N-Alkoxyacrylamides in Domino Reactions: Catalytic and Stereoselective Access to δ-Lactams

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Philippe Champetter,[a] Omar Castillo-Aguilera,[a] Catherine Taillier,[a] Jean-François Brière,[b] Vincent Dalla,[a] Sylvain Oudeyer[b] and Sébastien Comesse*[a]

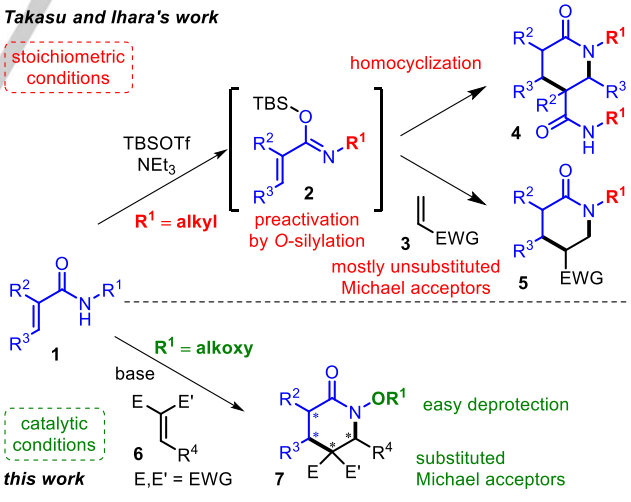
Dedication ((optional))

Abstract: The first domino aza-Michael/intramolecular-Michael reaction employing acrylamides as key ambivalent partners for the synthesis of δ-lactams is presented. It has been shown that the desired reactivity is contingent to the presence of an *N*-alkoxy group within the acrylamides. Thus, in a base-catalyzed process that operates under mild conditions, *N*-alkoxyacrylamides are readily converted into polysubstituted δ-lactams in good yields with good to excellent stereocontrol.

Introduction

Aza-Michael reaction is a powerful tool for the stereoselective synthesis of aza-heterocycles.[1] Telescoping these C-N bond forming reactions with a ring-closure event in a domino fashion,[2] based on the so-called aza-Michael-Induced Ring Closure (aza-MIRC) sequence, provides appealing opportunities for chemistry enhancement, as illustrated by the straightforward syntheses of numerous aza-heterocycles.[3] In that context, we hypothesized that an expedient entry to δ-lactam (δ-valerolactam or piperidin-2-one) compounds might be conceivable by a novel aza-MIRC process using bifunctional secondary acrylamide derivatives, which bear both a nucleophilic nitrogen atom and an electrophilic double bond (Scheme 1).[4] Curiously, in spite of their inherent ambivalent reactivity, and promising synthetic potential thereof, acrylamides have been largely neglected as formal dipolar building blocks for the synthesis of nitrogen heterocycles.[5] Thus, to the best of our knowledge, no direct aza-MIRC sequence using acrylamides to synthesize δ-lactams has been described to date.[6] In fact, we are aware of the single but indirect approach developed by Takasu, Ihara and co-workers, which exploits a pre-activated dienic silyl imidate 2 from *N*-alkylacrylamides **1** (Scheme 1, R^1 = alkyl).[7] Although an efficient access to δ-lactams **4** or **5** was demonstrated in this approach, some important drawbacks remained. There is a need for a stoichiometric amount of the expensive and sensitive TBSOTf reagent, and the sequence is limited in most cases to unsubstituted Michael acceptors **3**. Our work plan focuses on the use of the more reactive diactivated Michael acceptors **6**, in conjunction with *N*-alkoxy acrylamides as key reaction partners, to provide a general and expedient entry to lactams **7**. Our reasoning is based on the hypothesis that the *N*-alkoxy amide moiety is expected to positively impact the first stage of the Aza-MIRC process,[8] *i.e.* the aza-Michael reaction (Scheme 1, R^1 = alkoxy).[9] Specifically, the presence of the N-O bond should enhance the nucleophilicity of the nitrogen atom[10] either by an α-effect,[11] an increased acidity of the H-N[12] bond and/or the structural distortion of amide planarity.[13] There are, more-over, other potential interests associated with the presence of *N*-alkoxy group in the resulting lactams **7**, including the easy N-deprotection, as well as possible nucleophilic addi-tions onto this specific amide function to create wider structural diversity.[14] We report herein the successful realization of this cascade reaction design, by showcasing for the first time the use of secondary acrylamide derivatives[6] as a useful dipole-type reagent in the presence of Michael acceptors for the synthesis of highly functionalized δ-lactams in good yields and excellent stereocontrol.

We notably demonstrate that, as expected, the presence of a *N*-alkoxy subunit in the amide components is crucial for reactivity, and allows the cascade reaction to proceed in mild reaction conditions.



Scheme 1. Synthesis of δ-lactams from acrylamides.

Results and Discussion

The screening of the reaction conditions began in CH_3CN with **1a** and **6a** as model substrates. As expected, no reaction occurred in the absence of a base (Table 1, entry 1). Gratifyingly, in the presence of a catalytic amount of K_2CO_3 (20 mol %), the desired domino spiro-product **7a** was isolated in 64% yield

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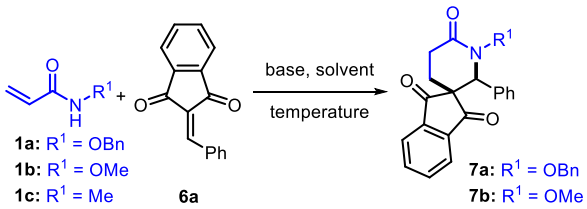
(Table 1, entry 2). Slight increase of the temperature considerably reduced the reaction time without affecting the final yield (Table 1, entries 2 vs 3). Other organic or mineral bases in CH_3CN (Table 1, entries 4-8), or K_2CO_3 in various solvents (Table 1, entries 9-11) were less efficient. Using 20 mol % of K_2CO_3 in CH_3CN at room temperature as optimal reaction conditions, we further evaluated the influence exerted by the R^1 group on the nitrogen atom. The acrylamide **1b** having a methoxy group appeared much more reactive than the one (**1a**) with a bulkier benzyloxy, and led to the desired product **7b** in 84% yield at room temperature in only 6 h instead of 120 h (Table 1, entries 2 vs 12). This striking result cannot be attributed only to steric effects, as attested by the absence of reactivity exhibited by the related *N*-methyl acrylamide **1c**, even at elevated temperature up to 80 °C (Table 1, entry 13). This underlines the decisive input of the N-O bond in this domino process, which is in full agreement with our working hypothesis.

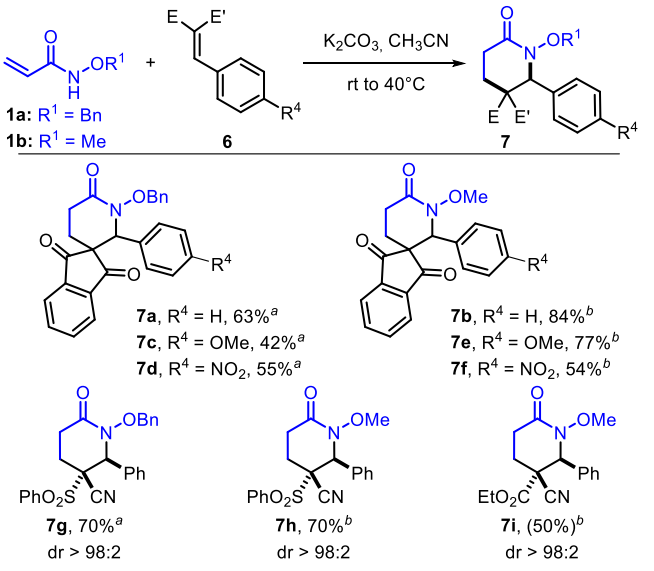
Table 1. Domino aza-Michael/Michael Reaction of Acrylamides **1a-c** with Michal Acceptor **6a**.



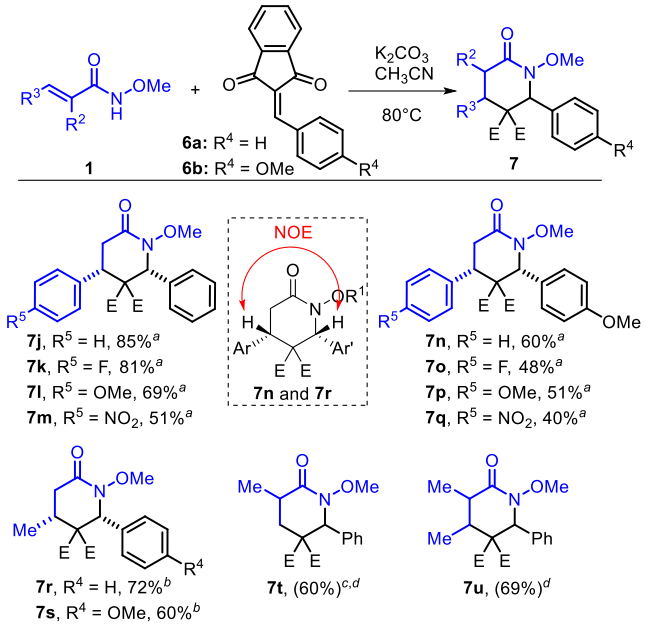
Entry[a]	R^1	Base	solvent/T (°C)	Yield (%)[b]
1	OBn	none	CH_3CN/20	nr[e]
2	OBn	K_2CO_3	CH_3CN/20[c]	64
3	OBn	K_2CO_3	CH_3CN/40	63
4	OBn	Et_3N	CH_3CN/40	24
5	OBn	DBU	CH_3CN/40	55
6	OBn	PhONa	CH_3CN/40	48
7	OBn	NaOAc	CH_3CN/40	nr[e]
8	OBn	$NaHCO_3$	CH_3CN/40	nr[e]
9	OBn	K_2CO_3	THF/40	deg[f]
10	OBn	K_2CO_3	DMF/40	nr[e]
11	OBn	K_2CO_3	$CHCl_3$/40	49
12	OMe	K_2CO_3	CH_3CN/20[d]	84
13	Me	K_2CO_3	CH_3CN/20-80	nr[e]

[a] Typical conditions: Michael acceptor **6a** (0.3 mmol, 1.2 equiv), acrylamide **1a-c** (0.25 mmol, 1 equiv) and base (0.2 equiv) in 2 mL of solvent for 24 h. [b] Isolated yield. [c] Reaction time of 120 h. [d] Reaction time of 6 h. [e] nr: no reaction. [b] deg: degradation of the starting material.

