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Organocatalytic domino formation of (3*R*,3a*S*,9b*R*)-configured 3-aryl-3a-benzamido-1,3a,4,9b-tetrahydrochromeno[4,3-*b*]pyrroles in carbon dioxide medium

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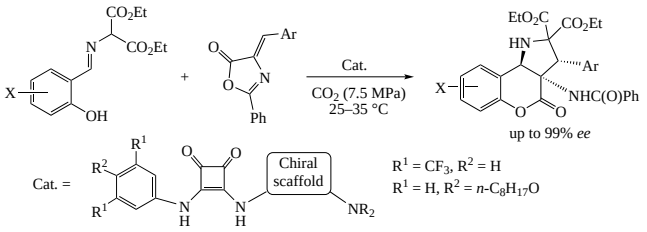
Asymmetric cycloaddition/intramolecular rearrangement domino reaction of 2-(2-hydroxybenzylideneamino)-malonates with 4-arylidene-2-phenyloxazol-5(4*H*)-ones can be efficiently carried out in sub- or supercritical carbon dioxide to afford (3*R*,3a*S*,9b*R*)-3-aryl-3a-benzamido-4-oxo-1,3a,4,9b-tetrahydrochromeno[4,3-*b*]pyrrole-2,2(3*H*)-dicarboxylates in high yields with up to 99% *ee*. Excellent stereoinduction is provided in this process by the use of bifunctional hybrid organocatalyst consisting of squaramide (thiourea) and chiral tertiary amine units.



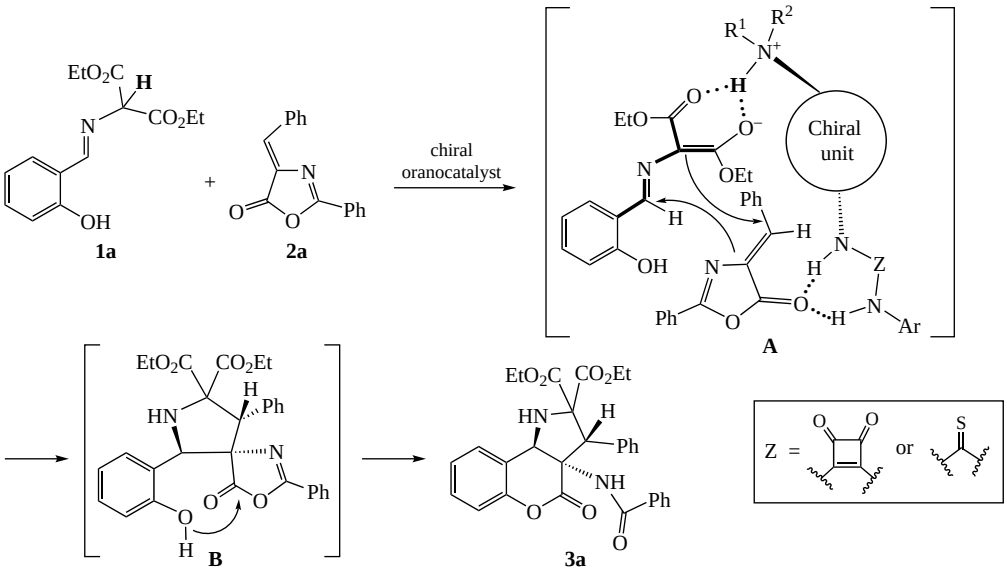
Keywords: organocatalysis, domino reactions, squaramides, 1,3a,4,9b-tetrahydrochromeno[4,3-*b*]pyrroles, liquid carbon dioxide, 2-(2-hydroxybenzylideneamino)malonates, 4-arylidene-2-phenyloxazol-5(4*H*)-ones.

α-Methyleneamino esters R^1–CH=N–CH(R^2)CO_2Alk may be regarded as synthetic equivalents of azomethine ylides R^1–CH=$\overset{+}{N}$(R^3)–$\overset{-}{C}$HR^2. Although α-deprotonation of α-methyleneamino esters should afford the corresponding carbanion lacking quaternary iminium grouping, such species would possess some 'quasi-zwitterionic' properties due to coordination of the imino group to metal cations present in the medium (see reviews[1,2]). Like true azomethine ylides, α-methyleneamino ester carbanions would undergo [3+2] cycloaddition (real or formal) to olefins giving pyrrolidines, the reaction often proceeding regio- and stereoselectively.[3–5] Of particular importance are α-methyleneaminomalonates R–CH=N–CH(CO_2Alk)$_2$ with much higher CH-acidity whose activation requires essentially more gentle impact,[6–9] *e.g.*, under the action of amines. Moreover, when the substituents in both reactants contain additional functional groups, the initially formed pyrrolidine adduct can undergo the subsequent intramolecular domino transformations with the formation of new chiral centers to finally afford unusual but promising polycyclic polyfunctional derivatives.[10–19] If the amine used for the deprotonation is chiral and specially designed, the cycloaddition and further domino transformations would afford diastereo- and enantioenriched product, often with very high *dr* and *ee* values.[13–19] In the cycloadditon of α-methylene-aminomalonates to activated olefins (Michael acceptors), such amines act as true organocatalysts.[13–19]

