst. Also a new spectroscopic method for discrimination of 5-((1*H*-indol-3-yl)(aryl)methyl)-2,2-dimethyl-1,3-dioxane-4,6-diones enantiomers was developed.

Conclusion: Enantioselective Friedel-Crafts alkylation of indole has been developed. In the presence of thiourea catalysts, 2,2-dimethyl-5-arylidene-1,3-dioxane-4,6-diones react with indole to give 2,2-dimethyl-5-(aryl(1*H*-indol-3-yl)methyl)-1,3-dioxane-4,6-diones with good yields and reasonable ee.

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

1. INTRODUCTION

The significant progress in enantioselective organocatalysis which has been made over the last few decades, enables the consideration of this methodology on an equal footing with well-established method of stereoselective synthesis of organic compounds means: transition-metal complexes and enzymatic catalysis [1-4]. So far, the organocatalyst approach has been used in chemical processes, e.g. Mannich condensation [5], Pudovik reaction [6], Michael addition [7], Strecker [8], domino [9], aldol [10] and Freidel-Crafts reaction [11]. In terms of their applicability and high degree of stereoselectivity, thiourea organocatalyst are one of the most important groups of organocatalysts. Their importance also stems from the fact that their structure can be easily tuned to the requirements of specific reactions [12]. We have focused our research efforts on stereoselctive Friedel-Crafts alkylation of indoles with 5-arylidene Meldrum's acid derivatives.



Scheme 1 Route to 3-aryl-3-(1*H*-indol-3-yl)methyl ketenes.

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The problem of enantioselective organocatalytic Friedel-Crafts alkylation has been studied thoroughly on many levels [11, 13]; however, to the best of our knowledge, there have been no reports of successfully stereocontrolled Friedel-Crafts alkylation of indoles with 5-arylidene-2,2-dimethyl-1,3-dioxane-4,6-diones (**1**) [14]. 2,2-Dimethyl-5-(aryl(1*H*-indol-3-yl)methyl)-1,3-dioxane-4,6-diones, (**3**) the products of Friedel-Crafts alkylation of indole, contain a thermal labile moiety, which can easily be converted to ketenes (**4**) and used for intra- and inter-molecular reaction with nucleophiles. (Scheme 1)

Fillion and co-workers demonstrated a series of examples for 2,2-dimethyl-5-benzyl-1,3-dioxane-4,6-diones transformation to useful bioactive 1-indanones through intramolecular Friedel-Crafts acylation [15]. Considering the versatility of the indole motif in biologically active compounds, we can anticipate that optically pure or enriched 2,2-dimethyl-5-(aryl(1*H*-indol-3-yl)methyl)-1,3-dioxane-4,6-diones (**3**) can be considered as a convenient starting point for the synthesis of a ring fused with cyclic ketones with biological activity (e.g; strigolactone [16], aurora kinase inhibitors [17], acetylcholinesterase inhibitors [18,] oxindole alkaloids [19] or Uhle ketones [20].)

2. RESULTS AND DISCUSSION

In the present study, we have explored the use of chiral organocatalysts for Friedel-Crafts type alkylation of a π-excess aromatic ring, especially an indole with 2,2-dimethyl-5-(aryl)methylene-1,3-dioxane-4,6-diones as electrophiles. In particular we have focused on the application of a thiourea catalyst as it is the most promising with such a combination of reagents; however, in preliminary experiments we screened a wide range of catalysts, such as MacMillan imidazolidinones, (*R*)-(−)-1,1′-binaphthyl-2,2′-diyl hydrogenphosphate and thioureas (Figure 1).

For the first screening experiments as model reagents we used 2,2-dimethyl-5-(4-chlorophenyl)methyl-1,3-dioxane-4,6-dione (**1a**) in combination with pyrrole (**2a**), N-methylpyrrole (**2b**) or indole (**2c**). The results of preliminary catalyst screening without determination of ee are presented in Table 1. Surprisingly, application of MacMillan imidazolidinones (**5-9**) resulted in high yields of **3aa-ac** in comparison to thiourea catalysts **10**, **11** or (*R*)-(−)-1,1′-binaphthyl-2,2′-diyl hydrogenphosphate (**12**). Such a phenomenon can't be simply attributed to acid-base catalysis of imidazolidinones salts, since application of free amine catalyst **6** and **7** caused almost identical yields for all three aromatic donors as salts **8**, **9**.