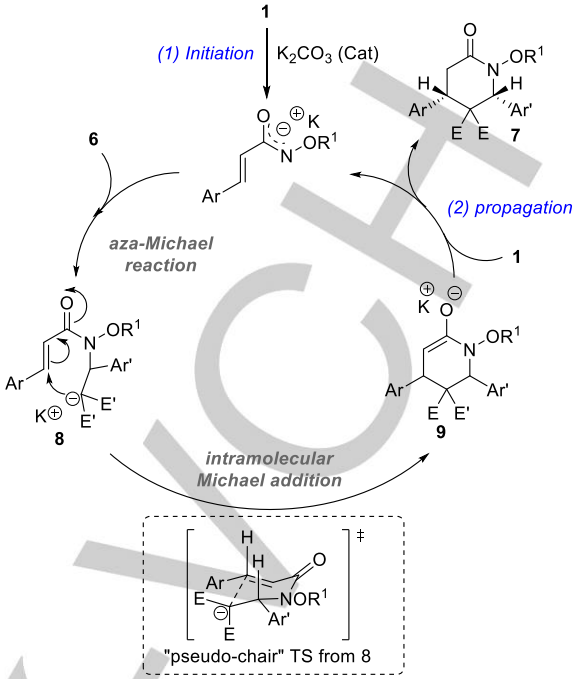
The scope of this domino aza-Michael/Michael reaction was first evaluated by employing a series of diactivated Michael acceptors **6** (Scheme 2).[15] In the case of 1,3-indanedione derivatives, the impact of electron-donating (EDG) or electron-withdrawing (EWG) groups was studied for both *N*-benzyloxy acrylamide **1a** and the *N*-methoxy analog **1b**. Based on our former results detailed in Table 1, reactions involving **1a** (R^1 = Bn) were carried out at 40 °C in order to increase the reaction rate. A para-methoxyphenyl group onto Michael acceptors **6** (R^4 = OMe) led to the formation of the spiro-product **7c** in a 42% yield, lower in comparison to the yield of the phenyl-substituted derivative **7a** (R^4 = H, 63%, Scheme 2). A less pronounced impact on the reaction yield was observed when a para-nitro functional group was present onto the aromatic ring (**7d**, R^4 = NO_2, 55% yield). Reactions involving the more reactive *N*-methoxyacrylamide **1b** were performed at rt as previously stated (see Table 1). In this case, only the presence of an EWG on the phenyl of 1,3-indanediones **6** appeared detrimental to the reaction efficiency (54% yield for the p-$NO_2C_6H_4$ derivative **7f**) while both Ph- and p-$MeOC_6H_4$-substituted indanediones **6a** and **6b** respectively afforded the corresponding δ-lactams in similar good yields (Scheme 2, **7b** *vs* **7e**). At this stage, the impact of the electronic effects on the domino process is somewhat puzzling and thus difficult to interpret. Next, unsymmetrical Michael acceptors were tested in the domino process in order to broaden the scope and to evaluate the stereoselectivity of this methodology. We were rewarded with a good 70% yield when the nitrile-sulphonyl containing Michael acceptor was engaged either with acrylamides **1a** or **1b**. Moreover, both δ-lactams **7g** and **7h** were isolated with a diastereomeric ratio (*dr*) superior than 98:2, demonstrating that the two contiguous stereocenters are fully controlled (Scheme 2).[16] Similarly, the reaction between *N*-methoxyacrylamide **1b** and the ethylcyanoacetate derived Michael acceptor gave product **7i** as a single diastereoisomer in 50% yield.



Scheme 2. Scope of Michael Acceptors **6**. [a]The reaction was carried out at 40°C. [b]The reaction was carried out at rt.



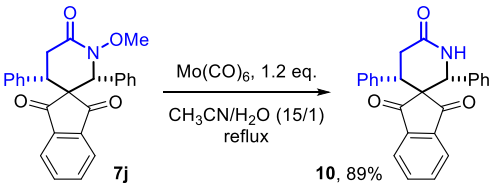
Scheme 3. Scope of acrylamides **1**. [a]*dr* = 4:1. [b]*dr* = 3:2. [c]The reaction was carried out at 60 °C. [d]Only one diastereoisomer was observed on the ^{1}H NMR of the crude product.



Scheme 4. Proposed mechanism.

We further explored the potency of this domino sequence by employing more challenging acrylamides which are substituted at the β or/and α-positions. For this purpose, various acrylamide derivatives of **1** bearing the more reactive *N*-methoxy pendant were reacted with 1,3-indanediones **6a** (R^4 = H) or **6b** (R^4 = OMe) as depicted in Scheme 3. First, with these more decorated acrylamides the reaction required heating at 80 °C in order to observe conversion into domino products **7**. In the case of reactions between Michael acceptor **6a** and *N*-methoxyacrylamides β-substituted with an aryl group, the δ-lactams **7j-m** were isolated in yields ranging from moderate to good (51 - 85%), and a moderate 4:1 dr. A similar stereoselectivity but lower yields (**7n-q** 40-60%) were obtained when Michael acceptor **6b** was employed. These results parallel those obtained previously with the benzyloxy acrylamide **1a** (see Scheme 2), and thus underscore the emergence of an adverse effect caused by the presence of an EWG on the Michael acceptor in the reactions of the least reactive acrylamide partners. Pleasingly, the crotonamide derivative **1** (R^2 = H, R^3 = Me) also displayed a very good reactivity to afford the desired products **7r** and **7s** in good yields albeit with a diminished 3:2 dr. The relative *cis* stereochemistry of products **7** was established thanks to NOE experiments performed on **7n** and **7r** and extrapolated for the other adducts (see Supporting Information, SI). In stark contrast, an excellent stereocontrol (> 98:2)[17] and synthetically useful yields of 60 and 69% for products **7t** and **7u** resulted from the reactions using respectively methacrylamide or its β-methyl analog.

A tentative mechanism for this catalytic domino reaction is proposed in Scheme 4. The sequence is initiated by the aza-Michael reaction between acrylamides **1** and Michael acceptors **6** that would be promoted (initiation step) by deprotonation of **1** by K_2CO_3 to give the corresponding potassium amide. However, a competitive assisted aza-Michael addition (concerted NH deprotonation-N addition process) is also plausible.[18] The resulting aza-Michael adduct **8**[19] then undergoes an intramolecular Michael addition leading to the enolate intermediate **9**, which finally reacts as a base to promote the formation of **8** (propagation step) with the concomitant release of the domino products **7**. The diastereoselectivity outcome of the domino process could be explained by the pseudo-chair like transition state resulting from **8** in which the two hindered aromatic rings are preferentially positioned in pseudo-equatorial positions (Scheme 4, dotted frame).



Scheme 5. Deprotection of δ-Lactam **7j**.

As stipulated above, the interest in the use of *N*-alkoxyacrylamides, besides their pivotal role in the domino reaction, resides on the easy cleavage of the N-O bond of the resulting domino products (Scheme 5).[20] As a matter of fact,

treatment of **7j** with $Mo(CO)_6$ in a refluxing mixture of CH_3CN/H_2O led to the deprotected amide **10** in 89% yield with no detectable epimerization.

Conclusions

In summary, we have developed a novel catalytic and stereoselective domino aza-Michael/Michael reaction that reveals the synthetic potential of readily available of *N*-alkoxyacrylamides for the synthesis of aza-heterocycles. Our new aza-MIRC protocol thus employs a catalytic amount of K_2CO_3 and operates at temperature below 80 °C. It is a fairly general process that allows an efficient access to different δ-lactams (including spiro systems) possessing up to three stereogenic centers with up to perfect level of stereocontrol. Enantioselective syntheses of lactams employing this domino strategy together with the construction of drug-like molecules, are currently underway in our laboratory.

Experimental Section

General Information. All commercially available starting materials have been used without further purification. Acetonitrile (MeCN) was distilled under argon over CaH_2. Melting points (Mp) were determined with a SMP10 capillary melting point apparatus (Stuart) and are uncorrected. FT-IR spectra were recorded with a Perkin-Elmer Frontier. The NMR spectra were recorded on a 300 UltraShield instrument (Bruker) from solutions in $CDCl_3$-*d*, CD_3CN-d_3 or DMSO-d_6 at 300 MHz (^1H) and 75 MHz (^{13}C), respectively, and chemical shifts (δ) are expressed in ppm. High-resolution mass spectra (HRMS) were performed on a 6530 Q-TOF (Agilent System) apparatus and the electrospray ionization (ESI)-MS was measured in positive ionization mode (ESI^+) by using Agilent Jet Stream spectrometer. Thin layer chromatography (TLC) was performed using silica gel analytical plates (F254) of 0.25 mm thickness. The detection on TLC plates was performed by UV light at 254 or 365 nm or using a potassium permanganate staining. All the Michael acceptors **6**[21] and acrylamides **1**[22] were synthesized using known procedures. In the case of diasteromeric mixtures, the diastereomeric ratios were determined on the ^1H NMR of the crude product, the yields given are global yields.