In all the abovementioned studies, the transformations were performed in hazardous organic solvents such as dichloro-methane, chloroform, THF, methyl *tert*-butyl ether, toluene, *etc*. In each particular case, screening the solvents usually revealed the dependence of their nature on the reaction outcome, namely, on the product yield as well as *dr* and *ee* values. In view of this, it seems interesting to verify whether any of α-methylene-aminomalonate cycloadditions can be accomplished in carbon dioxide medium. In fact, sub- or supercritical carbon dioxide has been recognized a promising medium for organic transformations since it is cheap, non-flammable, environmentally benign; moreover, in some cases it can influence the reaction outcome (see several recent reviews[20–23] and original papers[24–28]).

In this communication, we report on the asymmetric cycloaddition between 2-(2-hydroxybenzylideneamino)-malonates **1** and 4-arylidene-2-phenyloxazol-5(4*H*)-ones **2** in pressurized carbon dioxide leading to 1,3a,4,9b-tetra-hydrochromeno[4,3-*b*]pyrroles **3**. This transformation was previously[29] studied in detail with screening of several organocatalysts and solvents so it looked a reasonable prototype, the optimal solvent in the study[29] was dichloromethane. According to the reaction mechanism (Scheme 1), tertiary amino group of the catalyst would deprotonate malonate moiety of representative reactant **1a**, and thus formed ammonium cation is coordinated in the intermediate **A** at the β-dicarbonyl part. On the other hand, two NH amido groups (squaramide or thiourea type) of the bifunctional organocatalyst are hydrogen-bonded to the carbonyl group of azlactone **2a** while the chiral unit provides the necessary spatial arrangement of both reactants, which allows the cycloaddition to occur regio-, diastereo- and enantioselectively. The thus formed spiro adduct **B** undergoes intramolecular transesterification involving phenolic OH group to finalize domino process affording chromone-fused pyrrole derivative **3a**.

To find optimal conditions (Table 1), we examined several chiral organocatalysts **4a**–**g** of squaramide series and **5a**,**b** of thiourea series in the model reactions of compound **1a** with azlactones **2a** or **2b** in the pressurized CO_2 medium at 25 °C (in the prototype study in dichloromethane,[29] among six catalysts tested **4d** and **5a**,**b** showed good results). Apparently, in our

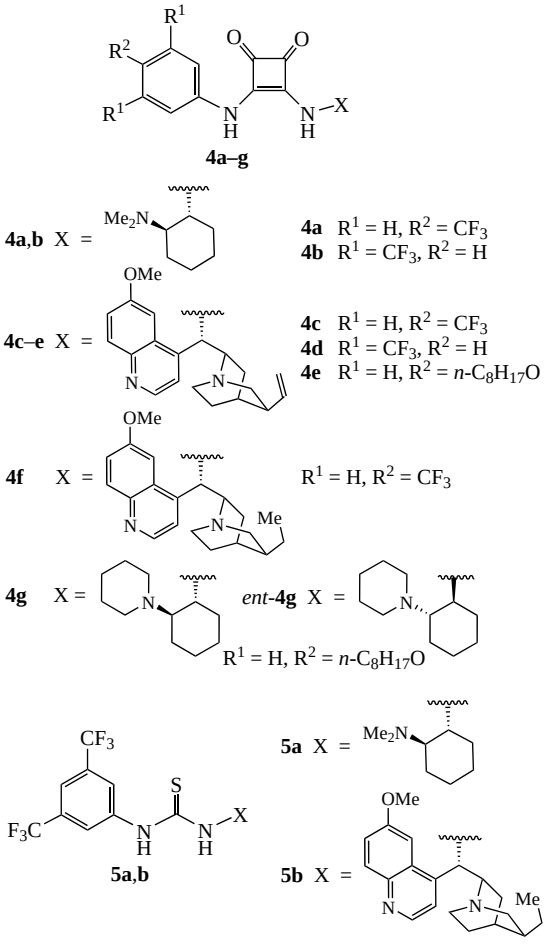


Scheme 1

Table 1 Optimization of the conditions for the reaction between diethyl 2-(2-hydroxybenzylideneamino)malonate **1a** and arylidene azlactones **2a**,**b** in carbon dioxide medium.[a]