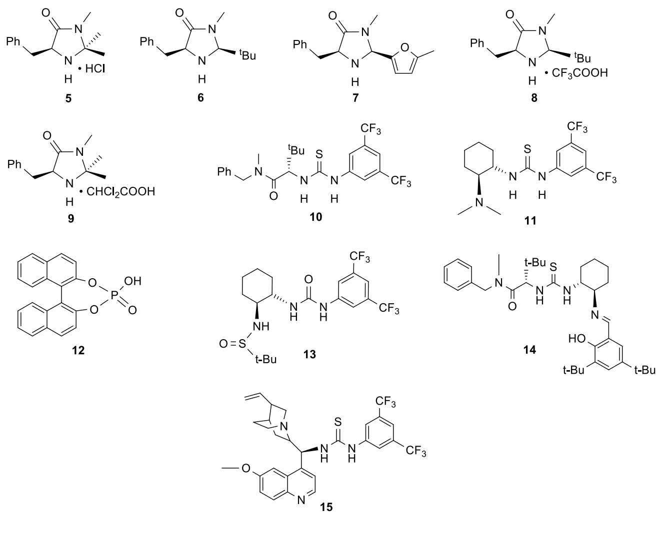
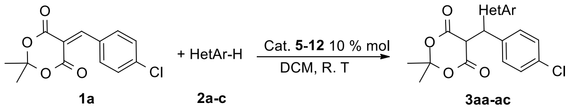


Figure 1 Organocatalysts used in Friedel-Crafts alkylation with 5-arylidene-2,2-dimethyl-1,3-dioxane-4,6-diones.

Table 1. Preliminary catalyst screening for Friedel-Crafts alkylation of indoles with 2,2-dimethyl-5-((4-chlorophenyl))methylene-1,3-dioxane-4,6-dione.

			
Organocatalyst	**HetAr 2**		
	Pyrrole **2a**	N-Methylpyrrole **2b**	Indole **2c**
	Yield of **3aa-3ac**		
	3aa	**3ab**	**3ac**
5	73 %	60 %	90 %
6	57 %	57 %	78 %
7	62 %	58 %	82 %
8	59 %	73 %	87 %
9	75 %	73 %	84 %
10	24 %	58 %	75 %
11	51 %	89 %	72 %
12	47 %	58 %	79 %

The standard estimation of enantiomeric excess for resulted reaction mixtures with chiral HPLC on phenylcarbamate modified cellulose [21] failed, due to rapid decomposition compounds **3aa-ac** when TFA was present in the eluent composition, whereas a lack of TFA caused insufficient peak separation. Therefore, we decided to check if direct NMR observation [22] of enantiotopic protons with a chiral shift reagent would be possible in the case of **3aa-ac**. We tested commercially available Pirkle's alcohol and europium tris[3-(trifluoromethylhydroxymethylene)-(+)-camphorate]. Unfortunately, in both cases signal separation was inadequate. Finally, we decided to exploit the acidic properties of Meldrum's acid derivatives for chemical shift derivatization of enantiotopic protons. Application of (*R*)-1-phenylethylamine just to an NMR tube with solution **3ac** before spectra acquisition led to the formation of diastereoisomeric salts and allowed for excellent methine protons signal separation (Figure 2).

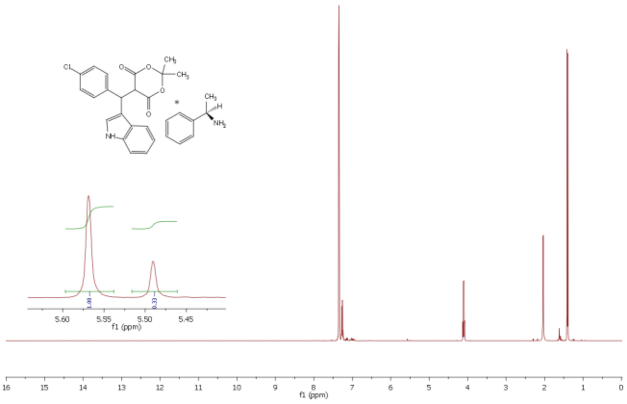
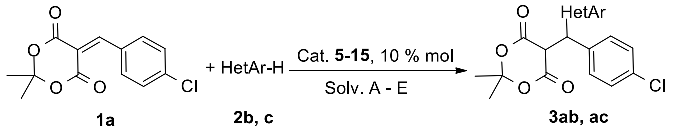


Figure 2 ^{1}H NMR spectra of **3ac** with 20 eq of (*R*)-1-phenylethylamine (relaxation time 40s).