Procedure for the Synthesis of (*E*)-*N*-methoxy-3-(4-nitrophenyl)acrylamide. To a solution of 4-nitrocinnamic acid (6.75 mmol) in CH_2Cl_2 (10mL) was added oxalyl chloride (0.85 mL, 10 mmol) and DMF (5 drops). The resulting mixture was stirred for 1h before methoxyamine hydrochloride (8.3 g, 10 mmol) was added at 0 °C. After stirring at this temperature for 1 hour, pyridine (0.8 mL, 10 mmol) was added dropwise and the reaction mixture was stirred overnight at room temperature. An aqueous solution of hydrogen chloride (20 mL, 1 M) and AcOEt (10 mL) were added to the reaction mixture resulting in the formation of a precipitate. The latter was filtered through a glass filter then washed with diethyl ether to give the desired compound without further purification.

(E)-N-methoxy-3-(4-nitrophenyl)acrylamide. This compound was obtained in 43% yield (650 mg) as a white solid. R_f = 0.23 (Cy/EtOAc, 50/50), Mp = 135-136 °C. IR (ν_{max} / cm^{-1}): 950, 1105, 1345, 1502, 1652. ^1H NMR (300 MHz, DMSO-d_6) δ 3.69 (s, 3H), 6.61 (d, *J* = 15.9 Hz, 1H), 7.60 (d, *J* = 15.6 Hz, 1H), 7.86 (d, *J* = 8.6 Hz, 2H), 8.25 (d, *J* = 8.7 Hz, 2H), 11.50 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 63.8, 123.4, 124.5, 129.2, 137.6, 141.7, 148.1, 162.3. HRMS (ESI^+) m/z: $[M+H]^+$ Calcd for $C_{10}H_{11}N_2O_4$ 223.0719; found 223.0717.

General Procedure for the Synthesis of 7. Michael acceptor derivative **6** (0.3 mmol, 1.2 equiv) and the acrylamide derivative **1** (0.25 mmol, 1 equiv) were dissolved in 2 mL of acetonitrile, and potassium carbonate (7 mg, 0.05 mmol, 0.2 equiv) was added in one portion. The mixture was stirred at room temperature (R^3 = H), 60°C (R^3 = Me) or 80°C (R^3 = Ar), until complete consumption of the acrylamide **1** (monitored by TLC). The reaction mixture was filtered through celite 545 pad *via* a glass filter. The resulting filtrate was concentrated and the residue was purified by flash chromatography (Cy/EtOAc 10:1 to 1:10) to afford the desired product.

*1'-(benzyloxy)-2'-phenylspiro[indene-2,3'-piperidine]-1,3,6'-trione (**7a**).* Following the general procedure, compound **7a** was obtained in 64% yield (66 mg) after stirring at rt for 120h as a yellow solid. R_f = 0.26 (Cy/EtOAc, 80/20), Mp = 209-210 °C. IR (ν_{max} / cm^{-1}): 700, 1221, 1673, 1702, 1739. ^1H NMR (300 MHz, $CDCl_3$) δ 1.92 (ddd, *J* = 14.0, 6.1, 2.6 Hz, 1H), 2.29 (td, *J* = 13.5, 5.3 Hz, 1H), 2.71 (ddd, *J* = 17.3, 5.4, 2.6 Hz, 1H), 3.33 (ddd, *J* = 17.2, 13.0, 6.0 Hz, 1H), 4.71 (d, *J* = 9.7 Hz, 1H), 5.04 (s, 1H), 5.14 (d, *J* = 9.7 Hz, 1H), 6.91-7.01 (m, 2H), 7.10 (s, 5H), 7.15-7.25 (m, 3H), 7.67-7.82 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.3, 29.6, 57.8, 68.5, 76.4, 123.4, 123.5, 128.23, 128.25, 128.3, 128.5, 128.5, 129.3, 134.1, 134.9, 135.9, 136.3, 140.1, 141.1, 168.6, 199.2, 199.3. HRMS (ESI^+) m/z: $[M+H]^+$ Calcd for $C_{26}H_{22}NO_4$ 412.1549; Found 412.1548.

*1'-methoxy-2'-phenylspiro[indene-2,3'-piperidine]-1,3,6'-trione (**7b**).* Following the general procedure, compound **7b** was obtained in 84% yield (70 mg) after stirring at rt for 6h as a yellow solid. R_f=0.26 (Cy/EtOAc, 80/20), Mp = 79-80 °C. IR (ν_{max} / cm^{-1}): 991, 1226, 1667, 1702, 1741. ^1H NMR (300 MHz, $CDCl_3$) δ 1.94 (dd, *J* = 14.1, 3.5 Hz, 1H), 2.36 (td, *J* = 13.5, 5.3 Hz, 1H), 2.67 (ddd, *J* = 17.2, 5.3, 2.5 Hz, 1H), 3.30 (ddd, *J* = 17.2, 13.1, 6.0 Hz, 1H), 3.66 (s, 3H), 5.27 (s, 1H), 6.92-7.23 (m, 5H), 7.60-7.94 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.3, 29.4, 55.0, 57.7, 61.8, 67.1, 123.4, 123.5, 127.9, 128.1, 128.5, 133.9, 136.0, 136.4, 140.1, 141.1, 168.4, 199.2, 199.3. HRMS (ESI^+) m/z: $[M+H]^+$ Calcd for $C_{20}H_{18}NO_4$ 336.1236; Found 336.1237.

*1'-(benzyloxy)-2'-(4-methoxyphenyl)spiro[indene-2,3'-piperidine]-1,3,6'-trione (**7c**).* Following the general procedure, compound **7c** was obtained in 42% yield (47 mg) after stirring at rt for 16h as a yellow solid. R_f = 0.3 (Cy/EtOAc, 80/20), Mp = 200-201 °C. IR (ν_{max} / cm^{-1}): 750, 1210, 1312, 1690, 1710, 1786. ^1H NMR (300 MHz, $CDCl_3$) δ 1.89 (ddd, *J* = 14.0, 6.0, 2.6 Hz, 1H), 2.25 (td, *J* = 13.5, 5.3 Hz, 1H), 2.68 (ddd, *J* = 17.3, 5.4, 2.6 Hz, 1H), 3.29 (ddd, *J* = 17.3, 13.0, 6.0 Hz, 1H), 3.63 (s, 3H), 4.68 (d, *J* = 9.7 Hz, 1H), 5.00 (s, 1H), 5.10 (d, *J* = 9.7 Hz, 1H), 6.61 (d, *J* = 8.8 Hz, 2H), 6.95-7.06 (m, 4H), 7.15-7.24 (m, 3H), 7.66-7.74 (m, 2H), 7.74-7.82 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.3, 29.6, 55.1, 58.0, 67.8, 76.3, 113.5, 123.4, 123.5, 126.0, 128.2, 128.5, 129.3, 129.5, 135.0, 136.0, 136.3, 140.2, 141.1, 159.4, 168.5, 199.3, 199.5. HRMS (ESI^+) m/z: $[M+H]^+$ Calcd for $C_{27}H_{24}NO_5$ 442.1654; Found 442.1651.

*1'-(benzyloxy)-2'-(4-nitrophenyl)spiro[indene-2,3'-piperidine]-1,3,6'-trione (**7d**).* Following the general procedure, compound **7d** was obtained in 55% yield (63 mg) after stirring at rt for 16h as a yellow solid. R_f = 0.25 (Cy/EtOAc, 80/20), Mp = 184-185 °C. IR (ν_{max} / cm^{-1}): 750, 1392, 1510, 1687, 1715, 1791. ^1H NMR (300 MHz, $CDCl_3$) δ 1.91 (ddd, *J* = 14.1, 6.0, 2.7 Hz, 1H), 2.24 (ddd, *J* = 14.1, 12.9, 5.3 Hz, 1H), 2.68 (ddd, *J* = 17.4, 5.2, 2.7 Hz, 1H),

3.19 (ddd, *J* = 17.4, 12.9, 6.0 Hz, 1H), 4.74 (d, *J* = 10.2 Hz, 1H), 5.06 (s, 1H), 5.09 (d, *J* = 10.2 Hz, 1H), 7.00-7.07 (m, 2H), 7.20-7.28 (m, 5H), 7.68-7.75 (m, 3H), 7.80-7.84 (m, 1H), 7.90 (d, J = 8.9 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.7, 29.4, 57.8, 67.2, 76.3, 123.2, 123.7, 123.8, 128.5, 128.9, 129.1, 129.3, 134.7, 136.5, 136.8, 139.8, 140.6, 141.6, 147.7, 167.7, 198.3, 198.4. HRMS (ESI^+) m/z: $[M+H]^+$ Calcd for $C_{26}H_{21}N_2O_6$ 457.1399; Found 457.1401.

