EurJOC
European Journal of Organic Chemistry

A Journal of
ChemPubSoc Europe

Accepted Article

Title: Enantioselective N-Acylation of Biginelli Dihydropyrimidines by Oxidative NHC Catalysis

Authors: Arianna Brandolese, Daniele Ragno, Costanza Leonardi, Graziano Di Carmine, Olga Bortolini, Carmela De Risi, and Alessandro Massi

To be cited as: *Eur. J. Org. Chem.* 10.1002/ejoc.202000151

Link to VoR: http://dx.doi.org/10.1002/ejoc.202000151

Supported by
ACES Asian Chemical Editorial Society

WILEY-VCH

WILEY-VCH

FULL PAPER

Enantioselective *N*-Acylation of Biginelli Dihydropyrimidines by Oxidative NHC Catalysis

Arianna Brandolese,[a] Daniele Ragno,[a] Costanza Leonardi,[a] Graziano Di Carmine,[b] Olga Bortolini,[a] Carmela De Risi,[a] and Alessandro Massi*[a]

In memory of Professor Cinzia Chiappe

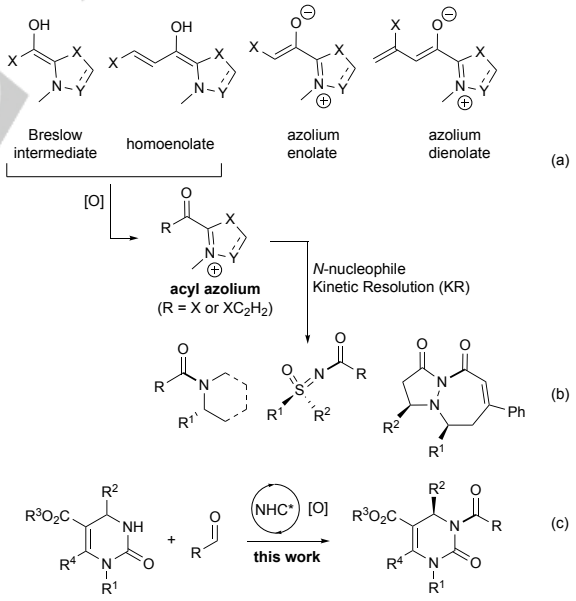
[a] A. Brandolese, Dr. D. Ragno, C. Leonardi, Prof. C. De Risi, Prof. O. Bortolini, Prof. A. Massi
Department of Chemical and Pharmaceutical Sciences
University of Ferrara
Via L. Borsari, 46, I-44121 Ferrara (Italy)
E-mail: alessandro.massi@unife.it
http://docente.unife.it/alessandro.massi?set_language=it
[b] Dr. G. Di Carmine
School of Chemical Engineering and Analytical Science
The University of Manchester
The Mill, Sackville Street, Manchester, M13 9PL, UK

Supporting information for this article is given via a link at the end of the document.

Abstract: The oxidative *N*-acylation reaction of 3,4-dihydropyrimidin-2-(1*H*)-ones (DHPMs) with enals and *N*-heterocyclic carbene (NHC) catalysts is described. The reaction proceeds in the presence of quinone oxidant without additional acyl transfer agents and in the asymmetric variant produces pharmaceutically relevant N3-acylated products with good-to-moderate enantioselectivity.

Introduction

Organocatalytic strategies by *N*-heterocyclic carbene (NHC) catalysis represent a useful tool for the execution of a broad range of asymmetric transformations including benzoin-type condensations, Stetter reactions, hydroacylations, annulations, and cycloadditions.[1] These processes proceed by normal polarity or umpolung reactivity through well-established activation modes involving key reactive species, namely the Breslow intermediate, homoenolate, and azolium (di)enolate intermediates (Scheme 1a).[1] Additionally, the synthetic opportunities given by NHC organocatalysts are further expanded by the application of redox protocols (internal and external oxidation strategies)[2] leading to the acyl azolium intermediate for the acylation of oxygen-, sulphur-, and nitrogen-nucleophiles in challenging kinetic resolution (KR),[3] macrolactonization,[4] desymmetrization,[3,5] and polymerization[6] processes. In particular, the *N*-acylation reaction using aldehydes as acylating agents in place of carboxylic acids/derivatives has proven to possess some practical advantages (mild reaction conditions, chemoselectivity, no need of coupling reagents) and it has been successfully applied to the functionalization of alkyl amines,[7] anilines,[8] amides,[9] sulfoximines,[10] azomethine imines,[11] and several nitrogen-containing heterocycles.[7c,e,i-12] In several occasions, the direct oxidative *N*-acylation with aldehydes has been precluded by the competing imine formation,[7] thus requiring the addition of oxygen nucleophiles as additives[7a,b] or the execution of a two-step procedure with activated ester intermediates.[7d,g] Of note, oxidative NHC catalysis has been fruitfully employed as synthetic platform for the acylative KR of secondary amines,[7,8] sulfoximines,[10] and azomethine imines[11] delivering optically active molecules with high stereoselectivities (Scheme 1b).



Scheme 1. (a) Common intermediates in NHC catalysis and generation of acyl azolium; (b) NHC-catalyzed *N*-acylation of nitrogen nucleophiles and kinetic resolutions; (c) this work.

The ureido functionality is an additional structural feature common to chiral compounds of synthetic and biological relevance,[13] as exemplified by the Biginelli dihydropyrimidines (3,4-dihydropyrimidin-2-(1*H*)-ones, DHPMs).[14] According to the Evans definition,[15] DHPMs are 'privileged' structures in medicinal

chemistry displaying a plethora of pharmacological properties.[14] Since enantiomeric DHPMs typically exhibit different or even opposite biological activity, enantioenriched DHPMs have been addressed by chemical resolution, chromatography on chiral stationary phases as well as by asymmetric metal/organo/biocatalytic approaches.[16] Enzymatic kinetic resolution has also been applied in a few cases through hydrolysis of activated ester derivatives of racemic DHPMs.[17] Within the class of Biginelli products, of particular relevance are the N3-acyl substituted compounds such as the potent calcium channel blockers SQ-32926[18] and SQ-32547[18] or the α_{1a} receptor antagonist agent L-771688.[19] These derivatives are close structural analogs of pharmaceutically active Hantzsch 1,4-dihydropyridines like Nifedipine displaying ester groups at C3 and C5 positions of the heterocyclic nucleus (Figure 1). Indeed, it has been observed that the substitution of DHPMs with carbonyl groups at the N3 position often leads to an increase of their biological activity and stability.[20] Optically active N3-acylated DHPMs are typically obtained from the corresponding enantioenriched substrate by treatment with stoichiometric, highly reactive acid chlorides or anhydrides at elevated temperatures in the presence of a base.[20] As part of our studies on oxidative NHC catalysis,[5,6,21] we herein present the direct asymmetric *N*-acylation of racemic DHPMs with aldehydes through catalytically generated acyl azolium as a mild reaction protocol, tolerant to substitutional variation around the DHPM scaffold (Scheme 1c).

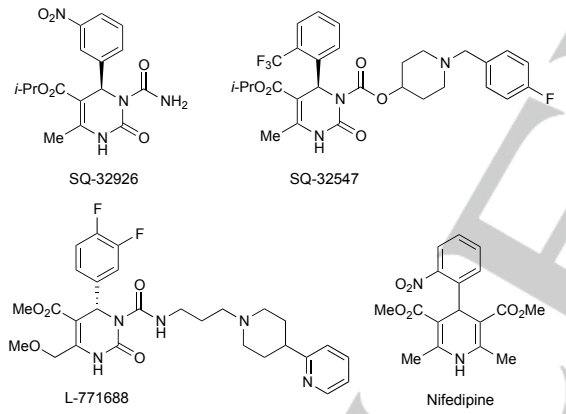
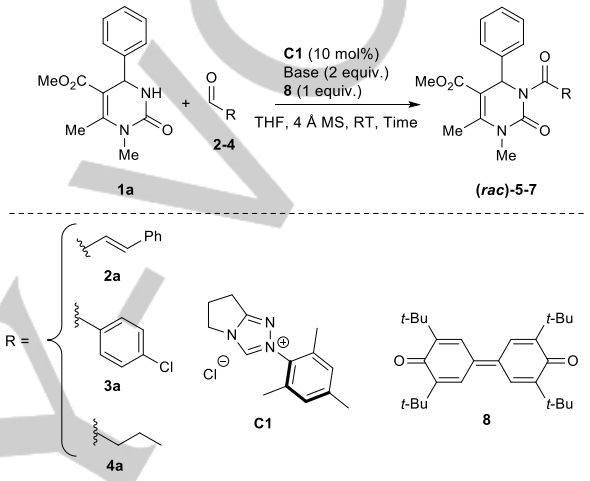


Figure 1. Biologically active N3-acylated DHPMs and Nifedipine.

Results and Discussion

Our study started evaluating the influence of the aldehyde reaction partner on the efficiency of the *N*-acylation of DHPM **1a** with the achiral triazolium pre-catalyst **C1** (10 mol%) and quinone **8** (1 equiv.) as the oxidant (Table 1). Under degassed conditions (Argon), the use of equimolar cinnamaldehyde **2a** and DBU (2 equiv.) in anhydrous THF with 4 Å molecular sieves at room temperature resulted in no formation of the corresponding N3-acylated DHPM **(*rac*)-5aa** (entry 1). The replacement of DBU with the stronger base NaH (2 equiv.) gave **(*rac*)-5aa** in 41% yield after one hour along with unreacted **1a** (48%; entry 2). Extension of the reaction time to 24 h as well as the use of excess aldehyde **2a** (2 equiv.) only led to a moderate increase of yield (47-50%) because of the consumption of **2a** into the corresponding acid (entries 3-4). Substitution of the α,β-unsaturated aldehyde **2a** with the aromatic 4-chlorobenzaldehyde **3a** resulted in marked decrease of reaction efficiency affording the acyl derivative **(*rac*)-6aa** in poor 10% yield (entry 5). As expected, utilization of the aliphatic *n*-butyraldehyde **4a** delivered a complex reaction mixture due to the competing aldol reaction with no evidence of product **(*rac*)-7aa** formation (entry 6). In conclusion of this explorative study, an improved reaction output was finally achieved with cinnamaldehyde **2a** using an excess (2 equiv.) of DHPM **1a**, being the acylated derivative **(*rac*)-5aa** recovered in 74% isolated yield (entry 7).