Table 2. Reaction conditions optimization for Friedel-Crafts alkylation with 2,2-dimethyl-5-((4-chlorophenyl))methylene-1,3-dioxane-4,6-diones.



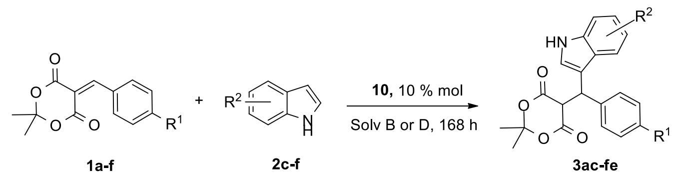
Entry	2	Cat.	Solv.[a]	Temp. [°C]	Time [h]	Yield [%]	3,3'	Ratio **3**:**3'**[b]
1	**2b**	**5**	A	RT	1	60	**ab**	50:50
2	**2b**	**6**	A	RT	1	57	**ab**	50:50
3	**2b**	**10**	A	RT	1	58	**ab**	49:51
4	**2c**	**5**	A	RT	1	90	**ac**	49:51
5	**2c**	**6**	A	RT	1	57	**ac**	49:51
6	**2c**	**10**	A	RT	1	75	**ac**	40:60
7	**2c**	**10**	A	-10°C	0,75	40	**ac**	40:60
8	**2c**	**10**	A	-70°C	1	41	**ac**	41:59
9	**2c**	**10**	A	-25°C	20	46	**ac**	39:61
10	**2c**	**10**	A	-80°C	168	61	**ac**	42:58
11	**2c**	**10**	A	0°C	20	53	**ac**	38:62
12	**2c**	**11**	A	0°C	24	72	**ac**	49:51
13	**2c**	**13**	A	0°C	24	65	**ac**	48:52
14	**2c**	**14**	A	0°C	24	59	**ac**	43:57
15	**2c**	**15**	A	0°C	24	51	**ac**	47:53
16	**2c**	**10**	B	0°C	24	50	**ac**	30:70
17	**2c**	**10**	B	0°C	48	48	**ac**	31:69
18	**2c**	**10**	B	0°C	168	96	**ac**	34:66
19	**2c**	**10**	C	0°C	24	68	**ac**	29:71
20	**2c**	**10**	C	0°C	48	83	**ac**	28:72
21	**2c**	**10**	C	0°C	168	99	**ac**	26:74
22	**2c**	**10**	D	7°C	168	99	**ac**	25:75
23	**2c**	**10**	E	0°C	24	58	**ac**	30:70
24	**2c**	**10**	F	8°C	24	62	**ac**	32:68

[a] Solvent: A = DCM, B = Toluene, C = Toluene : Cyclohexane 1:1, D = Cyclohexane, E = CCl$_4$, F = Hexafluorobenzene. [b] Determined by ^{1}H NMR spectra of **3ab**, **ac** with (*R*)-1-phenylethylamine.

With this new method at our disposal, we were able to begin systematic research to establish optimal reaction conditions leading to the highest enantiomeric excess. A quick check already prepared and purified products, showed low ee (Table 2, Entries 1-6) for reaction performed at RT and DCM as solvent.

The inefficiency of MacMillan imidazolidinones was not surprising due to their specific interaction with reagents, being limited mainly to aldehydes. Failure resulting from use (*R*)-(−)-1,1′-binaphthyl-2,2′-diylhydrogenphosphate may be attributed to its low solubility in reaction media. Further condition optimization was focused on thiourea catalysts **10**, **11**, **13-15**. Obviously, lowering reaction temperature should lead to higher enantiomeric excess [23]. The set of experiments (Table 2, Entries 7-11) performed between **1a**

Table 3. Friedel-Crafts alkylation of indoles with 2,2-dimethyl-5-(aryl)methylene-1,3-dioxane-4,6-diones