*1'-methoxy-2'-(4-methoxyphenyl)spiro[indene-2,3'-piperidine]-1,3,6'-trione (**7e**)*. Following the general procedure, compound **7e** was obtained in 77% yield (65 mg) for stirring at rt for 10h as a yellow solid. R_f = 0.25 (Cy/EtOAc, 60/40), Mp = 104-105 °C. IR (ν_{max} / cm^{-1}): 1248, 1523, 1692, 1710, 1791. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.87 (ddd, *J* = 14.0, 6.0, 2.6 Hz, 1H), 2.28 (ddd, *J* = 13.5, 13.1, 5.4 Hz, 1H), 2.59 (ddd, *J* = 17.2, 5.4, 2.7 Hz, 1H), 3.22 (ddd, *J* = 17.1, 13.0, 6.1 Hz, 1H), 3.58 (s, 6H), 5.19 (s, 1H), 6.56 (d, *J* = 8.9 Hz, 2H), 6.99 (d, *J* = 8.7 Hz, 2H), 7.66-7.83 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.3, 29.4, 55.0, 57.8, 61.8, 66.6, 113.4, 123.4, 123.5, 125.9, 129.2, 136.0, 136.4, 140.1, 141.1, 159.4, 168.3, 199.3, 199.4. HRMS (ESI^+) m/z: $[M+H]^+$ Calcd for $C_{21}H_{20}NO_5$ 366.1341; Found 366.1342.

*1'-methoxy-2'-(4-nitrophenyl)spiro[indene-2,3'-piperidine]-1,3,6'-trione (**7f**)*. Following the general procedure, compound **7f** was obtained in 54% yield (52 mg) after stirring at rt for 10h as a white solid. R_f = 0.25 (Cy/EtOAc, 60/40), Mp = 182-183 °C. IR (ν_{max} / cm^{-1}): 1225, 1518, 1690, 1708, 1785. $_1$H NMR (300 MHz, $CDCl_3$) δ 1.98 (ddd, *J* = 14.1, 5.9, 2.6 Hz, 1H), 2.39 (td, *J* = 13.7, 5.1 Hz, 1H), 2.68 (ddd, *J* = 17.2, 5.1, 2.6 Hz, 1H), 3.24 (ddd, *J* = 17.2, 13.3, 5.9 Hz, 1H), 3.69 (s, 3H), 5.44 (s, 1H), 7.34 (d, *J* = 8.7 Hz, 2H), 7.68-7.84 (m, 3H), 7.86-7.92 (m, 1H), 7.99 (d, *J* = 8.9 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.0, 29.4, 57.7, 61.8, 66.0, 123.4, 123.79, 123.85, 129.0, 136.6, 136.9, 139.8, 140.6, 141.6, 147.8, 168.0, 198.3, 198.7. HRMS (ESI^+) m/z: $[M+H]^+$ Calcd for $C_{20}H_{17}N_2O_6$ 381.1087; Found 381.1101.

*1-(benzyloxy)-6-oxo-2-phenyl-3-(phenylsulfonyl)piperidine-3-carbonitrile (**7g**)*. Following the general procedure, compound **7g** was obtained in 70% yield (81 mg, dr > 98:2) after stirring at 40 °C for 22h as a yellow powder. R_f = 0.26 (Cy/EtOAc, 60/40), Mp = 153-154 °C. IR (ν_{max} / cm^{-1}): 752, 1158, 1330, 1447, 1693. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.36 (dt, *J* = 14.1, 6.7 Hz, 1H), 2.49 (ddd, *J* = 13.9, 7.8, 5.9 Hz, 1H), 2.84 (ddd, *J* = 17.7, 7.8, 6.2 Hz, 1H), 3.01 (ddd, *J* = 17.7, 7.4, 6.0 Hz, 1H), 4.77 (d, *J* = 10.2 Hz, 1H), 5.03 (d, *J* = 10.2 Hz, 1H), 5.41 (s, 1H), 7.18 (dd, *J* = 6.7, 2.8 Hz, 2H), 7.27-7.34 (m, 5H), 7.39 (dd, *J* = 5.1, 2.0 Hz, 3H), 7.59 (t, *J* = 7.8 Hz, 2H), 7.72-7.81 (m, 1H), 7.88 (d, *J* = 9.3 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.9, 28.9, 64.7, 66.7, 77.1, 114.8, 128.3, 128.5, 128.8, 128.9, 129.4, 129.6, 129.9, 130.8, 133.5, 133.9, 134.7, 135.8, 166.0. HRMS (ESI^+) m/z: $[M+Na]^+$ Calcd for $C_{25}H_{22}N_2O_4S.Na$ 469.1198, found 469.1202.

*1-methoxy-6-oxo-2-phenyl-3-(phenylsulfonyl)piperidine-3-carbonitrile (**7h**)*. Following the general procedure, compound **7h** was obtained in 70% yield (65 mg, dr > 98:2) after stirring at rt for 10h as a white solid. This reaction was carried out on a 1 mmol scale and the titled compound was obtained in 66% yield (244 mg). R_f = 0.25 (Cy/EtOAc, 60/40), Mp = 203-204 °C. IR (ν_{max} / cm^{-1}): 718, 1099, 1195, 1385, 1690. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.34 (dt, *J* = 14.6, 7.2 Hz, 1H), 2.47 (dt, *J* = 13.4, 6.6 Hz, 1H), 2.78 (dt, *J* = 17.8, 6.6 Hz, 1H), 3.00 (dt, *J* = 18.0, 7.1 Hz, 1H), 3.73 (s, 3H), 5.57 (s, 1H), 7.32 (d, *J* = 3.3 Hz, 2H), 7.36-7.48 (m, 3H), 7.65 (t, *J* = 7.7 Hz, 2H), 7.80 (t, *J* = 7.5 Hz, 1H), 8.02 (d, J = 7.8 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.7, 28.7, 62.3, 63.2, 66.6, 114.7, 128.0, 129.0, 129.7, 129.9, 130.8, 133.4, 133.9, 135.9, 165.4. HRMS (ESI^+) m/z: $[M+H]^+$ Calcd for $C_{19}H_{19}N_2O_4S$ 371.1066; Found 371.1064.

*1-methoxy-6-oxo-2-phenyl-3-(phenylsulfonyl)piperidine-3-carbonitrile (**7i**)*. Following the general procedure, compound **7i** was obtained in 50% yield (38 mg, dr > 98:2) after stirring at rt for 24h as a white solid. R_f = 0.25 (Cy/EtOAc, 60/40), Mp = 144-145 °C. IR (ν_{max} / cm^{-1}): 751, 1184, 1286, 1701, 1790. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.25 (t, *J* = 7.2 Hz, 3H), 2.29 (dt, *J* = 13.7, 6.7 Hz, 1H), 2.48 (dt, *J* = 13.8, 6.8 Hz, 1H), 2.73 (dt, *J* = 17.8, 6.5 Hz, 1H), 2.90 (dt, *J* = 18.5, 7.2 Hz, 1H), 3.66 (s, 3H), 4.28 (q, *J* = 7.2 Hz, 2H), 5.32 (s, 1H), 7.27-.65 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.8, 26.8, 29.5, 50.7, 62.1, 64.0, 67.0, 115.8, 128.0, 128.7, 129.7, 133.4, 165.4, 166.4. HRMS (ESI^+) m/z: $[M+H]^+$ Calcd for $C_{16}H_{19}N_2O_4$ 303.1345; Found 303.1348.

*1'-methoxy-2',4'-diphenylspiro[indene-2,3'-piperidine]-1,3,6'-trione (**7j**)*. Following the general procedure, a separable 4:1 diastereomeric mixture of compound **7j** was obtained in 85% yield (88 mg) after stirring at 80 °C for 6h. ***Major diastereoisomer:*** yellow solid, R_f = 0.25 (Cy/EtOAc, 60/40), Mp = 214-215 °C. IR (ν_{max} / cm^{-1}): 761, 1253, 1457, 1685, 1705, 1740. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.75 (dd, *J* = 16.0, 4.0 Hz, 1H), 3.68 (s, 3H), 3.84 (dd, *J* = 14.0, 4.1 Hz, 1H), 3.90-4.08 (m, 1H), 5.40 (s, 1H), 6.97-7.04 (m, 8H), 7.11-7.13 (m, 2H), 7.38-7.46 (m, 3H), 7.47-7.53 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 35.3, 44.4, 62.0, 63.3, 67.9, 122.4, 122.7, 128.0, 128.0, 128.2, 128.5, 133.6, 135.4, 135.7, 135.8, 141.3, 142.7, 168.7, 199.3, 199.6. HRMS (ESI^+) m/z: $[M+H]^+$ Calcd for $C_{26}H_{22}NO_4$ 412.1549; Found 412.1547. ***Minor diastereoisomer:*** yellow solid, R_f = 0.18 (Cy/EtOAc, 60/40), Mp = 220-221 °C. IR (ν_{max} / cm^{-1}): 725, 1030, 1248, 1344, 1514, 1720. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.13 (dd, *J* = 17.6, 6.6 Hz, 1H), 3.50 (dd, *J* = 17.9, 10.7 Hz, 1H), 3.75 (s, 3H), 3.78-3.87 (m, 1H), 4.90 (s, 1H), 6.93-7.01 (m, 3H), 7.07 (dd, *J* = 8.1, 3.9 Hz, 2H), 7.33-7.39 (m, 4H), 7.54 (d, *J* = 7.3 Hz, 1H), 7.75-7.84 (m, 3H), 7.97-7.99 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 36.1, 39.7, 60.6, 61.6, 65.7, 123.5, 123.6, 127.8, 127.9, 128.2, 128.4, 128.5, 128.7, 128.8, 128.9, 135.2, 136.2, 136.2, 136.9, 140.7, 141.4, 166.6, 196.2, 199.6.