Table 1. Preliminary study on the achiral *N*-acylation of DHPM **1a** with model unsaturated-, aromatic-, and aliphatic aldehydes **2a**-**4a**.[a]



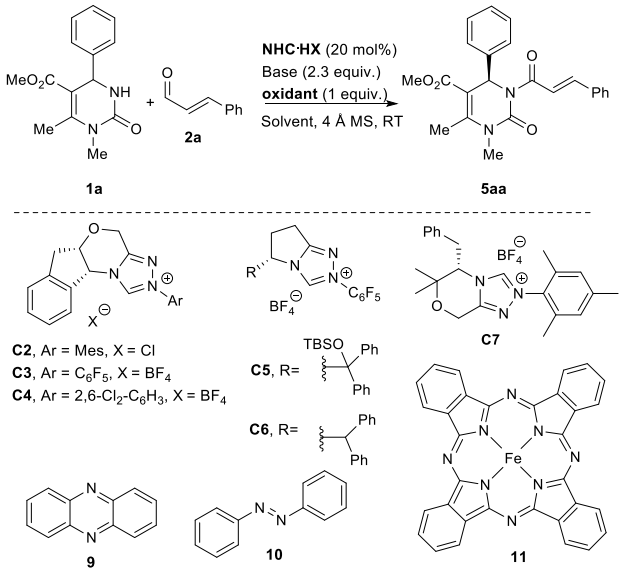
Entry	Aldehyde	Base	Time (h)	Product (%)[b]
1	**2a**	DBU	24	**(rac)-5aa** (-)
2	**2a**	NaH	1	**(rac)-5aa** (41)
3	**2a**	NaH	24	**(rac)-5aa** (47)
4[c]	**2a**	NaH	24	**(rac)-5aa** (50)
5	**3a**	NaH	24	**(rac)-6aa** (10)
6	**4a**	NaH	24	**(rac)-7aa** (-)
7[d]	**2a**	NaH	16	**(rac)-5aa** (74)

[a] Conditions: **1a** (0.2 mmol), aldehyde (0.2 mmol), **C1** (10 mol%), base (0.4 mmol), **8** (0.2 mmol), anhydrous THF (2 mL), 4 Å MS, RT. [b] Isolated yield. [c] Reaction run with 0.4 mmol of **2a** and **8**. [d] Reaction run with 0.4 mmol of **1a** and 0.46 mmol of NaH.

The asymmetric version of the model *N*-acylation of DHPM **1a** was next investigated with cinnamaldehyde **2a** as the limiting reagent using the set of chiral pre-catalysts **C2-C7** (Table 2). Under the conditions of the disclosed racemic process, the amino-indanol-derived triazolium salts **C2-C4** provided unsatisfactory results even at higher catalytic loading (20 mol%; entries 1-3). Indeed, only **C3** could promote the formation of **5aa** in very low yield (8%) but with an encouraging enantiomeric ratio (*er* = 78:22, entry 2). The pyrrole-derived triazolium pre-catalyst **C5** proved to be ineffective (entry 4), while the analogue **C6** gave **5aa** in 50% isolated yield and 80:20 *er* after 16 h (entry 5). These results seemed to confirm a diminished efficiency of the asymmetric *N*-acylation probably due to the higher steric hindrance of chiral pre-catalysts **C5-C6** compared to that of achiral **C1**. A similar yield of **5aa** (55%) accompanied, however, by a lower value of *er* (60:40) was detected with the morpholine-based triazolium salt **C7** (entry 6). The solvent and base screening with **C6** indicated THF as the optimal reaction medium (entries 5, 7-8) and *n*-BuLi (2.3 equiv.) as the preferred base (entries 9-11), thus allowing to slightly

increase the yield (55%) and the enantioselectivity of the process (*er* = 83:17, entry 11. See the Supporting Information for the full screening of solvents and bases). The addition of LiCl or $LiBF_4$ (25 mol%) as cooperative Lewis catalysts[22] left the enantiomeric ratio of **5aa** almost unaffected (entries 12-13).

Table 2. Optimization of the reaction conditions.[a]

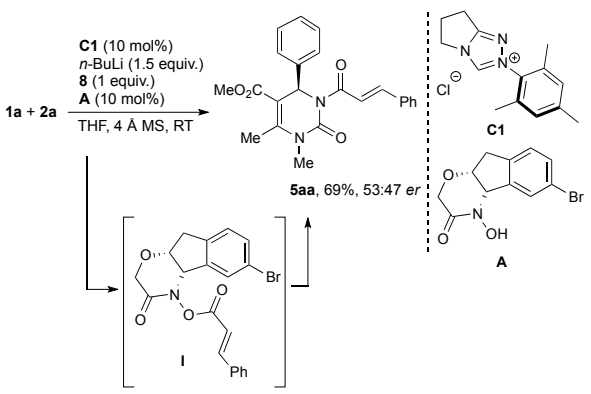


Entry	NHC·HX	Solvent	Base	Ox.	5aa (%)[b]	*er*[c]
1	**C2**	THF	NaH	**8**	-	-
2	**C3**	THF	NaH	**8**	8	78:22
3	**C4**	THF	NaH	**8**	-	-
4	**C5**	THF	NaH	**8**	-	-
5	**C6**	THF	NaH	**8**	50	80:20
6	**C7**	THF	NaH	**8**	55	60:40
7	**C6**	DCM	NaH	**8**	21	64:36
8	**C6**	DMF	NaH	**8**	16	62:38
9	**C6**	THF	KHMDS	**8**	20	61:39
10	**C6**	THF	*t*-BuOK	**8**	18	63:37
11	**C6**	THF	*n*-BuLi	**8**	55	83:17
12[d]	**C6**	THF	*n*-BuLi	**8**	30	72:18
13[e]	**C6**	THF	*n*-BuLi	**8**	42	80:20
14[f]	**C6**	THF	*n*-BuLi	**8**	60	75:25
15[g]	**C6**	THF	*n*-BuLi	**8**	25	85:15
16[h]	**C6**	THF	*n*-BuLi	**8**	32	82:18
17	**C6**	THF	*n*-BuLi	**9**	45	80:20
18	**C6**	THF	*n*-BuLi	**10**	48	80:20
19[i]	**C6**	THF	*n*-BuLi	air	20	78:22
20[j]	**C6**	THF	*n*-BuLi	**8**	35	81:19

[a] Conditions: **1a** (0.4 mmol), **2a** (0.2 mmol), **NHC·HX** (0.04 mmol), base (0.46 mmol), oxidant (0.2 mmol), anhydrous THF (4 mL), 4 Å MS, RT, 16 h. [b] Isolated yield. [c] Determined by chiral HPLC. [d] Addition of LiCl (0.05 mmol). [e] Addition of $LiBF_4$ (0.05 mmol). [f] Temperature: 45 °C. [g] Temperature: 0 °C, 32 h. [h] Conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), **C6** (0.08 mmol), *n*-BuLi (0.25 mmol), **8** (0.4 mmol), 24 h. [i] Addition of **8** (0.05 mmol) and **11** (0.01 mmol). [j] Conditions: **1a** (0.2 mmol), **2a** (0.2 mmol), 24 h. Recovered **1a** (59%; *er* = 61:39) with (4*S*)-configuration.

The study of the temperature effect showed a small improvement of the reaction yield (60%) at 45 °C together with a partial loss of enantioselectivity (*er* = 75:25, entry 14), whereas cooling the reaction mixture at 0 °C produced a drastic reduction of yield (25%) and only a little enhancement of *er* (85:15, entry 15). As expected on the basis of the results of the racemic process, the use of an excess (2 equiv.) of aldehyde **1a** resulted in a lower efficiency of the acylation procedure because of the side-oxidation to cinnamic acid (entry 16). The replacement of quinone **8** with different oxidants such as phenazine **9** and azobenzene **10** had little effect on the reaction outcome in terms of both chemical yield (45-48%) and enantiomeric ratio (*er* = 80:20, entries 17-18). Moreover, the possible use of air as the terminal oxidant was verified by applying the biomimetic system of electron-transfer mediators (ETMs) developed by Bäckvall[23] and Sundeń[12,24] groups. In brief, a catalytic amount (25 mol%) of quinone **8** (ETM') was employed in combination with iron(II) phthalocyanine **11** (5 mol%, ETM'') under air atmosphere affording **5aa** in poor yield (20%) and comparable enantioselectivity (*er* = 78:22, entry 19). The modest efficiency of **C6** in promoting the kinetic resolution of DHPM **1a** was finally confirmed by reacting **1a** and **2a** in equimolar amounts using **8** as the preferred oxidant (entry 20). Under these conditions, **5aa** (*er* = 81:19) was isolated in 35% yield, while unreacted **1a** (59%) was recovered with low enantioselectivity (*er* = 61:39) and (4*S*)-configuration (see below for stereochemical assignment). Finally, the occurrence of a partial racemization at the C4 position of DHPM **5aa** was excluded by a control experiment, which showed the maintenance of the stereochemical integrity of an authentic sample of **5aa** in the presence of excess *n*-BuLi (Supporting Information).

At this stage of the study, the NHC/hydroxamic acid co-catalysis approach developed by Bode and co-workers for the KR of cyclic secondary amines[7e] was also attempted with the aim to improve the enantioselectivity of the model *N*-acylation reaction. Accordingly, the achiral triazolium pre-catalyst **C1** (10 mol%) and the chiral hydroxamic acid co-catalyst **A** (10 mol%) were loaded into the reaction mixture (equimolar **1a**/**2a**/**8**, THF) to generate, after the addition of *n*-BuLi (1.5 equiv.), the key acylating agent **I** susceptible to nucleophilic attack by the deprotonated DHPM **1a** (Scheme 2). Unfortunately, while this strategy afforded **5aa** in higher yield (69%), this compound was recovered in almost racemic form (*er* = 53:47) likely because of the major incidence of the competitive achiral pathway directly promoted by **C1**.

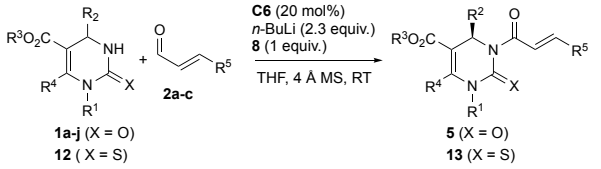


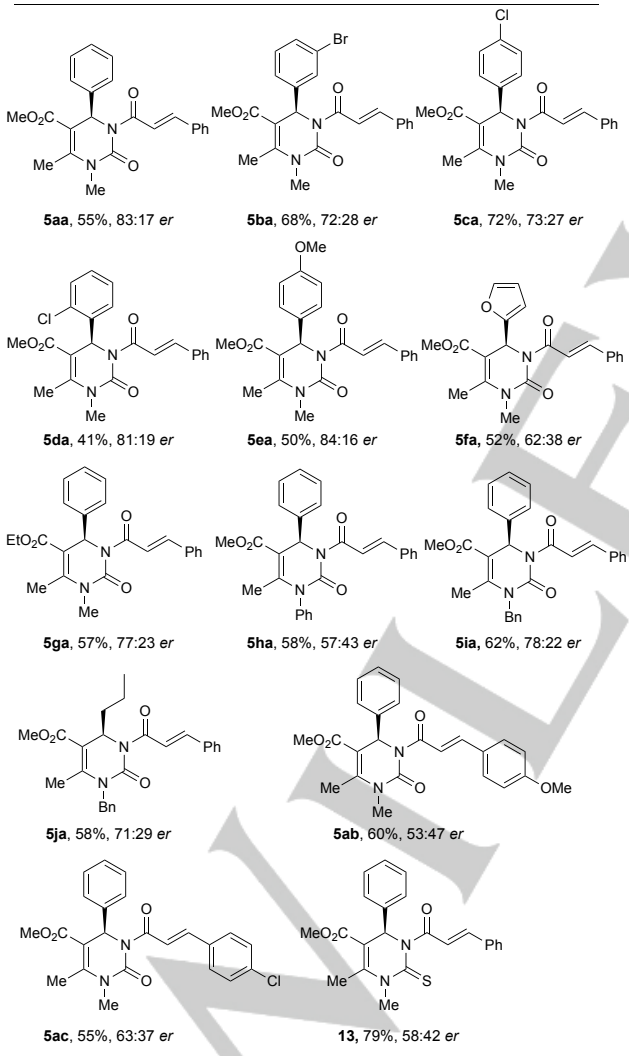
Scheme 2. NHC/hydroxamic acid co-catalysis approach for the synthesis of **5aa.**

To verify the scope and limitation of the present *N*-acylation method, the set of racemic DHPMs **1a-j** were examined under the optimized conditions with pre-catalyst **C6** (Table 3). The presence

of electron-withdrawing groups in *meta*- and *para* position of the C4 aromatic ring determined an increase of reactivity (**5ba**, 68%; **5ca**, 72%) with little effect on enantioselectivity compared to the model **5aa**. The *ortho*-chloro substituent, instead, led to a lower yield of product **5da** (41%) without inducing the enantiomeric enrichment (*er* = 81:19) that could be expected on the basis of the higher steric hindrance around the C4 stereocenter. A little improvement in terms of *er* was registered in DHPM **5ea** (*er* = 84:16) displaying the aromatic *para*-methoxy group, while a much lower enantiomeric ratio (*er* = 62:38) was detected in the furyl-functionalized compound **5fa**.