Entry	R^1	1	R^2	2	3	Solv.[a]	Yield [%]	3:3′ [b]	δ_R [24] (R^1)
1	OMe	**b**	H	**c**	**bc**	B	74	49:51	-0,56
2	F	**c**	H	**c**	**cc**	B	87	49:51	-0,39
3	CH_3	**d**	H	**c**	**dc**	B	87	45:55	-0,18
4	H	**e**	H	**c**	**ec**	B	84	32:68	0,00
5	NO_2	**f**	H	**c**	**fc**	B	81	32:68	+0,13
6	Cl	**a**	5-F	**d**	**ad**	B	62	34:66	-0.19
7	H	**e**	5-F	**d**	**ed**	B	32	46:54	0.00
8	NO_2	**f**	5-F	**d**	**fd**	B	59	35:65	+0,13
9	Cl	**a**	5-Cl	**e**	**ae**	B	77	35:65	-0.19
10	H	**e**	5-Cl	**e**	**ee**	B	42	44:56	0.00
11	NO_2	**f**	5-Cl	**e**	**fe**	B	60	37:63	+0,13
12	Cl	**a**	N-Me	**f**	**af**	B	79	41:59	-0.19
13	H	**e**	H	**c**	**ec**	D	58	45:55	0.00
14	Cl	**a**	5-F	**d**	**ad**	D	92	32:68	-0.19
15	Cl	**a**	5-Cl	**e**	**ae**	D	67	32:68	-0.19
16	NO_2	**f**	H	**c**	**fc**	D	65	30:70	+0,13

[a] Solvent: A = DCM, B = Toluene, C = Toluene : Cyclohexane 1:1, D = Cyclohexane, E = CCl_4, F = Hexafluorobenzene. [b] Determined by ^1H NMR spectra of **3ab**, **ac** with (R)-1-phenylethylamine.

and indole in the presence catalyst **10** demonstrated 0°C as being the best temperature in respect of yield and ee.

Moreover, we reran the same reaction continuously monitoring it with NMR. We started the experiment and acquisition of spectra from -70°C with 5K steps, successively raising the temperature up to 25°C. As a result, we observed that below 0°C the reaction was virtually stopped. To further optimize the reaction conditions, we examined other thiourea catalysts **11**, **13-15** and solvents with low dielectric constants. Among the tested catalysts, only 14 containing N-benzyl-N-methylamide moiety evoked a stereoselective reaction course with a modest 14% ee (Table 2, Entry 14). Optimization of solvent was performed using catalyst **10** as the most promising option. A selected set of pure or mixture solvents with dielectric constants between 2 and 3 was examined (Table 2, Entries 16-24). Hydrocarbons turned out to be the best solvent. When the reaction of **1a** and indole was carried out in cyclohexane at 7°C through 168 h, this resulted in ratios of enantiomers as 75 to 25% (Table 2, Entry 22). The developed optimal procedure has been applied for the reaction of a representative set of 2,2-dimethyl-5-arylidene-1,3-dioxadiones (**1a-f**) with indoles. Yields and ee value are presented in Table 3. As one can see there is weak correlation between the yield of **3** and the type of para-substituent, whereas ee drops dramatically when an electrodonating group is introduced into the phenyl ring. As a derivatives of benzaldehyde, 2,2-dimethyl-5-arylidene-1,3-dioxa-4,6-diones (**1a-f**) should exhibit any correlation of reaction rate with Hammett constants parameters. In the case of the examined reaction, some correlation is observed between ee and, in particular resonance parameters *R*, [24] with the highest ee for *R* in range -0.19 – 0.13.

The evident non-linearity of ee in the function of *R* or σ_p for the NO_2 group strongly suggests interaction between 2,2-dimethyl-5-arylidene-1,3-dioxadione and thiourea catalyst **10**, depending on the type of substituent.

3. EXPERIMENTAL SECTION

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, CCl_4, and hexafluorobenzene were distilled over P_4O_{10} and stored over molecular sieves. Commercially unavailable reagents 2,2-dimethyl-5-arylidene-1,3-dioxa-4,6-diones **2a-f** were prepared according to literature procedures [25]. 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 ^{1}H, ^{13}C were recorded on Varian Gemini 200 and Varian Unity Plus 500, chemical shifts (δ) in ppm rel. to internal Me_4Si; 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. Ratio of enantiomers was determined based on integration of ^{1}H.

Stereoselective preparation of 2,2-dimethyl-5-(aryl(heteroaryl)methyl)-1,3-dioxane-4,6-diones (3aa-fe). General Procedure.