*4'-(4-fluorophenyl)-1'-methoxy-2'-phenylspiro[indene-2,3'-piperidine]-1,3,6'-trione (**7k**)*. Following the general procedure (0.2 mmol of *N*-alkoxyacrylamide were used), a separable 4:1 diastereomeric mixture of compound **7k** was obtained in 81% yield (69 mg) after stirring at 80 °C for 5h. ***Major diastereoisomer:*** white solid, Rf = 0.23 (Cy/EtOAc, 60/40), Mp = 190-191 °C. IR (ν_{max} / cm^{-1}): 660, 1242, 1509, 1699, 1701, 1738. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.74 (dd, *J* = 15.6, 3.5 Hz, 1H), 3.67 (s, 3H), 3.84 (dd, *J* = 14.1, 3.4 Hz, 1H), 3.90-4.09 (m, 1H), 5.37 (s, 1H), 6.67 (t, *J* = 8.6 Hz, 2H), 6.94 (dd, *J* = 8.8, 5.3 Hz, 2H), 7.01 (d, *J* = 7.2 Hz, 3H), 7.10 (bs, 2H), 7.42-7.56 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 35.4, 43.6, 62.1, 63.2, 68.0, 115.4 (d, *J* = 20.9 Hz), 122.4, 122.7, 128.1, 128.2, 128.5, 129.71 (d, *J* = 8.3 Hz), 131.7 (d, *J* = 3.1 Hz), 133.5, 135.7, 135.9, 141.3, 142.6, 162.1 (d, *J* = 247.6 Hz), 168.6, 199.3, 199.7. HRMS (ESI^+) m/z: $[M+H]^+$ Calcd for $C_{26}H_{21}FNO_4$ 430.1455; Found 430.1472. ***Minor diastereoisomer:*** white solid, Rf = 0.23 (Cy/EtOAc, 60/40), Mp = 197-198 °C. IR (ν_{max} / cm^{-1}): 659, 1224, 1509, 1662, 1705, 1740. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.10 (dd, *J* = 17.7, 6.6 Hz, 1H), 3.49 (dd, *J* = 17.6, 11.5 Hz, 1H), 3.74 (s, 3H), 3.80 (dd, *J* = 11.4, 6.5 Hz, 1H), 4.87 (s, 1H), 6.75 (t, *J* = 8.7 Hz, 2H), 6.95 (dd, *J* = 8.8, 5.3 Hz, 2H), 7.08 (dd, *J* = 6.7, 2.9 Hz, 2H), 7.33-7.42 (m, 3H), 7.64-7.89 (m, 3H), 7.98 (d, *J* = 7.2 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 36.2, 38.7, 60.6, 61.7, 65.7, 115.3 (d, *J* = 20.9 Hz), 123.6, 123.7, 128.2, 128.4, 129.0, 130.3 (d, *J* = 4.0 Hz), 132.7 (d, *J* = 3.3 Hz), 135.1, 136.3, 136.4, 140.6, 141.4, 162.0 (d, *J* = 247.3 Hz), 166.3, 196.2, 199.5.

*1'-methoxy-4'-(4-methoxyphenyl)-2'-(4-nitrophenyl)spiro[indene-2,3'-piperidine]-1,3,6'-trione (**7l**)*. Following the general procedure (0.2 mmol of *N*-alkoxyacrylamide were used), a separable 4:1 diastereomeric mixture of compound **7l** was obtained in 69% yield (61 mg) after stirring at 80 °C for 5h. ***Major diastereoisomer:*** white solid, R_f = 0.25 (Cy/EtOAc, 60/40), Mp = 189-190 °C. IR (ν_{max} / cm^{-1}): 766, 1255, 1511, 1700, 1740. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.74 (dd, *J* = 16.1, 3.9 Hz, 1H), 3.58 (s, 3H), 3.70 (s, 3H), 3.81 (dd, *J* = 14.1, 3.9 Hz, 1H), 3.96 (dd, *J* = 16.1, 14.1 Hz, 1H), 5.38 (s, 1H), 6.52 (d, *J* = 8.8 Hz, 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 6.92-7.18 (m, 5H), 7.39-7.61 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 35.6, 43.6, 55.0, 62.0, 63.4, 67.9, 113.8, 122.4, 122.7, 127.9, 128.0, 128.2, 128.4, 129.1, 133.7, 135.4, 135.7, 141.4, 142.7, 158.9, 168.8, 199.5, 199.9. HRMS (ESI^+) m/z: $[M+H]^+$ Calcd for $C_{27}H_{24}NO_5$ 442.1654; Found 442.1665. ***Minor diastereoisomer:*** white solid, R_f = 0.17 (Cy/EtOAc, 60/40), Mp = 198-199 °C. IR (ν_{max} / cm^{-1}): 765, 1254, 1511, 1700, 1740. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.09 (dd, *J* = 17.7, 6.6 Hz, 1H), 3.47 (dd, *J* = 17.6, 11.2 Hz, 1H), 3.63 (s, 3H), 3.74 (s, 3H), 3.83 (s, 1H), 4.87 (s, 1H), 6.58 (d, *J* = 8.8 Hz, 2H), 6.89 (d, *J* = 8.8 Hz, 2H), 7.09 (dd, *J* = 6.7, 2.9 Hz, 2H), 7.33-7.41 (m, 3H), 7.67-7.76 (m, 2H), 7.80 (td, *J* = 7.2, 2.0 Hz, 1H), 7.97 (d, *J* = 7.2 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 36.3, 38.8, 55.1, 60.8, 61.6, 65.6, 113.8, 114.3, 123.5, 123.6, 128.2, 128.4, 128.9, 129.8, 135.3, 136.1, 136.2, 140.7, 141.5, 158.8, 166.6, 196.4, 199.7.

*1'-methoxy-4'-(4-nitrophenyl)-2'-phenylspiro[indene-2,3'-piperidine]-1,3,6'-trione (**7m**)*. Following the general procedure (0.2 mmol of *N*-alkoxyacrylamide were used), a separable 4:1 diastereomeric mixture of compound **7m** was obtained in 51% yield (47 mg) after stirring at 80 °C for 5h. ***Major diastereoisomer:*** red solid, R_f = 0.23 (Cy/EtOAc, 60/40), Mp = 204-205 °C. IR (ν_{max} / cm^{-1}): 762, 1348, 1524, 1751, 1763, 1775. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.91 (m, 1H), 3.16-3.70 (m, 2H), 3.87 (s, 3H), 4.99 (s, 1H), 6.94 (d, *J* = 8.4 Hz, 2H), 7.04-7.15 (m, 5H), 7.42-7.60 (m, 4H), 7.64 (d, *J* = 8.6 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 31.9, 46.5, 60.6, 62.9, 67.0, 122.6, 122.7, 123.1, 127.9, 128.3, 129.1, 130.2, 131.5, 135.6, 136.2, 140.9, 142.6, 144.4, 146.5, 172.1, 196.7, 198.2. HRMS (ESI^+) m/z: $[M+H]^+$ Calcd for $C_{26}H_{21}N_2O_6$ 457.1399; Found 457.1394. ***Minor diastereoisomer:*** red solid, R_f = 0.15 (Cy/EtOAc, 60/40), Mp = 213-214 °C. IR (ν_{max} / cm^{-1}): 760, 1345, 1528, 1755, 1769, 1785. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.93 (dd, *J* = 14.6, 11.6 Hz, 1H), 3.51 (dd, *J* = 14.7, 5.1 Hz, 1H), 3.70 (dd, *J* = 11.6, 5.1 Hz, 1H), 3.89 (s, 3H), 4.90 (s, 1H), 6.87-6.95 (m, 2H), 6.97 (d, *J* = 8.7 Hz, 2H), 7.30 (dd, *J* = 5.0, 2.2 Hz, 3H), 7.41 (d, *J* = 7.7 Hz, 1H), 7.61-7.72 (m, 3H), 7.82 (td, *J* = 7.5, 1.3 Hz, 1H), 7.96 (d, *J* = 7.7 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 31.9, 43.4, 58.3, 62.9, 65.0, 123.1, 123.3, 123.5, 126.9, 128.9, 129.3, 130.2, 133.2, 136.2, 136.4, 141.0, 141.4, 144.5, 146.5, 168.6, 195.5, 198.4.