Table 3. Reaction scope of the enantioselective *N*-acylation of DHPMs.[a]



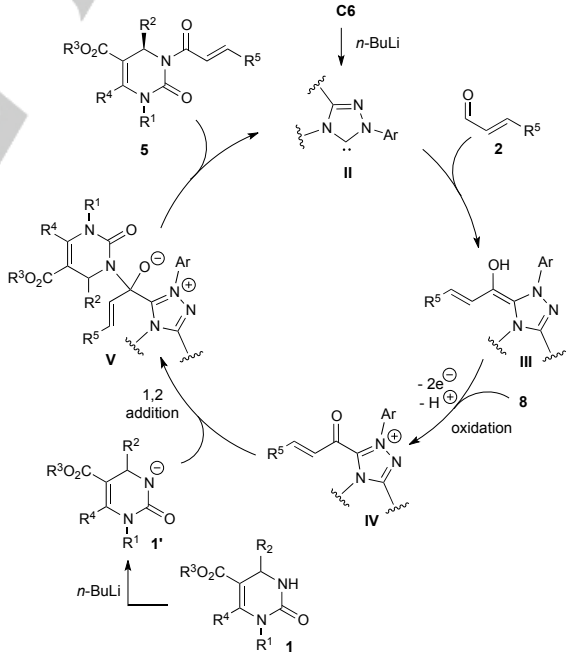


[a] Conditions: **1a** (0.4 mmol), aldehyde (0.2 mmol), **C6** (0.04 mmol), base (0.46 mmol), **8** (0.2 mmol), anhydrous THF (4 mL), 4 Å MS, RT, 16 h.

The effect of variation of the C5 ester group (**5ga**) and N1-substituent (**5ha**, **5ia**) was also investigated and no appreciable modification of reaction efficiency was observed in comparison with model **5aa**, apart from the marked drop of enantiomeric ratio shown by **5ha** (*er* = 57:43) bearing an aromatic N1 group. Also, the introduction of an aliphatic chain at the C4 position resulted in a diminished enantioselectivity (**5ja**; *er* = 71:29) compared to **5ia** with the same substitution pattern. Electron-rich and electron-poor cinnamaldehydes **2b,c** furnished the corresponding N3-acylated DHPMs **5ab** and **5ac** with low enantioselectivities, being **5ab** an almost racemic product (*er* = 53:47). Surprisingly, the same lack of enantiocontrol exerted by **C6** was detected moving from the model DHPM **1a** to the thio-analogue **12** as the substrate; the corresponding N3-acylated product **13**, in fact, was produced in good yield (79%) but negligible enantioselectivity (*er* = 58:42). It is important to stress that the stoichiometric oxidant **8** could be easily regenerated with air (see the Experimental section) and re-used in different runs.

The absolute configuration of products **5** was assigned through a dedicated experiment where the known DHPM **1g** was reacted with equimolar cinnamaldehyde **2a** (30% conversion). The recovery of DHPM **1g** (*er* = 60:40) with (4*S*)-configuration (optical rotation analysis)[25] allowed to deduce the opposite (4*R*)-configuration for the acylated counterpart **5ga** (*er* = 77:23). This assignment was then extended to all DHPMs **5** by analogy (see the Supporting Information for details).

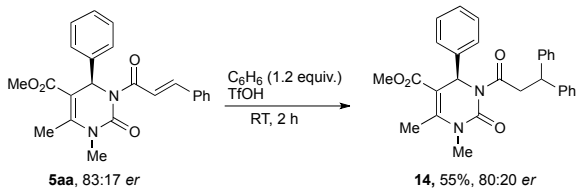
A proposed mechanism for the disclosed asymmetric *N*-acylation of DHPMs is shown in Scheme 3. The NHC **II** generated by deprotonation of triazolium salt **C6** reacts with aldehyde **2** to give the homoenolate intermediate **III**, which in turn is oxidized to the acyl azolium **IV** by the external oxidant **8**. Subsequent interception of **IV** by the deprotonated DHPM **1'** then leads to the product **5** and catalyst turnover through the intermediate **V**.



Scheme 3. Proposed reaction mechanism.

The acylated DHPMs **5** display an α,β-unsaturated functionality amenable to synthetic elaborations for the introduction of additional elements of diversity on the DHPM scaffold. As a proof of concept study, enantioenriched **5aa** (*er* = 83:17) was subjected to alkene hydroarylation[26] with benzene and triflic acid (TfOH)

affording the diaryl derivative **14** in satisfactory yield (55%) and almost unchanged enantiomeric purity (*er* = 80:20; Scheme 4)



5aa, 83:17 *er* **14,** 55%, 80:20 *er*

Scheme 4. Synthetic elaboration of enantioenriched DHPM **5aa**.

Conclusion

In conclusion, we have developed an asymmetric *N*-acylation strategy based on oxidative NHC catalysis to readily access the class of pharmaceutically relevant N3-acylated DHPMs in enantioenriched form. Although the enantioselectivity of the process was moderate, the use of aldehydes as mild acylating agents appear well suited for the (stereo)chemical decoration of the DHPM nucleus and, in general, for the direct *N*-acylation of molecules containing the ureido functionality.

Experimental Section

^{1}H and ^{13}C NMR spectra were recorded on 300 and 400 MHz spectrometers in $CDCl_3$ at room temperature. ^{13}C NMR spectra were acquired with the ^{1}H broad-band decoupled mode, and chemical shifts (δ) are reported in ppm relative to residual solvents signals. Reactions were monitored by TLC on silica gel 60 F_{254} with detection by UV lamp operating at 254 nm and by spraying with vanillin-sulphuric acid reagent (6% vanillin [w/v] and 1% H_2SO_4 [v/v] in ethanol) followed by a short, gentle heating. Flash column chromatography was performed on silica gel 60 (230−400 mesh). All reactions were performed in oven-dried (100 °C) glassware under an atmosphere of argon. Optical rotations were measured at 25 ± 2 °C in the stated solvent; $[\alpha]_D$ are given in 10^{-1} deg cm^2 g^{-1} (concentration *c* given as g/100 mL). The enantiomeric ratios were determined by chiral stationary phase HPLC (Daicel Chiralpak IA), using an UV detector operating at 254 nm. Melting points were measured on an Electrothermal 9100 apparatus and are uncorrected. All commercially available reagents and compounds **3a**, **8-11** were purchased from TCI and used as received without further purification. Solvents were distilled from appropriate drying agents. Liquid aldehydes **2a**, **4a** and DBU base were freshly distilled before their utilization. Catalysts **C4**,[27a] **C5**,[27b] and **C6**[21c] were prepared by following literature procedure. Catalysts **A**, **C1**, **C2**, **C3** and **C7** were purchased from Sigma-Aldrich. Compounds **1** were prepared following a slightly modified literature procedure.[28] DHPMs **1e**,[29a] **1g**,[29b] **1i**[29c] are known compounds.

General procedure for the synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones 1 and 12

A mixture of aldehyde (4 mmol), dicarbonyl compound (4 mmol), N-substituted urea/thiourea (6 mmol) and *p*-toluenesulfonic acid (100 mg) was refluxed in 5 mL of methanol for 16 h. Reaction progress was followed by TLC and after the completion, the reaction mixture was cooled down to 0 °C. In some cases, the products precipitated readily, otherwise nucleation was promoted by scratching the surface of the flask with a spatula. The solids were collected by filtration, washed with water and ice-cold methanol. In other cases, the organic mixture was concentrated and eluted from a column of silica gel with the suitable elution system to give the 3,4-dihydropyrimidin-2(1*H*)-one **1**.

Methyl 1,6-dimethyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate (1a)

The product readily precipitated from MeOH cooled at 0 °C. Filtration followed by washing with cold MeOH and drying under vacuum afforded the product **1a** as a white powder (0.93 g, 90%); m. p. 190-191 °C (Lit.[30] 190-192 °C). ^{1}H NMR (300 MHz, $CDCl_3$) δ= 7.40 - 7.14 (m, 5H, ArH), 5.44 (s, 1H, NH), 5.38 (d, *J* = 3.3 Hz, 1H, H-4), 3.65 (s, 3H, CO_2CH_3), 3.23 (s, 3H, NCH_3-1), 2.52 (s, 3H, CH_3-6); ^{13}C NMR (101 MHz, $CDCl_3$) δ= 166.6, 153.9, 149.7, 143.3, 128.8 (2C), 127.9, 126.2 (2C), 104.1, 54.0, 51.4, 30.4, 16.7; HRMS(ESI): calcd. for $C_{14}H_{17}N_2O_3^+$ (M + H$^+$): 261.1234; found: 261.1244.

Methyl 4-(3-bromophenyl)-1,6-dimethyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (1b)

The product readily precipitated from MeOH cooled at 0 °C. Filtration followed by washing with cold MeOH and drying under vacuum afforded the product **1b** as a yellowish powder (1.08 g, 80%); m. p. 138-140 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ= 7.38 (s, 2H, ArH), 7.18 (d, *J* = 5.0 Hz, 2H, ArH), 5.47 (s, 1H, NH), 5.36 (s, 1H, H-4), 3.67 (s, 3H, CO_2CH_3), 3.24 (s, 3H, NCH_3-1), 2.54 (s, 3H, CH_3-6); ^{13}C NMR (101 MHz, $CDCl_3$) δ= 166.3, 153.6, 150.2, 145.5, 131.1, 130.5, 129.4, 124.8, 122.9, 103.3, 53.6, 51.5, 30.5, 16.7; HRMS(ESI): calcd. for $C_{14}H_{16}BrN_2O_3^+$ (M + H$^+$): 339.0339; found: 339.0352.