To a solution of 2,2-dimethyl-5-arylidene-1,3-dioxane-4,6-dione 1a-f (0.2 mmol) in anhydrous solvent (5ml) (DCM (A), toluene (B), toluene : cyclohexane 1:1 (C), Cyclohexane (D), CCl_4 (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-(4-chlorophenyl(1H-pyrrol-2-yl)methyl)-1,3-dioxane-4,6-dione (3aa)

Purification by flash column chromatography, (EtOAc/Hex, 1:1), brown oil; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 9.22 (s, 1 H), 7.25(d, J = 8.8 Hz, 2H), 7.09 (d, J = 8.8 Hz, 2H) 6.80-6.71 (m, 1H), 6.26- 6.18 (m, 2H), 5.47 (d, J = 2.1 Hz, 1H), 4.16 (d, J = 2.1 Hz, 1H), 1.80 (s, 3H), 1.70 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 165.6, 165.2, 137.9, 133.2, 129.5, 128.9, 128.9, 118.9, 109.1, 108.3, 105.8, 52.1, 41.4, 28.4, 27.4. HRMS (ESI+): m/z [M + H]+ calcd for $C_{17}H_{17}ClNO_4$: 334.0845; found: 334.0848.

2,2-dimethyl-5-(4-chlorophenyl(1-methyl-1H-pyrrol-2-yl)methyl)-1,3-dioxane-4,6-dione (3ab)

Purification by flash column chromatography, (EtOAc/Hex, 1:1), yellow oil; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.26-7.17 (m, 4 H), 6.57-6.54 (m, 1 H), 6.246.22 (m, 1 H), 6.13-6.10 (m, 1 H), 5.30 (d, J = 2.5 Hz, 1 H), 4.22 (d, J = 2.5 Hz, 1 H), 3.33 (s, 3 H), 1.77 (s, 3 H), 1.63 (s, 3 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 164.9, 163.8, 137.4, 133.4, 130.9, 130.0, 128.7, 122.8, 108.6, 107.1, 105.3, 52.2, 40.6, 34.2, 28.4, 27.6. HRMS (ESI+): *m/z* $[M + H]^+$ calcd for $C_{18}H_{19}ClNO_4$: 348.1003; found: 348.0999.

2,2-dimethyl-5-(4-chlorophenyl(1*H*-indol-3-yl)methyl)-1,3-dioxane-4,6-dione (3ac)

Purification by flash column chromatography, (EtOAc/Hex, 1:3), yellow oil;

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 8.20 (s, 1 H), 7.40-7.34 (m, 5 H), 7.26-7.18 (m, 3 H), 7.07 (t, J = 7.3 Hz, 1 H), 5.64 (d, J = 2.4 Hz, 1 H), 4.28 (d, J = 2.4 Hz, 1 H), 1.73 (s, 3 H), 1.52 (s, 3 H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 165.5, 164.7, 138.6, 136.0, 133.2, 130.8, 128.7, 127.0, 124.2, 122.7, 120.1, 119.1, 114.8, 111.4, 105.4, 52.0, 40.7, 28.4, 27.9. HRMS (ESI+): *m/z* $[M + H]^+$ calcd for $C_{21}H_{19}ClNO_4$: 384.1002; found: 384.0988

2,2-dimethyl-5-(4-metoxyphenyl(1*H*-indol-3-yl)methyl)-1,3-dioxane-4,6-dione (3bc)

Purification by flash column chromatography, (EtOAc/Hex, 1:4), yellow oil; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 8.20 (s, 1 H), 7.42-7.43 (m, 5 H), 7.18 (t, J = 7.5 Hz, 1 H), 7.06 (t, J = 7.5 Hz, 1 H), 6.82-7.80 (m, 2 H), 5.60 (d, J = 2.5 Hz, 1 H), 4.28 (d, J = 2.5 Hz, 1 H), 3.77 (s, 3 H), 1.72 (s, 3 H), 1.44 (s, 3 H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 165.7, 164.6, 158.6, 135.8, 131.7, 130.3, 126.8, 123.9, 122.2, 119.6, 119.0, 115.4, 113.7, 111.1, 105.1, 55.2, 51.9, 41.2, 28.2, 27.9. HRMS (ESI-): *m/z* $[M - H]^-$ calcd for $C_{22}H_{20}NO_5$: 378.1341; found: 378.1327.