*1'-methoxy-2'-(4-methoxyphenyl)-4'-phenylspiro[indene-2,3'-piperidine]-1,3,6'-trione (**7n**)*. Following the general procedure (0.2 mmol of *N*-alkoxyacrylamide were engaged), a separable 4:1 diastereomeric mixture of compound **7n** was obtained in 60% yield (53 mg) after stirring at 80 °C for 5h. ***Major diastereoiso mer:*** white solid, R_f = 0.23 (Cy/EtOAc, 60/40), Mp = 179-180 °C. IR (ν_{max} / cm^{-1}): 753, 1220, 1673, 1702, 1739. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.74 (dd, *J* = 16.1, 3.9 Hz, 1H), 3.59 (s, 3H), 3.67 (s, 3H), 3.81 (dd, *J* = 14.0, 3.9 Hz, 1H), 3.96 (dd, *J* = 16.1, 14.1 Hz, 1H), 5.36 (s, 1H), 6.56 (d, *J* = 8.4 Hz, 2H), 6.89-6.99 (m, 5H), 7.02-7.09 (m, 2H), 7.38-7.52 (m, 3H), 7.53-7.59 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 35.3, 44.4, 55.0, 62.0, 63.4, 67.3, 113.4, 122.4, 122.7, 125.5, 127.9, 128.0, 128.4, 129.5, 135.4, 135.7, 135.8, 141.3, 142.7, 159.4, 168.6, 199.4, 199.9. HRMS (ESI^+) m/z: $[M+H]^+$ Calcd for $C_{27}H_{24}NO_5$ 442.1654; Found 442.1666. ***Minor diastereoisomer:*** white solid, R_f = 0.16 (Cy/EtOAc, 60/40), Mp = 187-188 °C. IR (ν_{max} / cm^{-1}): 763, 1121, 1248, 1623, 1657, 1704. ^{1}H NMR (300 MHz, CDCl3) δ 3.13 (dd, *J* = 17.7, 6.6 Hz, 1H), 3.47 (dd, *J* = 17.6, 10.8 Hz, 1H), 3.58 (m, 1H), 3.74 (s, 3H), 3.81 (s, 3H), 4.87 (s, 1H), 6.87 (d, *J* = 8.7 Hz, 2H), 6.94-7.10 (m, 6H), 7.38 (d, *J* = 6.7 Hz, 1H), 7.74 (dt, *J* = 20.9, 7.1 Hz, 3H), 7.97 (d, *J* = 7.6 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 36.1, 39.8, 55.2, 60.9, 61.6, 65.1, 113.8, 123.5, 123.6, 127.0, 127.8, 128.5, 128.6, 128.7, 128.9, 129.4, 136.1, 136.1, 137.1, 140.8, 141.4, 159.9, 166.5, 196.5, 199.5.

*4'-(4-fluorophenyl)-1'-methoxy-2'-(4-methoxyphenyl)spiro[indene-2,3'-piperidine]-1,3,6'-trione (**7o**)*. Following the general procedure (0.2 mmol of *N*-alkoxyacrylamide were used), a 4:1 diastereomeric mixture of compound **7o** was obtained in 48% yield (47 mg) after stirring at 80 °C for 5h. ***Major diastereoisomer:*** orange solid, R_f = 0.27 (Cy/EtOAc, 60/40), Mp = 179-180 °C. IR (ν_{max} / cm^{-1}): 748, 1245, 1508, 1682, 1701, 1740. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.72 (dd, *J* = 15.5, 3.4 Hz, 1H), 3.58 (s, 3H), 3.66 (s, 3H), 3.81 (dd, *J* = 14.1, 3.4 Hz, 1H), 3.87-3.98 (m, 1H), 5.32 (s, 1H), 6.55 (d, *J* = 8.8 Hz, 2H), 6.66 (t, *J* = 8.6 Hz, 2H), 6.92 (dd, *J* = 8.8, 5.2 Hz, 2H), 7.02 (s, 2H), 7.39-7.64 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 35.4, 43.5, 55.0, 62.0, 63.3, 67.4, 113.4, 115.4 (d, *J* = 21.5 Hz), 122.5, 122.7, 125.4, 129.4, 129.6 (d, *J* = 8.3 Hz), 131.7 (d, *J* = 3.1 Hz), 135.7, 135,9, 141.3, 142.6, 159.4, 162.0 (d, *J* = 247.6 Hz), 168.4, 199.3, 199.9. HRMS (ESI^+) m/z: $[M+H]^+$ Calcd for $C_{27}H_{23}FNO_5$ 460.1560; Found 460.1582. ***Minor diastereoisomer:*** not isolated.

*1'-methoxy-2',4'-bis(4-methoxyphenyl)spiro[indene-2,3'-piperidine]-1,3,6'-trione (**7p**)*. Following the general procedure (0.2 mmol of *N*-alkoxyacrylamide were used), a 4:1 diastereomeric mixture of compound **7p** was obtained in 51% yield (48 mg) after stirring at 80 °C for 5h. **Major diastereoisomer:** white solid, R_f = 0.27 (Cy/EtOAc, 60/40), Mp = 135-136°C. IR (ν_{max} / cm^{-1}): 1249, 1523, 1698, 1702, 1779. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.71 (dd, *J* = 16.1, 3.9 Hz, 1H), 3.56 (s, 3H), 3.58 (s, 3H), 3.66 (s, 3H), 3.77 (dd, *J* = 14.1, 3.8 Hz, 1H), 3.82-4.00 (m, 1H), 5.33 (s, 1H), 6.52 (dd, *J* = 16.9, 8.5 Hz, 4H), 6.86 (d, *J* = 8.7 Hz, 2H), 7.03 (s, 2H), 7.41-7.63 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 35.6, 43.6, 55.0, 62.0, 63.5, 67.3, 113.4, 113.8, 122.4, 122.7, 125.6, 127.9, 129.1, 129.5, 135.5, 135.7, 141.4, 142.7, 158.9, 159.3, 168.7, 199.6, 200.1. HRMS (ESI^+) m/z: $[M+H]^+$ Calcd for $C_{28}H_{26}NO_6$ 472.1760; Found 472.1760. ***Minor diastereoisomer:*** not isolated.

*1'-methoxy-2'-(4-methoxyphenyl)-4'-(4-nitrophenyl)spiro[indene-2,3'-piperidine]-1,3,6'-trione (**7q**)*. Following the general procedure (0.2 mmol of *N*-alkoxyacrylamide were used), a separable 4/1 diastereomeric mixture of compound **7q** was obtained in 40% yield (39 mg) after stirring at 80 °C for 5h. ***Major diastereoisomer:*** red solid, R_f = 0.23 (Cy/EtOAc, 60/40), Mp = 152-153 °C. IR (ν_{max} / cm^{-1}): 725, 1249, 1354, 1513, 1705. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.89 (dd, *J* = 15.8, 13.0 Hz), 3.54 (m, 2H), 3.65 (s, 3H), 3.84 (s, 3H), 4.94 (s, 1H), 6.62 (d, *J* = 8.7 Hz, 2H), 6.92-7.01 (m, 4H), 7.44 (d, *J* = 8.4 Hz, 1H), 7.50-7.60 (m, 3H), 7.63 (d, *J* = 8.5 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 31.9, 46.5, 55.1, 60.7, 62.9, 66.5, 113.7, 122.65, 122.74, 123.1, 123.2, 129.3, 130.2, 135.6, 136.3, 140.9, 142.7, 144.4, 146.5, 159.9, 171.8, 196.9, 198.4. HRMS (ESI^+) m/z: $[M+H]^+$ Calcd for $C_{27}H_{23}N_2O_7$ 487.1505; Found 487.1513. ***Minor diastereoisomer:*** red solid, R_f = 0.23 (Cy/EtOAc, 60/40), Mp = 159-160 °C. IR (ν_{max} / cm^{-1}): 746, 1251, 1344, 1516, 1686, 1702, 1739. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.93 (dd, *J* = 14.8, 11.4 Hz, 1H), 3.51 (dd, *J* = 14.5, 5.1 Hz, 1H), 3.70 (dd, *J* = 11.6, 5.0 Hz, 1H), 3.76 (s, 3H), 3.88 (s, 3H), 4.86 (s, 1H), 6.75-6.88 (m, 4H), 6.98 (d, *J* = 8.3 Hz, 2H), 7.42 (d, *J* = 7.7 Hz, 1H),

7.68 (dd, *J* = 11.1, 7.7 Hz, 3H), 7.81 (t, *J* = 7.4 Hz, 1H), 7.95 (d, *J* = 7.7 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 31.9, 43.4, 55.2, 58.4, 62.9, 64.7, 114.2, 123.1, 123.3, 123.4, 124.9, 128.2, 130.2, 136.2, 136.4, 141.1, 141.4, 144.6, 146.5, 160.2, 168.5, 195.7, 198.4.

*1'-methoxy-4'-methyl-2'-phenylspiro[indene-2,3'-piperidine]-1,3,6'-trione (**7r**)*. Following the general procedure (0.2 mmol of *N*-alkoxyacrylamide were used), a separable 3:2 diastereomeric mixture of compound **7r** was obtained in 72% yield (53 mg) after stirring at 80 °C for 5h. ***Major diastereoisomer:*** yellow solid, R_f = 0.29 (Cy/EtOAc, 60/40), Mp = 134-135 °C. IR (ν_{max} / cm^{-1}): 701, 1247, 1344, 1515, 1702, 1736. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.69 (d, *J* = 6.8 Hz, 3H), 2.56 (dd, *J* = 16.8, 4.8 Hz, 1H), 2.74 (dqd, *J* = 13.4, 6.7, 4.2 Hz, 1H), 3.26 (dd, *J* = 16.8, 13.3 Hz, 1H), 3.63 (s, 3H), 5.20 (s, 1H), 7.01 (bs, 5H), 7.56-7.74 (m, 3H,), 7.74-7.80 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.3, 33.5, 37.3, 62.0, 62.3, 67.9, 122.7, 122.9, 128.0, 128.4, 133.7, 135.8, 136.1, 141.6, 142.8, 168.8, 199.9, 200.3. HRMS (ESI$^+$) m/z: $[M+Na]^+$ Calcd for $C_{21}H_{19}NO_4Na$ 372.1212; Found 372.1211. ***Minor diastereoisomer:*** 15% of the major diastereoisomer as impurity, yellow solid, R_f = 0.21 (Cy/EtOAc, 60/40), Mp = 138-139 °C. IR (ν_{max} / cm^{-1}): 705, 1247, 1592, 1686, 1703, 1738. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.98 (d, *J* = 6.8 Hz, 3H), 2.52 (m, 1H), 2.70 (dd, *J* = 17.2, 7.8 Hz, 1H), 3.13 (dd, *J* = 17.1, 6.0 Hz, 1H), 3.68 (s, 3H), 5.04 (s, 1H), 7.08 (dd, *J* = 6.8, 2.9 Hz, 3H), 7.25 (d, *J* = 2.5 Hz, 2H), 7.85 (d, *J* = 5.9 Hz, 3H), 8.00 (d, *J* = 2.9 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.4, 29.6, 37.3, 60.6, 61.5, 64.5, 123.6, 123.7, 128.2, 128.2, 128.6, 134.9, 136.2, 136.4, 140.8, 141.3, 166.8, 198.0, 199.1.