Methyl 4-(4-chlorophenyl)-1,6-dimethyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (1c)

The product readily precipitated from MeOH cooled at 0 °C. Filtration followed by washing with cold MeOH and drying under vacuum afforded the product **1c** as a yellow powder (1.00 g, 85%); m. p. 118-120 °C (Lit.[31] 117-119 °C). ^{1}H NMR (300 MHz, $CDCl_3$) δ= 7.28 (d, *J* = 8.5 Hz, 2H, ArH), 7.18 (d, *J* = 8.5 Hz, 2H, ArH), 5.45 (s, 1H, NH), 5.36 (s, 1H, H-4), 3.66 (s, 3H, CO_2CH_3), 3.24 (s, 3H, NCH_3-1), 2.52 (s, 3H, CH_3-6); ^{13}C NMR (101 MHz, $CDCl_3$) δ= 166.4, 153.7, 149.9, 141.8, 133.7, 129.0 (2C), 127.6 (2C), 103.7, 53.4, 51.5, 30.5, 16.7; HRMS(ESI): calcd. for $C_{14}H_{16}ClN_2O_3^+$ (M + H$^+$): 295.0844; found: 295.0854.

Methyl 4-(2-chlorophenyl)-1,6-dimethyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (1d)

The product readily precipitated from MeOH cooled at 0 °C. Filtration followed by washing with cold MeOH and drying under vacuum afforded the product **1d** as a yellowish powder (0.95 g, 80%); m. p. 115-117 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ= 7.38 (dt, *J* = 5.1, 2.8 Hz, 1H, ArH), 7.25 - 7.08 (m, 3H, ArH), 5.76 (s, 1H, NH), 5.72 (s, 1H, H-4), 3.58 (s, 3H, CO_2CH_3), 3.22 (s, 3H, NCH_3-1), 2.65 (s, 3H, CH_3-6); ^{13}C NMR (101 MHz, $CDCl_3$) δ= 166.5, 159.1, 153.9, 149.2, 135.5, 127.3 (2C), 114.0, 104.2, 55.2, 53.3, 51.3, 30.3, 16.6; HRMS(ESI): calcd. for $C_{14}H_{16}ClN_2O_3^+$ (M + H$^+$): 295.0844; found: 295.0856.

Methyl 4-(4-methoxyphenyl)-1,6-dimethyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (1e)[29a]

Column chromatography on silica gel with cyclohexane/EtOAc = 1:1 afforded **1e** as a yellowish powder (0.81 g, 70%); m. p. 148-150 °C (Lit.[29a] 149-151 °C). ^{1}H NMR (300 MHz, $CDCl_3$) δ= 7.22 - 7.09 (m, 2H, ArH), 6.87 -6.76 (m, 2H, ArH), 5.59 (s, 1H, NH), 5.32 (d, *J* = 3.2 Hz, 1H, H-4), 3.78 (s, 3H, CO_2CH_3), 3.65 (s, 3H, ArO$\underline{CH_3}$), 3.23 (s, 3H, NCH_3-1), 2.51 (s, 3H, CH_3-6); ^{13}C NMR (101 MHz, $CDCl_3$) δ= 166.5, 159.1, 153.9, 149.2, 135.5,

127.3 (2C), 114.0 (2C), 104.2, 55.2, 53.3, 51.3, 30.3, 16.6; HRMS(ESI): calcd. for $C_{15}H_{19}N_2O_4^+$ (M + H^+): 291.1339; found: 291.1328.

Methyl 4-(furan-2-yl)-1,6-dimethyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (1f)

Column chromatography on silica gel with cyclohexane/EtOAc = 1:1.5 afforded **1f** as a white powder (0.70 g, 70%); m. p. 155-157 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ= 7.34 - 7.26 (m, 1H, ArH), 6.24 (dd, *J* = 3.1, 1.8 Hz, 1H, ArH), 6.10 - 6.01 (m, 1H, ArH), 5.85 (s, 1H, NH), 5.41 (d, *J* = 3.4 Hz, 1H, H-4), 3.68 (s, 3H, CO_2CH_3), 3.19 (s, 3H, NCH_3-1), 2.52 (s, 3H, CH_3-6); ^{13}C NMR (101 MHz, $CDCl_3$) δ= 166.1, 154.6, 154.3, 151.2, 142.3, 110.1, 105.6, 101.2, 51.4, 47.5, 30.4, 16.5; HRMS(ESI): calcd. for $C_{12}H_{15}N_2O_4^+$ (M + H^+): 251.1026; found: 251.1034.

Ethyl 1,6-dimethyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate (1g)[29b]

The product readily precipitated from MeOH cooled at 0 °C. Filtration followed by washing with cold MeOH and drying under vacuum afforded the product **1g** as a white powder (0.98 g, 90%); m. p. 181-183 °C (Lit.[29b] 180-182 °C). ^{1}H NMR (300 MHz, $CDCl_3$) δ= 7.42 - 7.21 (m, 5H, ArH), 5.66 (s, 1H, NH), 5.40 (s, 1H, H-4), 4.11 (q, *J* = 7.1 Hz, 2H, $CO_2\underline{CH_2}CH_3$), 3.24 (s, 3H, NCH_3-1), 2.52 (s, 3H, CH_3-6), 1.18 (t, *J* = 7.1 Hz, 3H, $CO_2CH_2\underline{CH_3}$); ^{13}C NMR (101 MHz, $CDCl_3$) δ= 166.0, 154.0, 149.1, 143.2, 128.8 (2C), 128.0, 126.3 (2C), 104.5, 60.3, 54.1, 30.4, 16.6, 14.2; HRMS(ESI): calcd. for $C_{15}H_{19}N_2O_3^+$ (M + H^+): 275.1390; found: 275.1379.

Methyl 6-methyl-2-oxo-1,4-diphenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate (1h)

Column chromatography on silica gel with cyclohexane/EtOAc = 2:1 afforded **1h** as a white powder (0.97 g, 75%); m. p. 140-142 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ= 7.57 - 7.27 (m, 8H, NArH-1 and ArH-4), 7.24 (d, *J* = 11.9 Hz, 2H, ArH-4), 5.54 (s, 1H, NH), 5.49 (d, *J* = 3.0 Hz, 1H, H-4), 3.68 (s, 3H, CO_2CH_3), 2.11 (s, 3H, CH_3-6); ^{13}C NMR (101 MHz, $CDCl_3$) δ= 166.5, 153.1, 149.1, 143.3, 137.6, 129.4 (2C), 129.0 (2C), 128.6 (2C), 128.1 (2C), 126.3 (2C), 104.8, 54.5, 51.5, 18.7; HRMS(ESI): calcd. for $C_{19}H_{19}N_2O_3^+$ (M + H^+): 323.1390; found: 323.1403.

Methyl 1-benzyl-6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate (1i)[29c]

Column chromatography on silica gel with cyclohexane/EtOAc = 2:1 afforded **1i** as a white powder (0.99 g, 74%); m. p. 139-140 °C (Lit.[29c] 136-137 °C). ^{1}H NMR (300 MHz, $CDCl_3$) δ= 7.33 - 7.15 (m, 8H, Ar-4 and $NCH_2\underline{ArH}$-1), 7.10 (d, *J* = 7.7 Hz, 2H, $NCH_2\underline{ArH}$-1), 6.27 (s, 1H, NH), 5.44 (d, *J* = 3.2 Hz, 1H, H-4), 5.21 (d, *J* = 16.6 Hz, 1H, $N\underline{CH_2}Ar$-1), 4.86 (d, *J* = 16.6 Hz, 1H, $N\underline{CH_2}Ar$-1), 3.63 (s, 3H, CO_2CH_3), 2.44 (s, 3H, CH_3-6); ^{13}C NMR (101 MHz, $CDCl_3$) δ= 166.5, 154.1, 149.4, 143.0 (2C), 137.9 (2C), 128.7 (4C), 127.8, 127.2, 126.4, 126.3, 104.6, 53.7, 51.4, 45.9, 16.5; HRMS(ESI): calcd. for $C_{20}H_{21}N_2O_3^+$ (M + H^+): 337.1547; found: 337.1559.

Methyl 1-benzyl-6-methyl-2-oxo-4-propyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate (1j)

Column chromatography on silica gel with cyclohexane/EtOAc = 3:1 afforded **1j** as a white powder (0.43 g, 35%); m. p. 131-133 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ= 7.42 - 7.12 (m, 5H, ArH), 5.75 (s, 1H, NH), 5.14 (d, *J* = 16.7 Hz, 1H, NCH_2Ar-1), 4.85 (d, *J* = 16.6 Hz, 1H, NCH_2Ar-1), 4.28 (s, 1H, H-4), 3.72 (s, 3H, CO_2CH_3), 2.36 (s, 3H, CH_3-6), 1.59 - 1.23 (m, 4H, $CH_2CH_2CH_3$), 0.91 (t, *J* = 7.1 Hz, 3H, $CH_2CH_2CH_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ= 166.7, 154.8, 149.2, 138.3, 128.7 (2C), 127.1, 126.3 (2C), 105.2, 51.29, 50.1, 45.9, 39.2, 17.9, 16.4, 13.8; HRMS(ESI): calcd. for $C_{17}H_{23}N_2O_3^+$ (M + H^+): 303.1703; found: 303.1716.

Methyl 1,6-dimethyl-4-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (12)

The product readily precipitated from MeOH cooled at 0 °C. Filtration followed by washing with cold MeOH and drying under vacuum afforded the product **12** as a white powder (0.98 g, 89%); m. p. 117-118 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ= 7.54 - 6.95 (m, 6H, ArH and NH), 5.41 (s, 1H, H-4), 3.72 (s, 3H, CO_2CH_3), 3.62 (s, 3H, NCH_3-1), 2.52 (s, 3H, CH_3-6); ^{13}C NMR (101 MHz, $CDCl_3$) δ= 179.7, 166.0, 146.9, 141.5, 128.9 (2C), 128.2, 126.0 (2C), 107.4, 53.7, 51.7, 37.1, 16.9; HRMS(ESI): calcd. for $C_{14}H_{17}N_2O_2S^+$ (M + H^+): 277.1005; found: 277.1014.

General procedure for the synthesis of racemic N3-acylated DHPMs ((*rac*)-5,6) (Table 1)

A stirred mixture of **1a** (stated amount) and anhydrous THF (2.0 mL) was degassed under vacuum and saturated with argon (by an Ar-filled balloon) three times. Then the reaction mixture was cooled at 0 °C with an ice bath and NaH (stated amount) was added slowly. After 15 min at 0 °C, the ice bath was removed allowing the reaction to warm up till room temperature and the reaction mixture was stirred for an additional 15 min. Then, oxidant **8** (82 mg, 0.20 mmol), catalyst **C1** (6 mg, 0.02 mmol) and 4 Å MS were added under an argon environment. Aldehyde **2-4** (0.20 mmol) was finally added and the reaction was stirred at room temperature for the stated time (Table 1). The resulting solution was quenched with 0.5 M HCl (3.0 mL), partially concentrated under vacuum to reduce the amount of THF, extracted with DCM (3 × 15 mL), dried (anhydrous Na_2SO_4), and concentrated. Elution of the resulting residue from a column of silica with the suitable elution system afforded **(*rac*)-5,6**.