2,2-dimethyl-5-(4-fluorophenyl(1*H*-indol-3-yl)methyl)-1,3-dioxane-4,6-dione (3cc)

Purification by flash column chromatography, (EtOAc/Hex, 1:2), yellow oil; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 8.17 (s, 1 H), 7.40-7.36 (m, 5 H), 7.19 (t, J = 7.3 Hz, 1 H), 7.06 (t, J = 7.8 Hz, 1 H), 6.97-6.94 (m, 2 H), 5.64 (d, J = 2.4 Hz, 1 H), 4.28 (d, J = 2.4 Hz, 1 H), 1.73 (s, 3 H), 1.49 (s, 3 H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 165.7, 164.8, 162.1 (d, J = 245.9 Hz), 136.1, 135.7 (d, J = 3.0 Hz), 131.1 (d, J = 7.9 Hz), 127.0, 124.2, 122.6, 120.0, 119.2, 115.3 (d, J = 21.5 Hz), 115.0, 111.5, 105.5, 52.2, 40.9, 28.4, 27.9. HRMS (ESI+): *m/z* $[M + H]^+$ calcd for $C_{21}H_{19}FNO_4$: 368.1297 found: 368.1287.

2,2-dimethyl-5-(p-tolyl(1*H*-indol-3-yl)methyl)-1,3-dioxane-4,6-dione (3dc)

Purification by flash column chromatography, (EtOAc/Hex, 1:2), yellow oil; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 8.18 (s, 1 H), 7.44 (d, J = 7.8 Hz, 1 H), 7.37-7.34 (m, 2 H), 7.30-7.25 (m, 2 H), 7.21-7.14 (m, 2 H), 7.09-7.05 (m, 2 H), 5.61 (d, J = 1.9 Hz, 1 H), 4.29 (d, J = 2.5 Hz, 1 H), 2.30 (s, 3 H), 1.71 (s, 3 H), 1.43 (s, 3 H). ^{13}C NMR ($CDCl_3$, 125

MHz): δ = 165.8, 164.9, 137.0, 136.9, 136.0, 129.5, 129.3, 129.1, 124.3, 122.5, 119.9, 119.3, 115.4, 111.4, 105.4, 52.1, 41.6, 28.4, 28.2, 27.8. HRMS (ESI+): *m/z* $[M + H]^+$ calcd for $C_{22}H_{22}NO_4$: 364.1549; found: 364.1572

2,2-dimethyl-5-(phenyl(1*H*-indol-3-yl)methyl)-1,3-dioxane-4,6-dione (3ec) [26]

Purification by flash column chromatography, (EtOAc/Hex, 1:2), yellow oil; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 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 ($CDCl_3$, 125 MHz): δ = 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.

2,2-dimethyl-5-(4-nitrophenyl(1*H*-indol-3-yl)methyl)-1,3-dioxane-4,6-dione (3fc)

Purification by flash column chromatography, (EtOAc/Hex, 4:1), yellow oil; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 8.33 (s, 1 H), 8.10 (d, J = 8.7 Hz, 2 H), 7.58 (d, J = 8.7 Hz, 2 H), 7.38-7.35 (m, 3 H), 7.22-7.19 (m, 1 H), 7.08 (t, J = 7.8 Hz, 1 H), 5.76 (d, *J* = 2.4 Hz, 1 H), 4.35 (d, *J* = 2.4 Hz, 1 H), 1.78 (s, 3 H), 1.60 (s, 3 H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 165.1, 164.3, 147.8, 147.1, 135.9, 130.7, 130.3, 124.3, 123.6, 122.9, 120.3, 118.9, 113.8, 111.6, 105.6, 52.1, 40.4, 28.4, 27.7. HRMS (ESI+): *m/z* $[M + H]^+$ calcd for $C_{21}H_{19}N_2O_6$: 395.1243; found: 395.1268

5-((4-chlorophenyl)(5-fluoro-1H-indol-3-yl)methyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (3ad)

Purification by flash column chromatography, (EtOAc/Hex, 1:2), yellow oil; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 8.20 (s, 1 H), 7.40 (d, *J* = 2 Hz, 1 H), 7.34-7.32 (m, 2H), 7.29-7.24 (m, 3 H), 7.01 (dd, *J* = 10.0 Hz, *J* = 2.5 Hz, 1 H), 6.94 (td, *J* = 10.0 Hz, *J* = 2.5 Hz, 1 H), 5.54 (d, *J* = 2.0 Hz, 1 H), 4.28 (d, *J* = 2.0 Hz, 1 H), 1.76 (s, 3 H), 1.54 (s, 3 H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 165.1, 164.4, 157.8 (d, *J* = 234.1 Hz), 137.9, 133.1, 132.2, 130.4, 128.5, 127.2 (d, *J* = 9.7 Hz), 125.6, 114.6 (d, *J* = 4.6 Hz), 111.8 (d, *J* = 9.7 Hz), 110.9 (d, *J* = 26.2 Hz), 105.2, 104.0 (d, *J* = 23.7 Hz), 51.7, 40.5, 28.2, 27.7. HRMS (ESI-): *m/z* $[M - H]^-$ calcd for $C_{21}H_{16}ClFNO_4$: 400.0752 found: 400.0742