*1'-methoxy-2'-(4-methoxyphenyl)-4'-methylspiro[indene-2,3'-piperidine]-1,3,6'-trione (**7s**)*. Following the general procedure (0.2 mmol of *N*-alkoxyacrylamide were used), a separable 3:2 diastereomeric mixture of compound **7s** was obtained in 60% yield (45 mg) after stirring at 80 °C for 5h. ***Major diastereoisomer:*** yellow solid, R_f = 0.27 (Cy/EtOAc, 60/40), Mp = 130-131 °C. IR (ν_{max} / cm^{-1}): 710, 1241, 1511, 1681, 1702, 1739. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.69 (d, *J* = 6.7 Hz, 3H), 2.56 (dd, *J* = 16.7, 4.8 Hz, 1H), 2.63-2.84 (m, 1H), 3.24 (dd, *J* = 16.8, 13.2 Hz, 1H), 3.62 (s, 3H), 3.63 (s, 3H), 5.17 (s, 1H), 6.57 (d, *J* = 8.9 Hz, 2H), 6.93-7.15 (m, 2H), 7.47-7.96 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.3, 33.5, 37.3, 55.1, 61.9, 62.4, 67.3, 113.4, 122.7, 122.9, 125.7, 129.3, 135.8, 136.2, 141.7, 142.8, 159.3, 168.7, 200.1, 200.4. HRMS (ESI$^+$) m/z: $[M+H]^+$ Calcd for $C_{22}H_{22}NO_5$ 380.1498; Found 380.1500. ***Minor diastereoisomer:*** 1:1 ratio of starting acrylamide as impurity, yellow solid, R_f = 0.2 (Cy/EtOAc, 60/40), Mp = 138-139 °C. IR (ν_{max} / cm^{-1}): 710, 1246, 1515, 1689, 1708, 1745. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.99 (d, *J* = 6.8 Hz, 3H), 2.49 (q, *J* = 6.8 Hz, 1H), 2.67 (dd, *J* = 17.3, 7.6 Hz, 1H), 3.12 (dd, *J* = 17.2, 5.9 Hz, 1H), 3.74 (s, 3H), 3.77 (s, 3H), 5.02 (s, 1H), 6.77 (d, *J* = 8.5 Hz, 2H), 7.00 (d, *J* = 8.6 Hz, 2H), 7.69-7.91 (m, 3H), 7.91-8.05 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.4, 29.6, 37.2, 55.2, 60.8, 61.5, 63.9, 113.6, 123.6, 123.7, 126.7, 129.4, 136.2, 136.3, 140.8, 141.3, 159.6, 166.8, 198.2, 199.1.

*1'-methoxy-5'-methyl-2'-phenylspiro[indene-2,3'-piperidine]-1,3,6'-trione (**7t**)*. Following the general procedure (0.2 mmol of *N*-alkoxyacrylamide were engaged), compound **7t** was obtained in 60% yield (42 mg, dr > 98:2) after stirring at 60 °C for 5h as a yellow solid (Mp = 181-182 °C), R_f = 0.29 (Cy/EtOAc, 60/40). IR (ν_{max} / cm^{-1}): 704, 1250, 1331, 1662, 1706, 1737. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.43 (d, *J* = 7.2 Hz, 3H), 1.83 (dd, *J* = 14.6, 7.0 Hz, 1H), 2.22 (dd, *J* = 14.5, 11.8 Hz, 1H), 3.21 (dt, *J* = 11.5, 7.0 Hz, 1H), 3.68 (s, 3H), 4.84 (s, 1H), 6.82-7.11 (m, 2H), 7.31-7.41 (m, 3H), 7.76-8.00 (m, 3H), 8.02-8.13 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.4, 29.5, 33.5, 55.6, 61.4, 65.9, 123.8, 124.1, 127.8, 128.4, 128.8, 135.4, 136.4, 136.5, 139.9, 141.0, 169.9, 197.1, 199.8. HRMS (ESI$^+$) m/z: $[M+H]^+$ Calcd for $C_{21}H_{20}NO_4$ 350.1392; Found 350.1388.

*1'-methoxy-4',5'-dimethyl-2'-phenylspiro[indene-2,3'-piperidine]-1,3,6'-trione (**7u**)*. Following the general procedure (0.2 mmol of *N*-alkoxyacrylamide were engaged), compound **7u** was obtained in 69% yield (51 mg, dr > 98:2) after stirring at 80 °C for 5h as a yellow solid (Mp = 178 °C), R_f = 0.31 (Cy/EtOAc, 60/40). IR (ν_{max} / cm^{-1}): 708, 1258, 1362, 1659, 1714, 1749. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.70 (d, *J* = 6.7 Hz, 3H), 1.54 (d, *J* = 7.3 Hz, 3H), 2.69-3.07 (m, 2H), 3.64 (s, 3H), 5.22 (s, 1H), 6.74-7.14 (m, 5H), 7.69 (ddd, *J* = 9.1, 4.8, 3.3 Hz, 3H), 7.79 (dd, *J* = 6.2, 2.7 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.2, 14.0, 35.6, 42.0, 61.8, 63.4, 68.1, 122.8, 127.8, 128.28, 128.33, 133.7, 135.6, 136.0, 141.6, 143.0, 173.3, 199.5, 200.9. HRMS (ESI$^+$) m/z: $[M+H]^+$ Calcd for $C_{22}H_{22}NO_4$ 364.1548; Found 364.1543.

Procedure for the Synthesis of 10. To a solution of **7j** (25 mg, 0.11 mmol, 1.0 eq.) in CH_3CN-H_2O (15/1, 3.5 mL) was added $Mo(CO)_6$ (37 mg, 0.14 mmol, 1.2 eq.) and the reaction was refluxed for 13 h. After cooling to room temperature, the black reaction mixture was concentrated under reduced pressure and the residue was purified by flash chromatography on silica gel (Cy/EtOAc 10:1 to 1:10) to afford the desired product **10**.

*2',4'-diphenylspiro[indene-2,3'-piperidine]-1,3,6'-trione (**10**).* **10** was obtained in 89% yield (36 mg) as a yellow solid (Mp = 204-205 °C), R_f = 0.25 (Cy/EtOAc, 60/40). IR (ν_{max} / cm^{-1}): 778, 1230, 1710, 1775, 1791. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.80 (dd, *J* = 17.9, 5.5 Hz, 1H), 3.60 (dd, *J* = 17.9, 13.4 Hz, 1H), 3.94 (dd, *J* = 13.4, 5.5 Hz, 1H), 5.26 (s, 1H), 6.16 (s, 1H), 6.94-7.10 (m, 8H), 7.16 (d, *J* = 7.7 Hz, 2H), 7.40-7.51 (m, 3H), 7.57 (d, *J* = 8.3 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 34.2, 45.2, 61.2, 61.8, 122.3, 122.5, 127.4, 127.8, 128.2, 128.5, 128.8, 128.9, 135.3, 135.5, 135.7, 136.7, 141.8, 142.8, 171.4, 199.9, 200.3. HRMS (ESI$^+$) m/z: $[M+H]^+$ Calcd for $C_{25}H_{20}NO_3$ 382.1443; Found 382.1448.

Procedure for the Synthesis of Product Resulting from the Reprotonation of 8. This uncyclized product results from the reprotonation of the aza-Michael adduct supporting the two steps sequence of the proposed mechanism. Diethyl 2-(ethoxymethylene)malonate (0.32 mmol, 1.05 eq) was added to a solution of acrylamide (0.30 mmol, 1 eq.) in freshly distilled acetonitrile (2 mL) in a sealed tube. Anhydrous K_2CO_3 (0.3 mmol, 1 eq.) was added to the previous mixture and it was stirred for 48 hours at room temperature under argon. The reaction mixture was filtered and the filtrate was concentrated in vacuo. The resulting residue was purified by flash chromatography on silica gel to provide the desired compound.

(E)-diethyl 2-((N-methoxycinnamamido)(phenyl)methyl) malonate. This compound was obtained in 59% yield (75 mg) as a transparent oil, R_f = 0.3 (Cy/EtOAc, 80/20). IR (ν_{max} / cm^{-1}): 1620, 1665, 1736. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.02 (t, *J* = 6.0 Hz, 3H), 1.27 (t, *J* = 6.0 Hz, 3H), 3.63 (s, 3H), 3.98-4.06 (m, 2H), 4.22-4.27 (m, 2H), 4.65 (d, *J* = 12.0 Hz, 1H), 6.15 (d, *J* = 12.0 Hz, 1H), 6.92 (d, *J* = 15.0 Hz, 1H), 7.33-7.39 (m, 6H), 7.50-7.56 (m, 4H), 7.76 (d, *J* = 15.0 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.7, 14.0, 30.9, 53.5, 61.6, 62.0, 64.8, 116.3, 128.1, 128.5, 128.6, 128.8, 130.0, 134.9, 144.4, 166.4, 167.0, 167.9. HRMS (ESI$^+$) m/z: $[M+Na]^+$ Calcd for $C_{24}H_{27}NNaO_6$ 448.1736; Found: 448.1759.