Methyl (*E*)-3-cinnamoyl-1,6-dimethyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate ((*rac*)-5aa)

Column chromatography on silica gel with cyclohexane/EtOAc = 3:1 afforded **(*rac*)-5aa** as a pale yellow oil (58 mg, 74%; Table 1, entry 7). See below for full characterization.

Methyl (*E*)-3-(4-chlorobenzoyl)-1,6-dimethyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate ((*rac*)-6aa)

Column chromatography on silica gel with cyclohexane/EtOAc = 3:1 afforded **(*rac*)-6aa** as a pale yellow oil (8 mg, 10%). ^{1}H NMR (300 MHz, $CDCl_3$) δ= 7.48 (d, *J* = 8.4 Hz, 2H, COArH), 7.40 - 7.30 (m, 7H, COArH and ArH-4), 6.46 (s, 1H, H-4), 3.79 (s, 3H, CO_2CH_3), 3.15 (s, 3H, NCH_3-1), 2.63 (s, 3H, CH_3-6); ^{13}C NMR (101 MHz, $CDCl_3$) δ= 170.2, 165.7, 152.4, 149,2, 138.5, 137.7, 134.1, 129.2, 128.7, 128.5, 128.1, 126.4, 109.6, 53.4, 51.9, 31.2, 16.3; HRMS(ESI): calcd. for $C_{21}H_{20}ClN_2O_4^+$ (M + H^+): 399.1106; found: 399.1121.

General procedure for the synthesis of N3-acylated DHPMs (5) and thione (13)

A stirred mixture of **1** or **12** (0.40 mmol) and anhydrous THF (4.0 mL) was degassed under vacuum and saturated with argon (by an Ar-filled balloon) three times. Then the reaction mixture was cooled at 0 °C with an ice bath and *n*-BuLi (230 µL of a 2.0 M solution in *n*-hexane, 0.46 mmol) was added slowly. After 15 min at 0 °C, the ice bath was removed allowing the reaction to warm up till room temperature for another 15 min. Then, oxidant **8** (82 mg, 0.20 mmol), catalyst **C6** (22 mg, 0.04 mmol) and 4Å MS were added under an argon environment. Aldehyde **2** (0.2 mmol) was finally added and the reaction was stirred for 16 h at room temperature. The resulting

solution was quenched with 0.5 M HCl (5 mL) and partially concentrated under vacuum to reduce the amount of THF. The crude of the reaction was extracted with DCM (3 × 15 mL), dried (anhydrous Na_2SO_4), and concentrated. Elution of the resulting residue from a column of silica with the suitable elution system afforded **5** or **13**.

Methyl (*R,E*)-3-cinnamoyl-1,6-dimethyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate (5aa)

Column chromatography on silica gel with cyclohexane/EtOAc = 3:1 afforded **5aa** as a pale yellow oil (42 mg, 55%). Chiral HPLC analysis 83:17 *er* (Chiralpak IA column, *n*-Hexane/*i*-PrOH = 95:5, flow rate = 1.0 mL/min, λ = 254 nm, t_R = 26.0 min for minor isomer, t_R = 29.6 min for major isomer); $[\alpha]^{25}_D$ = +49.7 (*c* = 0.3, CH_3OH); ^{1}H NMR (300 MHz, $CDCl_3$) δ= 7.84 (d, *J* = 15.6 Hz, 1H, C=CH), 7.62 - 7.54 (m, 2H, ArHCH=C), 7.48 - 7.35 (m, 4H, ArHCH=C and C=CH), 7.32 - 7.26 (m, 5H, ArH-4), 6.76 (s, 1H, H-4), 3.77 (s, 3H, CO_2CH_3), 3.22 (s, 3H, NCH_3-1), 2.59 (s, 3H, CH_3-6); ^{13}C NMR (101 MHz, $CDCl_3$) δ= 167.1, 165.8, 149.3, 144.6, 142.8, 138.9, 134.9, 130.1, 128.8 (2C), 128.6 (2C), 128.3 (2C), 127.9, 126.3 (2C), 120.2, 109.1, 51.8, 51.4, 31.3, 16.2; HRMS(ESI): calcd. for $C_{23}H_{23}N_2O_4^+$ (M + H^+): 391.1652; found: 391.1638.

Methyl (*R,E*)-4-(3-bromophenyl)-3-cinnamoyl-1,6-dimethyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (5ba)

Column chromatography on silica gel with cyclohexane/EtOAc = 3.5:1 afforded **5ba** as a pale yellow oil (63 mg, 68%). Chiral HPLC analysis 72:28 *er* (Chiralpak IA column, *n*-Hexane/*i*-PrOH = 95:5, flow rate = 1.0 mL/min, λ = 254 nm, t_R = 22.6 min for minor isomer, t_R = 25.8 min for major isomer); $[\alpha]^{25}_D$ = +35.6 (*c* = 0.5, CH_3OH); ^{1}H NMR (300 MHz, $CDCl_3$) δ= 7.84 (d, *J* = 15.6 Hz, 1H, C=CH), 7.63 - 7.53 (m, 2H, ArHCH=C), 7.49 - 7.27 (m, 6H, ArHCH=C, Ar-4 and C=CH), 7.25 - 7.07 (m, 2H, ArH-4), 6.72 (s, 1H, H-4), 3.77 (s, 3H, CO_2CH_3), 3.22 (s, 3H, NCH_3-1), 2.60 (s, 3H, CH_3-6);^{13}C NMR (101 MHz, $CDCl_3$) δ= 167.0, 165.5, 152.3, 149.8, 145.0, 141.2, 134.8, 131.1, 130.2, 130.2, 129.6, 128.8 (2C), 128.4 (2C), 125.1, 122.8, 119.9, 108.3, 51.9, 51.0, 31.4, 16.2; HRMS(ESI): calcd. for $C_{23}H_{22}BrN_2O_4^+$ (M + H^+): 469.0757; found: 469.0774.

Methyl (*R,E*)-4-(4-chlorophenyl)-3-cinnamoyl-1,6-dimethyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (5ca)

Column chromatography on silica gel with cyclohexane/EtOAc = 3:1 afforded **5ca** as a pale yellow oil (61 mg, 72%). Chiral HPLC analysis 73:27 *er* (Chiralpak IA column, *n*-Hexane/*i*-PrOH = 80:20, flow rate = 1.0 mL/min, λ = 254 nm, t_R = 12.3 min for major isomer, t_R = 13.8 min for minor isomer); $[\alpha]^{25}_D$ = +10.3 (*c* = 0.3, CH_3OH); ^{1}H NMR (300 MHz, $CDCl_3$) δ= 7.84 (d, *J* = 15.6 Hz, 1H, C=CH), 7.62 - 7.52 (m, 2H, ArHCH=C), 7.45 - 7.34 (m, 4H, ArHCH=C and C=CH), 7.30 - 7.26 (m, 1H, ArH-4), 7.25 - 7.18 (m, 3H, ArH-4), 6.69 (s, 1H, H-4), 3.76 (s, 3H, CO_2CH_3), 3.22 (s, 3H, NCH_3-1), 2.59 (s, 3H, CH_3-6); ^{13}C NMR (101 MHz, $CDCl_3$) δ= 167.2, 165.7, 152.4, 149.7, 145.0, 137.5, 134.9, 133.9, 130.3, 128.9 (4C), 128.5 (2C), 128.0 (2C), 120.1, 108.7, 52.0, 51.1, 31.4, 16.3; HRMS(ESI): calcd. for $C_{23}H_{22}ClN_2O_4^+$ (M + H^+): 425.1263; found: 425.1244.

Methyl (*S,E*)-4-(2-chlorophenyl)-3-cinnamoyl-1,6-dimethyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (5da)

Column chromatography on silica gel with cyclohexane/EtOAc = 3:1 afforded **5da** as a pale yellow oil (34 mg, 41%). Chiral HPLC analysis 81:19 *er* (Chiralpak IA column, *n*-Hexane/*i*-PrOH = 85:15, flow rate = 1.0 mL/min, λ = 254 nm, t_R = 13.2 min for minor isomer, t_R = 17.2 min for major isomer); $[\alpha]^{25}_D$ = +12.5 (*c* = 0.4, CH_3OH); ^{1}H NMR (300 MHz, $CDCl_3$) δ= 7.78 (d, *J* = 15.6 Hz, 1H, C=CH), 7.59 - 7.51 (m, 2H, ArHCH=C), 7.45 (d, *J* = 15.6 Hz, 1H, C=CH), 7.40 - 7.31 (m, 4H, ArHCH=C and Ar-4), 7.23 - 7.14 (m, 3H, ArH-4), 6.89 (s, 1H, H-4), 3.74 (s, 3H, CO_2CH_3), 3.33 (s, 3H, NCH_3-1), 2.52 (s, 3H, CH_3-6); ^{13}C NMR (75 MHz, $CDCl_3$) δ= 167.2, 166.0, 152.9, 147.9, 145.0, 137.6, 135.3, 133.8, 131.0, 130.4, 129.6, 129.1 (2C), 128.7 (2C), 128.5, 127.5, 120.6, 109.3, 52.0, 51.5, 31.6, 16.6; HRMS(ESI): calcd. for $C_{23}H_{22}ClN_2O_4^+$ (M + H^+): 425.1263; found: 425.1246.

Methyl (*R,E*)-3-cinnamoyl-4-(4-methoxyphenyl)-1,6-dimethyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (5ea)

Column chromatography on silica gel with cyclohexane/EtOAc = 2.5:1 afforded **5ea** as a pale yellow oil (42 mg, 50%). Chiral HPLC analysis 84:16 *er* (Chiralpak IA column, *n*-Hexane/*i*-PrOH = 90:10, flow rate = 1.0 mL/min, λ = 254 nm, t_R = 23.5 min for minor isomer, t_R = 28.2 min for major isomer); $[\alpha]^{25}_D$ = +67.5 (*c* = 0.2, CH_3OH); ^{1}H NMR (300 MHz, $CDCl_3$) δ= 7.83 (d, *J* = 15.6 Hz, 1H, C=CH), 7.64 - 7.52 (m, 3H, ArHCH=C), 7.44 - 7.36 (m, 3H, ArHCH=C and C=CH), 7.20 (d, *J* = 8.6 Hz, 2H, ArH-4), 6.82 (d, *J* = 8.6 Hz, 2H, ArH-4), 6.70 (s, 1H, H-4), 3.77 (s, 3H, CO_2CH_3), 3.75 (s, 3H, ArOCH_3), 3.23 (s, 3H, NCH_3-1), 2.59 (s, 3H, CH_3-6); ^{13}C NMR (101 MHz, $CDCl_3$) δ= 167.1, 165.8, 159.2, 144.8, 144.5, 134.9, 132.8, 130.8, 130.1, 128.9, 128.7, 128.6, 128.5, 128.4, 128.3, 127.8, 122.1, 120.3, 114.0, 55.2, 51.8, 51.1, 31.3, 16.1; HRMS(ESI): calcd. for $C_{24}H_{25}N_2O_5^+$ (M + H^+): 421.1758; found: 421.1739.