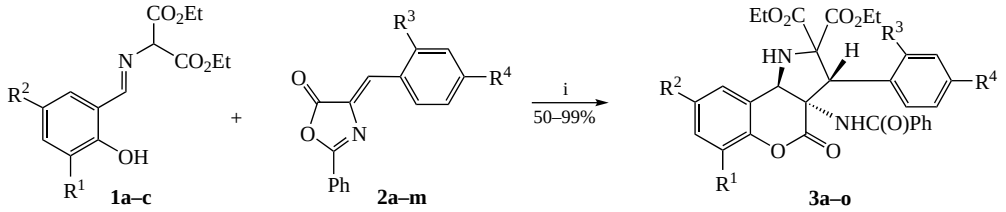
Entry	Azlactone	Catalyst (mol%)	*T*/°C	Reaction outcome		
				Product	Yield (%)	*ee* (%)
1	**2a**	**4a** (10)	25	**3a**	71	78
2	**2a**	**4b** (10)	25	**3a**	93	99
3	**2a**	**4c** (10)	25	**3a**	94 (80[b])	97 (95[b])
4	**2a**	**4c** (2/1)	25	**3a**	95/92	98/97
5	**2a**	**4d** (10/2)	25	**3a**	98/93	>99
6	**2a**	**4d** (1)	25	**3a**	98	97
7	**2a**	**4d** (1)	35	**3a**	75	95
8	**2a**	**4d** (0.5)	25	**3a**	64	97
9	**2a**	**4e** (10)	25	**3a**	97	98
10	**2a**	**4e** (1)	25	**3a**	100	99
11	**2a**	**4e** (1)	35	**3a**	95 (58[c])	99 (89[c])
12	**2a**	**4e** (0.5)	25	**3a**	83	96
13	**2a**	**4f** (10/2)	25	**3a**	99/84	>99
14	**2a**	**4g**/*ent*-**4g** (10)	25	**3a**	76/55	89/70
15	**2a**	**5a** (10)	25	**3a**	93	99
16	**2a**	**5b** (10/5/1)	25	**3a**	98/99/96	>99/>99/97
17	**2b**	**4e** (1)	25	**3b**	n.r.[d]	–
18	**2b**	**4e** (1)	35	**3b**	94	94
19	**2b**	**4d** (1)	35	**3b**	77	95

[a] *Reaction conditions*: **1a** (0.1 mmol), **2a** (0.15 mmol), organocatalyst **4a**–**g** or **5a**,**b**, CO_2 (7.5 MPa), 1–2 h. [b] At 11.0 MPa CO_2. [c] At 1.0 MPa CO_2. [d] No reaction even in 16 h.



cases not only compatibility of the catalysts with the reactants but also their solubility in non-polar carbon dioxide should significantly influence the catalytic efficiency. Very good results provided catalysts **4d**,**e** and **5b** at 1 mol% loading at room temperature and 7.5 MPa CO_2 pressure (entries 6, 10, 16). Carrying out the reaction at 35 °C (slightly higher than 31.1 °C, a critical temperature for CO_2) provided satisfactory yields and *ee* values (entries 7 and 11), although a bit lower ones.

However, when expanding conditions of entry 10 (see Table 1) on another azlactone **2b** with *p*-chlorophenyl substituent we could not detect formation of product **3b** even upon 16 h processing (entry 17). Luckily, carrying out the reaction at 35 °C [yet in supercritical (sc) CO_2] provided formation of product **3b** with good yields and *ee* values with any of catalysts, **4d** or **4e** (entries 18, 19). Therefore, the further study of substrate scope (Scheme 2) was performed with both catalysts **4d**,**e** in sc-CO_2 at 35 °C and 7.5 MPa. Although in all cases the results were acceptable, with catalyst **4e** they were noticeably better (see Online Supplementary Materials, Table S1). It is of note that organocatalyst **4d** contains two CF_3 groups while **4e** bears $C_8H_{17}O$ substituent, whereas according to general concept fluorinated groups would provide better solubility of a compound in sc-CO_2. Anyway, with non-fluorinated organocatalyst **4e**, products **3b**–**o** were obtained in generally good yields and with excellent *ee* values. The exceptional substrate was salicylidene-substituted azlactone of type **2** (R^3 = OH, R^4 = H) which did not form the corresponding tricycle of type **3**, apparently, due to its