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[1] a) M. G. Vinogradov, O. V. Turova, S. G. Zlotin, *Org. Biomol. Chem.* **2019**, *17*, 3670-3708; b) A. Yu. Rulev, *Russ. Chem. Bull. Int. Ed.* **2016**, *65*, 1687-1699.

[2] For reviews, see: a) A. El Bouakher, A. Martel, S. Comesse, *Org. Biomol. Chem.* **2019**, *17*, 8467-8485; b) H. Pellissier, *Chem. Rev.* **2013**, *113*, 442-524.

[3] For a recent paper on the subject, see: a) C. Duan, Y. Yao, L. Ye, Z. Shi, Z. Zhao, X. Li, *Tetrahedron* **2018**, *74*, 7179-7185; for our contribution, see: b) R. Le Goff, A. Martel, M. Sanselme, A. M. Lawson, A. Daïch, S. Comesse, *Chem. Eur. J.* **2015**, *21*, 2966-2979; c) I. Allous, S. Comesse, M. Sanselme, A. Daïch, *Eur. J. Org. Chem.* **2011**, 5303-5310; d) S. Comesse, A. Martel, A. Daïch, *Org. Lett.* **2011**, *13*, 4004-4007; e) M. Saber, S. Comesse, V. Dalla, A. Daïch, M. Sanselme, P. Netchitaïlo, *Synlett* **2010**, *2010*, 2197-2201; f) S. Comesse, M. Sanselme, A. Daïch,. *J. Org. Chem.* **2008**, *73*, 5566-5569.

[4] For a review presenting polysubstituted piperidin-2-ones (δ-lactams) exhibiting anti-cancer activities, see: a) G. Liao, D. Yang, L. Ma, W. Li, L. Hu, L. Zeng, P. Wu, L. Duan, Z. Liu, *Eur. J. Med. Chem.* **2018**, *159*, 1-9; for examples of naturally occurring and biologically relevant structures, see: b) E. G. Bowen, D. J. Wardrop, *J. Am. Chem. Soc.* **2009**, *131*, 6062-6063; c) J.-H. Jang, K. Kanoh, K. Adachi, Y. Shizuri, *J. Nat. Prod.* **2006**, *69*, 1358-1360; d) A. De Leon, *Proc. Bayl. Univ. Med. Cent.* **2006**, *19*, 413-416.

[5] For an intramolecular and not catalytic aza-Michael/Michael domino reaction, see: Jin, J.; Qiu, F. G. Total Synthesis of (±)-1-Acetylaspidoalbidine and (±)-1-Methylaspidospermidine. *Adv. Synth. Catal.* **2014**, *356*, 340-346.

[6] For the use of acrylamides in metal-catalyzed domino reactions for the access to δ-lactam derivatives see: a) D. N. Garad, S. B. Mhaske, *J. Org. Chem.* **2019**, *84*, 1863-1870; b) Y. Xu, B. Li, X. Zhang, X. Fan, *Adv. Synth. Catal.* **2018**, *360*, 2613-2620; for an organocatalytic entry into enantioenriched pyrrolidin-2-ones using acrylamide esters as dipolarophile equivalents, see: c) T. Yokosaka, A. Hamajima, T. Nemoto, Y. Hamada, *Tetrahedron Lett.* **2012**, *53*, 1245-1248.

[7] For intermolecular processes employing this strategy, see: a) K. Takasu, N. Nishida, A. Tomimura, M. Ihara, *J. Org. Chem.* **2005**, *70*, 3957-3962; b) K. Takasu, N. Nishida, M. Ihara, *Tetrahedron Lett.* **2003**, *44*, 7429-7432; for intramolecular approaches employing this strategy, see: c) K. Mekouar, Y. Genisson, S. Leue, A. E. Greene, *J. Org. Chem.* **2000**, *65*, 5212-5215; d) M. Suzuki, M. Ihara, *Heterocycles* **2000**, *52*, 1083-1085; e) M. Ihara, Y. Ishida, Y. Tokunaga, C. Kabuto, K. Fukumoto, *J. Chem. Soc., Chem. Commun.* **1995**, 2085-2086.

[8] For a recent example about the synthesis of spiro γ-lactams *via* a domino process employing *N*-alkoxy α-haloamides demonstrating the enhanced reactivity of *N*-alkoxy amides, see: C.-C. Wang, J. Zhou, Z.-W. Ma, X.-P. Chen, Y.-J. Chen, *Org. Biomol. Chem.* **2019**, *17*, 9200-9208.

[9] For a selection of recent organocatalytic conjugate addition of *N*-alkoxy amine derivatives, see : a) Y. K. Chen, M. Yoshida, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2006**, *128*, 9328-9329; b) J. Vesely, I. Ibrahem, R. Rios, G.-L. Zhao, Y. Xu, A. Córdova, *Tetrahedron Lett.* **2007**, *48*, 2193-2198; c) X. Lu, L. Deng, *Angew. Chem. Int. Ed.* **2008**, *47*, 7710-7713;. for some cascade reactions induced by the use of nucleophilic *N*-alkoxy amine derivatives, see : d) Z. Q. He, Q. Zhou, L. Wu, Y. C. Chen, *Adv. Synth. Catal.* **2010**, *352*, 1904-1908; e) C. Appayee, S. E. Brenner-Moyer, *Org. Lett.* **2010**, *12*, 3356-3359.

[10] For an enhanced nucleophilicity of the nitrogen atom of *N*-alkoxyamides, see: M. Yoritate, T. Meguro, N. Matsuo, K. Shirokane, T. Sato, N. Chida, *Chem. Eur. J.* **2014**, *20*, 8210-8216.

[11] J. O. Edwards, R. G. Pearson, *J. Am. Chem. Soc.* **1962**, *84*, 16-24.

[12] The enhanced reactivity could be the result of an increased acidity of the hydrogen onto the nitrogen atom facilitating its deprotonation instead of an α-effect: T. A. Nigst, A. Antipova, H. Mayr, *J. Org. Chem.* **2012**, *77*, 8142-8155.

[13] S. Adachi, N. Kumagai, M. Shibasaki, *Tetrahedron Lett.* **2018**, *59*, 1147-1158.

[14] For a review on the subject, see: T. Sato, M. Yoritate, H. Tajima, N. Chida, *Org. Biomol. Chem.* **2018**, *16*, 3864-3875 and references therein.

[15] We have verified that the use of highly electrophilic Michael acceptors having two EWG-groups is essential to achieve this domino process. Simple enones did not react properly under a set of reaction conditions.

[16] The *cis* relationship between the CN and the phenyl groups were extrapolated from our previous findings regarding domino reactions employing similar Michael acceptors, see references 3e,f.

[17] The relative stereochemistry for **7t** and **7u** was not determined.

[18] A concerted mechanism employing *N*-alkoxyamides and potassium carbonate as a base was recently reported: J. Zhou, H. Zhang, X.-L. Chen, Y.-L. Qu, Q. Zhu, C.-G Feng, Y.-J. Chen, *J. Org. Chem.* **2019**, *84*, 9179-9187.

[19] One product resulting from the reprotonation of **8** was isolated supporting the two steps sequence, see the experimental section and the SI.

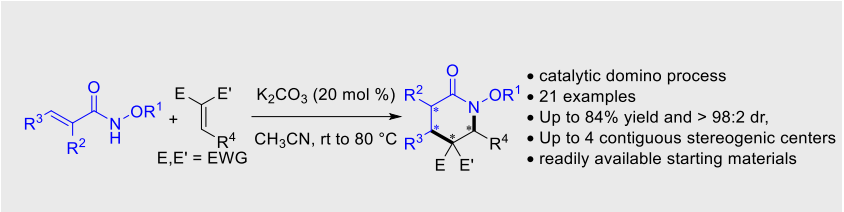
[20] D. J. Wardrop, M. S. Burge, *J. Org. Chem.* **2005**, *70*, 10271-10284.

[21] a) K. B. Manjappa, Y.-T. Peng, W.-F. Jhang, D.-Y. Yang, *Tetrahedron* **2016**, *72*, 853-861; b) C.-J. Lee, C.-N. Sheu, C.-C. Tsai, Z.-Z. Wu, W. Lin, *Chem. Commun.* **2014**, *50*, 5304-5306; c) S. Rajkumar, K. Shankland, J. M. Goodman, A. J. A. Cobb, *Org. Lett.* **2013**, *15*, 1386-1389.

[22] a) Z. Zhou, G. Liu, X. Lu, *Org. Lett.* **2016**, *18*, 5668-5671; b) Z. Hu, X. Tong, G. Liu, *Org. Lett.* **2016**, *18*, 1702-1705; c) M. Jäkel, J. Qu, T. Schnitzer, G. Helmchen, *Chem. Eur. J.* **2013**, *19*, 16746-16755.

Layout 2:

COMMUNICATION



The use of N-alkoxyacrylamides in a domino aza-Michael/intramolecular-Michael reaction for the synthesis of δ-lactams is presented. This base-catalyzed process operates under mild conditions and the polysubstituted aza-heterocycles are isolated in good yields with good to excellent stereocontrol.

Domino reactions

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N-Alkoxyacrylamides in Domino Reactions: Catalytic and Stereoselective Access to δ-Lactams