Methyl (*S,E*)-3-cinnamoyl-4-(furan-2-yl)-1,6-dimethyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (5fa)

Column chromatography on silica gel with cyclohexane/EtOAc = 4:1 afforded **5fa** as a pale yellow oil (39 mg, 52%). Chiral HPLC analysis 62:38 *er* (Chiralpak IA column, *n*-Hexane/*i*-PrOH = 90:10, flow rate = 1.0 mL/min, λ = 254 nm, t_R = 19.1 min for minor isomer, t_R = 22.6 min for major isomer); $[\alpha]^{25}_D$ = +12.5 (*c* = 0.2, CH_3OH); ^{1}H NMR (300 MHz, $CDCl_3$) δ= 7.82 (d, *J* = 15.6 Hz, 1H, C=CH), 7.60 - 7.53 (m, 2H, ArHCH=C), 7.45 - 7.33 (m, 4H, ArHCH=C and C=CH), 7.32 - 7.27 (m, 1H, ArH-4), 6.74 (s, 1H, H-4), 6.29 - 6.24 (m, 1H, ArH-4), 6.20 (d, *J* = 3.3 Hz, 1H, ArH-4), 3.76 (s, 3H, CO_2CH_3), 3.29 (s, 3H, NCH_3-1), 2.58 (s, 3H, CH_3-6);^{13}C NMR (101 MHz, $CDCl_3$) δ= 166.9, 165.5, 152.5, 151.7, 150.2, 144.9, 142.9, 135.2, 130.4, 129.0 (2C), 128.6 (2C), 120.5, 110.4, 107.6, 106.7, 52.0, 46.9, 31.6, 16.4; HRMS(ESI): calcd. for $C_{21}H_{21}N_2O_5^+$ (M + H^+): 381.1445; found: 381.1429.

Ethyl (*R,E*)-3-cinnamoyl-1,6-dimethyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate (5ga)

Column chromatography on silica gel with cyclohexane/EtOAc = 3:1 afforded **5ga** as a pale yellow oil (46 mg, 57%). Chiral HPLC analysis 77:23 *er* (Chiralpak IA column, *n*-Hexane/*i*-PrOH = 90:10, flow rate = 1.0 mL/min, λ = 254 nm, t_R = 13.6 min for minor isomer, t_R = 15.9 min for major isomer); $[\alpha]^{25}_D$ = +33.9 (*c* = 0.13, CH_3OH); ^{1}H NMR (300 MHz, $CDCl_3$) δ= 7.83 (d, *J* = 15.6 Hz, 1H, C=CH), 7.62 - 7.55 (m, 2H, ArHCH=C), 7.48 - 7.32 (m, 4H, ArHCH=C and C=CH), 7.30 - 7.26 (m, 5H, ArH-4), 6.74 (s, 1H, H-4), 4.35 - 4.14 (m, 2H, $CO_2CH_2CH_3$), 3.22 (s, 3H, NCH_3-1), 2.58 (s, 3H, CH_3-6), 1.29 (t, *J* = 7.1 Hz, 3H, $CO_2CH_2CH_3$);^{13}C NMR (101 MHz, $CDCl_3$) δ= 167.3, 165.4, 150.0, 144.7, 139.1, 135.0, 130.2 (2C), 128.9 (2C), 128.7, 128.6, 128.4 (2C), 127.9, 126.4 (2C), 120.4, 109.7, 60.9, 51.8, 31.4, 16.3, 14.3; HRMS(ESI): calcd. for $C_{24}H_{25}N_2O_4^+$ (M + H^+): 405.1809; found: 405.1827.

Methyl (*R,E*)-3-cinnamoyl-6-methyl-2-oxo-1,4-diphenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate (5ha)

Column chromatography on silica gel with cyclohexane/EtOAc = 5:1 afforded **5ha** as a pale yellow oil (52 mg, 58%). Chiral HPLC analysis 57:43 *er* (Chiralpak IA column, *n*-Hexane/*i*-PrOH = 90:10, flow rate = 1.0 mL/min, λ = 254 nm, t_R = 11.4 min for major isomer, t_R = 15.9 min for minor isomer); $[\alpha]^{25}_D$ = -8.2 (*c* = 0.6, CH_3OH); ^{1}H NMR (300 MHz, $CDCl_3$) δ= 7.88 (d, *J* = 15.6 Hz, 1H, C=CH), 7.62 - 7.55 (m, 2H, ArCH=C), 7.51 (d, *J* = 15.6 Hz, 1H, C=CH), 7.48 - 7.26 (m, 12H, NAr-1 and Ar-4), 7.07 (bs, 1H, NAr-1), 6.90 (s, 1H, H-4), 3.81 (s, 3H, CO_2CH_3), 2.19 (s, 3H, CH_3-6); ^{13}C NMR (101 MHz, $CDCl_3$) δ= 167.2, 165.8, 151.9, 149.5, 145.0 (2C), 139.4, 136.9,

134.9, 130.2, 129.4 (2C), 129.2, 128.9 (3C), 128.7 (2C), 128.4 (2C), 128.0, 126.4 (2C), 120.1, 109.7, 51.9, 51.8, 17.9; HRMS(ESI): calcd. for $C_{28}H_{25}N_2O_4^+$ (M + H$^+$): 453.1809; found: 453.1789.

Methyl (*R,E*)-1-benzyl-3-cinnamoyl-6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate (5ia)

Column chromatography on silica gel with cyclohexane/EtOAc = 6:1 afforded **5ia** as a pale yellow oil (57 mg, 62%). Chiral HPLC analysis 78:22 *er* (Chiralpak IA column, *n*-Hexane/*i*-PrOH = 90:10, flow rate = 1.0 mL/min, λ = 254 nm, t_R = 17.3 min for minor isomer, t_R = 19.4 min for major isomer); $[\alpha]^{25}_D$ = +22.5 (*c* = 0.6, CH_3OH);^{1}H NMR (300 MHz, $CDCl_3$) δ= 7.89 (d, *J* = 15.5 Hz, 1H, C=CH), 7.63 - 7.56 (m, 2H, ArHCH=C), 7.44 (d, *J* = 15.6 Hz, 1H, C=CH), 7.40 - 7.34 (m, 3H, ArHCH=C), 7.29 - 7.08 (m, 8H, ArH-4 and NCH_2ArH-1), 6.80 (s, 1H, H-4), 6.71 (d, *J* = 7.3 Hz, 2H, NCH_2ArH-1), 5.43 (d, *J* = 16.5 Hz, 1H, NCH_2Ar-1), 4.61 (d, *J* = 16.4 Hz, 1H, NCH_2Ar-1), 3.77 (s, 3H, CO_2CH_3), 2.50 (s, 3H, CH_3-6); ^{13}C NMR (101 MHz, $CDCl_3$) δ= 167.3, 166.0, 149.3, 144.9 (2C), 139.0, 136.4, 135.0, 130.3 (2C), 128.9 (2C), 128.8 (2C), 128.7 (2C), 128.5 (2C), 127.9, 127.5, 126.8 (2C), 126.5 (2C), 120.2, 52.0, 51.4, 46.7, 16.3; HRMS(ESI): calcd. for $C_{29}H_{27}N_2O_4^+$ (M + H$^+$): 467.1965; found: 467.1946.

Methyl (*R,E*)-1-benzyl-3-cinnamoyl-6-methyl-2-oxo-4-propyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate (5ja)

Column chromatography on silica gel with cyclohexane/EtOAc = 6:1 afforded **5ja** as a pale yellow oil (50 mg, 58%). Chiral HPLC analysis 71:29 *er* (Chiralpak IA column, *n*-Hexane/*i*-PrOH = 90:10, flow rate = 1.0 mL/min, λ = 254 nm, t_R = 14.1 min for minor isomer, t_R = 17.8 min for major isomer); $[\alpha]^{25}_D$ = +5.5 (*c* = 0.2, CH_3OH); ^{1}H NMR (300 MHz, $CDCl_3$) δ= 7.78 (d, *J* = 15.6 Hz, 1H, C=CH), 7.58 - 7.51 (m, 2H, ArHC=CH), 7.40 - 7.27 (m, 9H, ArHC=CH, NCH_2ArH-1 and C=CH), 5.59 (t, *J* = 7.0 Hz, 1H, H-4), 5.30 (d, *J* = 16.3 Hz, 1H, NCH_2Ar-1), 4.85 (d, *J* = 16.0 Hz, 1H, NCH_2Ar-1), 3.75 (s, 3H, CO_2CH_3), 2.47 (s, 3H, CH_3-6), 1.45 - 1.36 (m, 4H, $CH_2CH_2CH_3$), 0.84 (t, *J* = 7.2 Hz, 3H, $CH_2CH_2CH_3$);^{13}C NMR (101 MHz, $CDCl_3$) δ= 167.0, 165.9, 152.9, 147.4, 144.1, 136.8, 135.0, 130.0, 128.8 (2C), 128.7 (2C), 128.3 (2C), 127.7, 127.1 (2C), 120.3, 111.1, 51.6, 49.3, 46.9, 36.1, 18.4, 16.2, 13.9; HRMS(ESI): calcd. for $C_{26}H_{29}N_2O_4^+$ (M + H$^+$): 433.2122; found: 433.2139.

Methyl (*R,E*)-3-(3-(4-methoxyphenyl)acryloyl)-1,6-dimethyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate (5ab)

Column chromatography on silica gel with cyclohexane/EtOAc = 3:1 afforded **5ab** as a pale yellow oil (50 mg, 60%). Chiral HPLC analysis 53:47 *er* (Chiralpak IA column, *n*-Hexane/*i*-PrOH = 90:10, flow rate = 1.0 mL/min, λ = 254 nm, t_R = 31.3 min for major isomer, t_R = 33.1 min for minor isomer); $[\alpha]^{25}_D$ = +10.1 (*c* = 0.2, CH_3OH); ^{1}H NMR (300 MHz, $CDCl_3$) δ= 7.82 (d, *J* = 15.6 Hz, 1H, C=CH), 7.53 (d, *J* = 8.7 Hz, 2H, ArHCH=C), 7.37 - 7.26 (m, 6H, C=CH and ArH-4), 6.89 (d, *J* = 8.8 Hz, 2H, ArHCH=C), 6.77 (s, 1H, H-4), 3.84 (s, 3H, CO_2CH_3), 3.77 (s, 3H, ArOCH_3), 3.21 (s, 3H, NCH_3-1), 2.58 (s, 3H, CH_3-6); ^{13}C NMR (101 MHz, $CDCl_3$) δ= 167.2, 165.8, 161.3, 149.4, 144.6, 139.0, 130.1 (2C), 128.6 (2C), 127.8, 127.7, 126.3 (2C), 117.7, 114.2 (2C), 114.1, 109.0, 55.3, 51.8, 51.3, 31.3, 16.1; HRMS(ESI): calcd. for $C_{24}H_{25}N_2O_5^+$ (M + H$^+$): 421.1758; found: 421.1741.