5-((5-fluoro-1H-indol-3-yl)(phenyl)methyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (3ed)

Purification by flash column chromatography, (EtOAc/Hex, 1:2), yellow oil; ^{1}H NMR (acetone-d_6, 500 MHz): δ = 10.36 (s, 1 H), 7.48 (s, 1 H), 7.43-7.40 (m, 3H), 7.29-7.25 (m, 2 H), 7.22-7.19 (m, 1 H), 6.99 (dd, *J* = 10.0 Hz, *J* = 2.5 Hz, 1 H), 6.88 (td, *J* = 10.0 Hz, *J* = 2.5 Hz, 1 H), 5.54 (s, 1 H), 4.95 (d, *J* = 2.5 Hz, 1 H), 1.87 (s, 3 H), 1.54 (s, 3 H). ^{13}C NMR (acetone-d_6, 125 MHz): δ = 165.2, 164.7, 157.3 (d, *J* = 230.6 Hz), 140.9 (d, *J* = 1.4 Hz), 132.9, 129.1, 127.8, 127.7, 126.5 (d, *J* = 7.1 Hz), 126.3, 114.3, 112.1 (d, *J* = 9.6 Hz), 109.5 (d, *J* = 26.2 Hz), 104.8, 103.6 (d, *J* = 23.4 Hz), 51.7, 40.7, 27.5, 26.4. HRMS (ESI-): *m/z* $[M - H]^-$ calcd for $C_{21}H_{17}FNO_4$: 366.1142 found: 366.1139

5-((5-fluoro-1H-indol-3-yl)(4-nitrophenyl)methyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (3fd)

Purification by flash column chromatography, (EtOAc/Hex, 2:1), yellow oil; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 8.44 (s, 1 H), 8.10 (d, *J* = 8.5 Hz, 2 H), 7.55 (d, *J* = 8.5 Hz, 2 H), 7.39 (d, *J* = 2.5 Hz, 1 H), 7.31-7.28 (m, 1H), 7.00 (dd, *J* = 10.0 Hz, *J* = 2.5 Hz, 1 H), 6.94 (td, *J* = 10.0 Hz, *J* = 2.5 Hz, 1 H), 5.65 (d, *J* = 2.0 Hz, 1 H), 4.36 (d, *J* = 2.0 Hz, 1 H), 1.79 (s, 3 H), 1.62 (s, 3 H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 164.7, 164.0, 157.9 (d, *J* = 234.7 Hz), 147.3, 146.9, 132.2, 130.0, 127.1 (d, *J* = 9.7 Hz), 125.8, 123.4, 113.6 (d, *J* = 4.7 Hz), 112.0 (d, *J* = 9.7 Hz), 111.1 (d, *J* = 21.8 Hz), 105.4, 103.8 (d, *J* = 23.8 Hz), 51.7, 40.0, 28.1, 27.4. HRMS (ESI-): *m/z* $[M - H]^-$ calcd for $C_{21}H_{16}FN_2O_6$: 411.0992 found: 411.1003.

5-((5-chloro-1H-indol-3-yl)(4-chlorophenyl)methyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (3ae)

Purification by flash column chromatography, (EtOAc/Hex, 1:2), yellow oil; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 8.23 (s, 1 H), 7.40 (d, *J* = 2 Hz, 1 H), 7.36 (d, *J* = 1.5 Hz, 1 H), 7.33-7.24 (m, 5 H), 7.14 (dd, *J* = 8.5 Hz, *J* = 2.0 Hz, 1 H), 5.55 (d, *J* = 2.0 Hz, 1 H), 4.24 (d, *J* = 2.0 Hz, 1 H), 1.76 (s, 3 H), 1.56 (s, 3 H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 165.1, 164.3, 137.8, 134.1, 133.1, 130.4, 128.5, 127.9, 125.7, 125.3, 122.9, 118.3, 114.4, 112.2, 105.2, 51.8, 40.3, 28.2, 27.7. HRMS (ESI-): *m/z* $[M - H]^-$ calcd for $C_{21}H_{16}Cl_2NO_4$: 416.0456 found: 416.0441