a $R^1 = R^2 = H$
b $R^1 = H$, $R^2 = Br$
c $R^1 = R^2 = Cl$

a $R^3 = R^4 = H$
b $R^3 = H$, $R^4 = Cl$
c $R^3 = H$, $R^4 = OMe$
d $R^3 = H$, $R^4 = NO_2$
e $R^3 = H$, $R^4 = Br$
f $R^3 = H$, $R^4 = F$
g $R^3 = Cl$, $R^4 = H$
h $R^3 = NO_2$, $R^4 = H$
i $R^3 = Me$, $R^4 = H$
j $R^3 = OMe$, $R^4 = H$
k $R^3 = CF_3$, $R^4 = H$
l $R^3 = Br$, $R^4 = H$
m $R^3 = F$, $R^4 = H$

a $R^1 = R^2 = R^3 = R^4 = H$; *ee* 99%
b $R^1 = R^2 = R^3 = H$, $R^4 = Cl$; *ee* 94%
c $R^1 = R^2 = R^3 = H$, $R^4 = OMe$; *ee* 95%
d $R^1 = R^2 = R^3 = H$, $R^4 = NO_2$; *ee* 92%
e $R^1 = R^2 = R^3 = H$, $R^4 = Br$; *ee* 90%
f $R^1 = R^2 = R^3 = H$, $R^4 = F$; *ee* 92%
g $R^1 = R^2 = R^4 = H$, $R^3 = Cl$; *ee* 97%
h $R^1 = R^2 = R^4 = H$, $R^3 = NO_2$; *ee* 98%
i $R^1 = R^2 = R^4 = H$, $R^3 = Me$; *ee* 97%
j $R^1 = R^2 = R^4 = H$, $R^3 = OMe$; *ee* 99%
k $R^1 = R^2 = R^4 = H$, $R^3 = CF_3$; *ee* >99%
l $R^1 = R^2 = R^4 = H$, $R^3 = Br$; *ee* 99%
m $R^1 = R^2 = R^4 = H$, $R^3 = F$; *ee* >99%
n $R^1 = R^3 = R^4 = H$, $R^2 = Br$; *ee* 99%
o $R^1 = R^2 = Cl$, $R^3 = R^4 = H$; *ee* 98%

Scheme 2 *Reagents and conditions*: i, **1** (0.1 mmol), **2** (0.15 mmol), organocatalyst **4e** (0.001 mmol, 1 mol%), CO_2 (7.5 MPa), 35 °C, 1–2 h.

poor solubility in CO_2. The herein obtained compounds **3h**,**j**,**k**,**o** are new.

An essential point of the investigations involves the determination of absolute configuration of the products. In the prototype work,[29] the absolute configuration of the 1,3a,4,9b-tetrahydrochromeno[4,3-*b*]pyrrole core in the whole series of compounds was declared as (3*R*,3a*S*,9b*R*), which was derived from the single crystal X-ray study for bromo derivative **3l**. Herein, we repeated the X-ray experiment for the same compound **3l** and found that our sample possessed the same configuration and exactly the same crystal parameters as documented previously[29] (see also Online Supplementary Materials). In the work,[29] all the compounds were found to be levorotatory; in our hands, known compounds **3a**–**g**,**i**,**l**–**n** were also levorotatory as well as three new compounds **3j**,**k**,**o**. Surprisingly, new *o*-nitrophenyl-containing analogue **3h** turned to be dextrorotatory ($[\alpha]_D^{25} = +36.5$), however we may suppose that it possesses the same (3*R*,3a*S*,9b*R*) absolute configuration. In fact, this compound was obtained with the same catalyst under the same conditions as other analogues of the series. Moreover, it had higher retention time on chiral HPLC column compared to minor enantiomer; the same phenomenon was observed for all other compounds of the series **3**. Apparently, the positive rotation of **3h** is determined by specific action of the *o*-nitrophenyl substituent on polarized light; it is of note that the rotation value of its *p*-nitrophenyl-containing isomer **3d** is low enough ($[\alpha]_D^{25} = -13.90$) while the values for the other representatives are essentially greater (see Table S1).

In conclusion, the enantioselective domino reaction between 2-(2-hydroxybenzylideneamino)malonates **1** and 4-arylidene-2-phenyloxazol-5(4*H*)-ones **2** was successfully accomplished with the organocatalyst assistance in carbon dioxide medium. Interestingly, among other domino transformations based on [3 + 2] cycloaddition reactions 'salicylideneamino' malonates **1** were the most popular azomethine ylide-type substrates.[9,10,13–19] They were added to other than **2** electron-deficient Michael acceptors, which gave promising polycyclic products. This may be a good challenge for more detailed investigations of azomethine ylide-type cycloadditions in carbon dioxide medium. It is of note that our preliminary attempts to recycle organocatalyst **4e** were not successful, maybe due to its co-extraction with the products. In view of this, design of analogous catalysts attached to some special 'anchors' and capable of operating in carbon dioxide medium also looks promising.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2024.09.022.

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