Methyl (*R,E*)-3-(3-(4-chlorophenyl)acryloyl)-1,6-dimethyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate (5ac)

Column chromatography on silica gel with cyclohexane/EtOAc = 4:1 afforded **5ac** as a yellowish oil (46 mg, 55%). Chiral HPLC analysis 63:37 *er* (Chiralpak IA column, *n*-Hexane/*i*-PrOH = 90:10, flow rate = 1.0 mL/min, λ = 254 nm, t_R = 22.9 min for minor isomer, t_R = 24.9 min for major isomer); $[\alpha]^{25}_D$ = +24.2 (*c* = 0.2, CH_3OH); ^{1}H NMR (300 MHz, $CDCl_3$) δ= 7.77 (d, *J* = 15.6 Hz, 1H, C=CH), 7.50 (d, *J* = 8.5 Hz, 2H, ArHCH=C), 7.44 - 7.26 (m, 7H, C=CH, ArHCH=C and ArH-4), 7.25 - 7.18 (m, 1H, ArH-4), 6.75 (s, 1H, H-4), 3.77 (s, 3H, CO_2CH_3), 3.21 (s, 3H, NCH_3-1), 2.58 (s, 3H, CH_3-6); ^{13}C NMR (101 MHz, $CDCl_3$) δ= 166.9, 165.8, 152.7, 149.4, 143.1, 138.86, 136.1, 133.5, 129.6 (2C), 129.1 (2C), 128.7 (2C), 128.0, 126.4 (2C), 120.9, 109.2, 51.9, 51.6, 31.4, 16.3; HRMS(ESI): calcd. for $C_{23}H_{22}ClN_2O_4^+$ (M + H$^+$): 425.1263; found: 425.1246.

Methyl (*R*)-3-cinnamoyl-1,6-dimethyl-4-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (13)

Column chromatography on silica gel with cyclohexane/EtOAc = 5:1 afforded **13** as a pale yellow oil (64 mg, 79%). Chiral HPLC analysis 58:42 *er* (Chiralpak IA column, *n*-Hexane/*i*-PrOH = 95:5, flow rate = 1.0 mL/min, λ = 254 nm, t_R = 17.8 min for major isomer, t_R = 18.7 min for minor isomer); $[\alpha]^{25}_D$ = +12.2 (*c* = 0.6, CH_3OH); ^{1}H NMR (300 MHz, $CDCl_3$) δ= 7.70 (d, *J* = 15.5 Hz, 1H, C=CH), 7.57 - 7.49 (m, 2H, ArHCH=C), 7.44 - 7.35 (m, 4H, ArHCH=C and C=CH), 7.33 - 7.26 (m, 5H, ArH-4), 6.64 (s, 1H, H-4), 3.79 (s, 3H, CO_2CH_3), 3.50 (s, 3H, NCH_3-1), 2.62 (s, 3H, CH_3-6); ^{13}C NMR (101 MHz, $CDCl_3$) δ= 178.8, 169.1, 165.5, 147.8, 141.3, 137.9, 135.2, 130.0, 128.9 (2C), 128.6 (2C), 128.4 (2C), 128.1, 126.4 (2C), 121.8, 113.8, 52.8, 52.2, 37.8, 16.9; HRMS(ESI): calcd. for $C_{23}H_{23}N_2O_3S^+$ (M + H$^+$): 407.1424; found: 407.1409.

Recycle of oxidant 8

The alcohol resulting from oxidant **8** reduction (3,3',5,5'-tetra-*tert*-butyl-[1,1'-biphenyl]-4,4'-diol) was recovered by column chromatography after each run of Table 3. The subsequent oxidation to **8** was performed stirring the 3,3',5,5'-tetra-*tert*-butyl-[1,1'-biphenyl]-4,4'-diol (578 mg, 1.41 mmol) with **11** (80 mg, 0.14 mmol) in THF (10 mL) under air atmosphere (1 atm, balloon) for 16 h. Filtration over a pad of Celite and subsequent concentration under reduced pressure afforded **8** as a dark red amorphous solid (572 mg, 88%).[5,6]

Methyl (*R*)-3-(3,3-diphenylpropanoyl)-1,6-dimethyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate (14)

A mixture of DHPM **5aa** (39 mg, 0.1 mmol), TfOH (50 μL, 0.56 mmol), benzene (22 μL, 0.24 mmol) and DCM (0.5 mL) was stirred at room temperature for 2 h. The mixture was poured into ice water (3 mL) and extracted with DCM (3 x 10 mL). The combined extracts were washed with water (5 mL), saturated aqueous solution of $NaHCO_3$ (5 mL), water again (5 mL), dried (anhydrous Na_2SO_4), concentrated, and eluted from a column of silica gel with cyclohexane/EtOAc = 3:1 to afford **14** as a white amorphous solid (25 mg, 55%). Chiral HPLC analysis 80:20 *er* (Chiralpak IA column, *n*-Hexane/*i*-PrOH = 90:10, flow rate = 1.0 mL/min, λ = 254 nm, t_R = 15.9 min for minor isomer, t_R = 17.2 min for major isomer); $[\alpha]^{25}_D$ = +45.2 (*c* = 0.2, CH_3OH); ^{1}H NMR (300 MHz, $CDCl_3$) δ= 7.31 - 7.26 (m, 5H, ArH), 7.23 - 7.21 (m, 5H, ArH), 7.18 - 7.03 (m, 5H, ArH), 6.55 (s, 1H, H-4), 4.64 (t, *J* = 7.8 Hz, 1H, Ar_2CH-), 3.76 (d, *J* = 8.4 Hz, 2H, Ar_2CHCH_2-), 3.70 (s, 3H, CO_2CH_3), 3.12 (s, 3H, NCH_3-1), 2.49 (s, 3H, CH_3-6); ^{13}C NMR (101 MHz, $CDCl_3$) δ= 173.1, 165.6, 152.4, 149.0, 143.8, 143.6, 138.7, 128.5 (2C), 128.4 (2C), 128.3 (2C), 127.9 (2C), 127.8 (2C), 127.7 (2C), 126.4, 126.3, 126.2, 108.6, 51.7, 50.8, 47.7, 43.0, 31.2, 16.1; HRMS(ESI): calcd. for $C_{29}H_{29}N_2O_4^+$ (M + H$^+$): 469.2122; found: 469.2102.

Acknowledgements

We gratefully acknowledge the University of Ferrara (fondi FAR) for financial support. Thanks are also given to Paolo Formaglio for NMR experiments and to Tatiana Bernardi for MS analysis.

Keywords: acylation • carbenes • dihydropyrimidines • organocatalysis • oxidation

[1] Selected reviews: a) S. J. Ryan, L. Candish, D. W. Lupton, *Chem. Soc. Rev.* **2013**, *42*, 4906-4917; b) M. N. Hopkinson, C. Richter, M. Schedler, F. Glorius, *Nature* **2014**, *510*, 485-496; c) D. M. Flanigan, F. Romanov-Michailidis, N. A. White, T. Rovis, *Chem. Rev.* **2015**, *115*, 9307-9387; d) X.-Y. Chen, Q. Liu, P. Chauhan, D. Enders, *Angew. Chem. Int. Ed.* **2018**, *57*, 3862-3873; *Angew. Chem*. **2018**, *130*, 3924-3935; e) M. Zhao, Y.-T. Zhang, J. Chen, L. Zhou, *Asian J. Org. Chem.* **2018**, *7*, 54-69.

[2] Selected reviews: a) H. U. Vora, P. Wheeler, T. Rovis, *Adv. Synth. Catal.* **2012**, *354*, 1617-1639; b) C. E. I. Knappke, A. Imami, A. J. von Wangelin, *ChemCatChem* **2012**, *4*, 937-941; c) S. De Sarkar, A. Biswas, R. C. Samanta, A. Studer, *Chem. Eur. J.* **2013**, *19*, 4664-4678; d) J. Mahatthananchai, J. W. Bode, *Acc. Chem. Res.* **2014**, *47*, 696-707; e) M. H. Wang, K. A. Scheidt, *Angew. Chem. Int. Ed.* **2016**, *55*, 14912-14922; *Angew. Chem.* **2016**, *128*, 15134-15145.

[3] For recent reviews, see: a) Z. Wang, D. Pan, T. Li, Z. Jin, *Chem. Asian J.* **2018**, *13*, 2149-2163; b) C. De Risi, O. Bortolini, G. Di Carmine, D. Ragno, A. Massi, *Synthesis* **2019**, *51*, 1871-1891.

[4] K. Lee, H. Kim, J. Hong, *Angew. Chem. Int. Ed.* **2012**, *51*, 5735-5738; *Angew. Chem.* **2012**, *124,* 5833-5836.

[5] G. Di Carmine, D. Ragno, A. Brandolese, O. Bortolini, D. Pecorari, F. Sabuzi, A. Mazzanti, A. Massi, *Chem. Eur. J.* **2019**, *25*, 7469-7474.

[6] D. Ragno, G. Di Carmine, A. Brandolese, O. Bortolini, P. P. Giovannini, G. Fantin, M. Bertoldo, A. Massi, *Chem. Eur. J.* **2019**, *25*, 14701-14710.

[7] a) J. W. Bode, S. S. Sohn, *J. Am. Chem. Soc.* **2007**, *129*, 13798-13799; b) H. U. Vora,T. Rovis, *J. Am. Chem. Soc.* **2007**, *129*, 13796-13797; c) P.-C. Chiang, Y. Kim, J. W. Bode, *Chem. Commun.* **2009**, 4566-4568; d) S. De Sarkar, A. Studer, *Org. Lett.* **2010**, *12*, 1992-1995; e) M. Binanzer, S.-Y. Hsieh, J. W. Bode, *J. Am. Chem. Soc.* **2011**, *133*, 19698-19701; f) S. Iwahana, H. Iida, E. Yashima, *Chem. Eur. J.* **2011**, *17*, 8009-8013; g) B. Zhang, P. Feng, Y. Cui, N. Jiao, *Chem. Commun.* **2012**, *48*, 7280-7282; h) P. Wheeler, H. U. Vora, T. Rovis, *Chem. Sci.* **2013**, *4*, 1674-1679; i) C. A. Gondo, J. W. Bode, *Synlett* **2013**, *24*, 1205-1210; j) R. W. M. Davidson, M. J. Fuchter, *Chem. Commun.* **2016**, *52*, 11638-11641; k) R. A. Green, D. Pletcher, S. G. Leach, R. C. D. Brown, *Org. Lett.* **2016**, *18*, 1198-1201; l) S. Premaletha, A. Ghosh, S. Joseph, S. R. Yetra, A. T. Biju, *Chem. Commun.* **2017**, *53*, 1478-1481; m) V. Kumar, S. J. Connon, *Chem. Commun.* **2017**, *53*, 10212-10215.

[8] a) N. T. Reynolds, J. Read de Alaniz, T. Rovis, *J. Am. Chem. Soc.* **2004**, *126*, 9518-9519; b) S. Dong, M. Frings, D. Zhang, Q. Guo, C. G. Daniliuc, H. Cheng, C. Bolm, *Chem. Eur. J.* **2017**, *23*, 13888-13892.