5-((5-chloro-1H-indol-3-yl)(phenyl)methyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (3ee)

Purification by flash column chromatography, (EtOAc/Hex, 1:3), yellow oil; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 8.22 (s, 1 H), 7.44 (d, *J* = 2 Hz, 1 H), 7.39-7.37 (m, 3 H), 7.31-7.23 (m, 4 H), 7.13 (dd, *J* = 8.5 Hz, *J* = 2.0 Hz, 1 H), 5.56 (d, *J* = 2.5 Hz, 1 H), 4.27 (d, *J* = 2.5 Hz, 1 H), 1.73 (s, 3 H), 1.45 (s, 3 H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 165.3, 164.5, 139.3, 134.1, 128.9, 128.5, 128.1, 127.3, 125.5, 125.4, 122.7, 118.5, 114.7, 112.1, 105.2, 51.8, 41.4, 28.1, 27.9. HRMS (ESI-): *m/z* $[M - H]^-$ calcd for $C_{21}H_{17}ClNO_4$: 382.0846 found: 382.0852

5-((5-chloro-1H-indol-3-yl)(4-nitrophenyl)methyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (3fe)

Purification by flash column chromatography, (EtOAc/Hex, 2:1), yellow oil; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 8.42 (s, 1 H), 8.11 (d, *J* = 9.0 Hz, 2 H), 7.55 (d, *J* = 9.0 Hz, 2 H), 7.40 (d, *J* = 2.5 Hz, 1 H), 7.35 (d, *J* = 1.5 Hz, 1 H), 7.32-7.30 (m, 1 H), 7.15 (dd, *J* = 8.5 Hz, *J* = 2.0 Hz, 1 H), 5.58 (d, *J* = 2.0 Hz, 1 H), 4.34 (d, *J* = 2.0 Hz, 1 H), 1.80 (s, 3 H), 1.64 (s, 3 H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 164.7, 163.9, 147.1, 146.9, 134.0, 129.9, 127.8, 125.9, 125.4, 123.4, 123.1, 118.1, 113.3, 112.4, 105.4, 51.9, 39.8, 28.1, 27.4. HRMS (ESI-): *m/z* $[M - H]^-$ calcd for $C_{21}H_{16}ClN_2O_6$: 427.0697 found: 427.0708

5-((4-chlorophenyl)(1-methyl-1H-indol-3-yl)methyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (3af).

Purification by flash column chromatography, (EtOAc/Hex, 1:2), yellow oil; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.43-7.31 (m, 4 H), 7.25-7.22 (m, 4 H), 7.08 (t, *J* = 7.5 Hz, 1 H), 5.65 (d, *J* = 2.5 Hz, 1 H), 4.28 (d, *J* = 2.5 Hz, 1 H), 3.80 (s, 3 H), 1.75 (s, 3 H), 1.55 (s, 3 H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 165.2, 164.4, 138.6, 136.5, 132.8, 130.5, 128.7, 128.3, 127.3, 122.0, 119.3, 118.9, 112.9, 109.3, 105.1, 52.0, 40.3, 32.9, 28.1, 27.7. HRMS (ESI-): *m/z* [M - H]$^-$ calcd for $C_{22}H_{19}ClNO_4$: 396.1003 found: 396.0987.

CONCLUSION

In summary, enantioselective Friedel-Crafts alkylation of indole has been developed. In the presence of thiourea catalysts, 2,2-dimethyl-5-arylidene-1,3-dioxane-4,6-diones react with indole to give 2,2-dimethyl-5-(aryl(1H-indol-3-yl)methyl)-1,3-dioxane-4,6-diones (**3aa-fc**) with good yields and reasonable ee.

The obtained results strongly suggest the influence of phenyl ring substitution in compounds **1** on interaction with thiourea catalysts. For enantioselectively prepared **3aa-fc,** we developed a new spectroscopic method for the valuation of the enantiomeric excess, applying (*R*)-(+)-1-phenylethylamine as a chemical shift reagent.

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SUPPLEMENTARY MATERIAL

Supplementary material is available on the publisher’s web site along with the published article.

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