[9] a) G.-Q. Li, Y. Li, L. Dai, S. You, *Org. Lett.* **2007**, *9*, 3519-3521; b) N. Duguet, C. D. Campbell, A. M. Z. Slawin, A. D. Smith, *Org. Biomol. Chem.* **2008**, *6*, 1108-1113; c) K. Thai, L. Wang, T. Dudding, F. Bilodeau, M. Gravel, *Org. Lett.* **2010**, *12*, 5708-5711; d) C. Zheng, X. Liu, C. Ma, *J. Org. Chem.* **2017**, *82*, 6940-6945.

[10] a) S. Dong, M. Frings, H. Cheng, J. Wen, D. Zhang, G. Raabe, C. Bolm, *J. Am. Chem. Soc.* **2016**, *138*, 2166-2169; b) A. Porey, S. Santra, J. Guin, *Asian J. Org. Chem.* **2016**, *5*, 870-873.

[11] M. Wang, Z. Huang, J. Xu, Y. R. Chi, *J. Am. Chem. Soc.* **2014**, *136*, 1214-1217.

[12] a) L. Ta, H. Sundeń, *Chem. Commun.* **2018**, *54*, 531-534; b) L. Ta, A. Axelsson, H. Sundeń, *J. Org. Chem.* **2018**, *83*, 12261-12268.

[13] a) J. A. Joule, K. Mills, Heterocyclic Chemistry; 4th ed.; Blackwell: Oxford, **2000**; b) T. Eicher, S. Hauptmann, The Chemistry of Heterocycles; Wiley-VCH: Weinheim, **2003**; c) A. R. Katrizky, A. F. Pozharskii, Handbook of Heterocyclic Chemistry; 2nd ed.; Pergamon: Amsterdam, **2000**.

[14] a) C. O. Kappe, *Eur. J. Med. Chem.* **2000**, *35*, 1043-1052; b) J.-P. Wan, Y. Pan, *Mini-Rev. Med. Chem.* **2012**, *12*, 337-349.

[15] B. E. Evans, K. E. Rittle, M. G. Bock, R. M. DiPardo, R. M. Freidinger, W. L. Whitter, G. F. Lundell, D. F. Veber, P. S. Anderson, R. S. L. Chang, V. J. Lotti, D. J. Cerino, T. B. Chen, P. J. Kling, K. A. Kunkel, J. P. Springer, J. Hirshfield, *J. Med. Chem.* **1988**, *31*, 2235-2246.

[16] For reviews, see: a) L.-Z. Gong, X.-H. Chen, X.-Y. Xu, *Chem. Eur. J.* **2007**, *13*, 8920-8926; b) Suresh, J. S. Sandhu, *ARKIVOC*, **2012**, 66-133; c) M. M. Heravi, S. Asadi, B. M. Lashkariani, *Mol. Diversity* **2013**, *17*, 389-407; d) E. Marcantoni, M. Petrini, *Adv. Synth. Catal.* **2016**, *358*, 3657-3682; e) H. Nagarajaiah, A. Mukhopadhyay, J. N. Moorthy, *Tetrahedron Lett.* **2016**, *57*, 5135-5149; f) M. M. Heravi, R. Moradi, L. Mohammadkhani, B. Moradi, *Mol. Diversity* **2018**, *22*, 751-767.

[17] a) B. Schnell, W. Krenn, K. Faber, C.O. Kappe, *J. Chem. Soc., Perkin Trans. 1* **2000**, 4382-4389; b) B. Schnell, U. T. Strauss, P. Verdino, K. Faber, C. O. Kappe, *Tetrahedron: Asymmetry* **2000**, *11*, 1449-1453; c) D. R. Sidler, N. Barta, W. Li, E. Hu, L. Matty, N. Ikemoto, J. S. Campbell, M. Chartrain, K. Gbewonyo, R. Boyd, E. G. Corley, R. G. Ball, R. D. Larsen, P. J. Reider, *Can. J. Chem.* **2002**, *80*, 646-652; d) Poonam, A. K. Prasad, C. Mukherjee, G. Shakya, G. K. Meghwanshi, J. Wengel, R. K. Saxena, V. S. Parmar, *Pure Appl. Chem.* **2005**, *77*, 237-243; e) A. K. Prasad, C. Mukherjee, S. K. Singh, R. Brahma, R. Singh, R. K. Saxena, C. E. Olsen, V. S. Parmar, *J. Mol. Catal. B: Enzym.* **2006**, *40*, 93-100.

[18] a) K. S. Atwal, G. C. Rovnyak, S. D. Kimball, D. M. Floyd, S. Moreland, B. N. Swanson, J. Z. Gougoutas, J. Schwartz, K. M. Smillie, M. F. Malley, *J. Med. Chem.* **1990**, *33*, 2629-2635; b) G. C. Rovnyak, K. S. Atwal, A. Hedberg, S. D. Kimball, S. Moreland, J. Z. Gougoutas, B. C. O'Reilly, J. Schwartz, M. F. Malleys, *J. Med. Chem.* **1992**, *35*, 3254-3263.

[19] J. C. Barrow, P. G. Nantermet, H. G. Selnick, K. L. Glass, K. E. Rittle, K. F. Gilbert, T. G. Steele, C. F. Homnick, R. M. Freidinger, R. W. Ransom, P. Kling, D. Reiss, T. P. Broten, T. W. Schorn, R. S. L. Chang, S. S. OMalley, T. V. Olah, J. D. Ellis, A. Barrish, K. Kassahun, P. Leppert, D. Nagarathnam, C. Forray, *J. Med. Chem.* **2000**, *43*, 2703-2718.

[20] a) C. O. Kappe, *Tetrahedron,* **1993**, *49*, 6937-6963; b) H. Namazi, Y. R. Mirzaei, H. Azamat, *J. Heterocycl. Chem.* **2001**, *38*, 1051-1054; c) D. Dallinger, N. Yu. Gorobets, C. O. Kappe, *Org. Lett.* **2003**, *5*, 1205-1208.

[21] a) O. Bortolini, C. Chiappe, M. Fogagnolo, P. P. Giovannini, A. Massi, C. S. Pomelli, D. Ragno, *Chem. Commun.* **2014**, *50*, 2008-2011; b) O. Bortolini, C. Chiappe, M. Fogagnolo, A. Massi, C. S. Pomelli, *J. Org. Chem.* **2017**, *82*, 302- 312; c) G. Di Carmine, D. Ragno, O. Bortolini, P. P. Giovannini, A. Mazzanti, A. Massi, M. Fogagnolo, *J. Org. Chem.* **2018**, *83*, 2050-2057; d) A. Brandolese, D. Ragno, G. Di Carmine, T. Bernardi, O. Bortolini, P. P. Giovannini, O. Ginoble Pandoli, A. Altomare, A. Massi, *Org. Biomol. Chem.* **2018**, *16*, 8955-8964; e) D. Ragno, A. Brandolese, D. Urbani, G. Di Carmine, C. De Risi, O. Bortolini, P. P. Giovannini, A. Massi, *React. Chem. Eng.* **2018**, *3*, 816-825.

[22] For selected examples of NHC catalyzed reactions in the presence of a Lewis acid additive, see: a) D. E. A. Raup, B. Cardinal-David, D. Holte, K. A. Scheidt, *Nat. Chem.* **2010**, *2*, 766-771; b) D. T. Cohen, K. A. Scheidt, *Chem. Sci.* **2012**, *3*, 53-57; c) J. Mo, X. Chen, Y. R. J. Chi, *J. Am. Chem. Soc.* **2012**, *134*, 8810-8813; d) J. Dugal-Tessier, E. A. O'Bryan, T. B. H. Schroeder, D. T. Cohen, K. A. Scheidt, *Angew. Chem. Int. Ed.* **2012**, *51*, 4963-4967; *Angew. Chem.* **2012**,*124*, 5047-5051; e) Y. Zhang, Y. Lu, W. Tang, T. Lu, D. Du, *Org. Biomol. Chem.* **2014**, *12*, 3009-3015; f) S. Bera, R. C. Samanta, C. G. Daniliuc, A. Studer, *Angew. Chem. Int. Ed.* **2014**, *53*, 9622-9626; *Angew. Chem.* **2014**,*126*, 9776-9780.

[23] J. Piera, J.-E. Bäckvall, *Angew. Chem. Int. Ed.* **2008**, *47*, 3506-3523; *Angew. Chem.* **2008**, *120*, 3558-3576.

[24] a) A. Axelsson, A. Antoine-Michard, H. Sundeń, *Green Chem.* **2017**, *19*, 2477-2481. For a selected example of direct use of air as oxidant, see: b) D. Xie, D. Shen, Q. Chen, J. Zhou, X. Zeng, G. Zhong, *J. Org. Chem,* **2016**, *81*, 6136-6141.

[25] K. Singh, K. Singh, H. Kaur, *Tetrahedron*, **2012**, *68*, 6169-6176.

[26] N. D. Zakusilo, D. S. Ryabukhin, I. A. Boyarskaya, O. S. Yuzikhin, A. V. Vasilyev, *Tetrahedron*, **2015**, *71*, 102-108.

[27] a) N. A. White, T. Rovis, *J. Am. Chem. Soc.* **2014**, *136*, 14674-1467 ; (*b*) D. A. Di Rocco, T. Rovis, *J. Am. Chem. Soc.* **2012**, *134*, 8094-8097.

[28] D. B. Zlatković, N. S. Radulović, *RSC Adv.* **2016**, *6*, 115058-115067.

[29] a) N. October, N. D. Watermeyer, V. Yardley, T. J. Egan, K. Ncokazi, K. Chibale, *ChemMedChem* **2008**, *3*, 1649-1653; b) K. Singh, D. Arora, D. Falkowski, Q. Liu, R. S. Moreland, *Eur. J. Org. Chem.* **2009**, 3258-3264; c) S. Lou, B. M. Taoka, A. Ting, S. E. Schaus, *J. Am. Chem. Soc.* **2005**, *127*, 11256-11257.

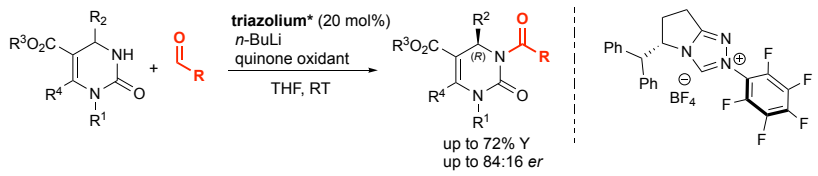
[30] H. Salehi, Q.-X. Guo, *Chin. J. Chem*. **2005**, *23*, 91-97.

[31] A. A. A. Abdel-Fattah, *Synthesis* **2003**, *15*, 2358-2362.

WILEY-VCH

FULL PAPER

Entry for the Table of Contents



NHC-catalysis under oxidative conditions is an effective synthetic platform for the production of enantioenriched biologically relevant N3-acylated 3,4-dihydropyrimidin-2-(1*H*)-ones (DHPMs, Biginelli products)

Key Topic: Oxidative Acylation

Institute and/or researcher Twitter usernames: ((optional))