EurJOC
European Journal of Organic Chemistry

A Journal of
ChemPubSoc Europe

Accepted Article

Title: Atom Economical Catalytic Direct Substitution of N,O-Acetals with Simple Ketones

Authors: Vincent Dalla, Bahria Touati, Mohamed Salah Azizi, Abderrhamane el Bouakher, Catherine Taillier, Sylvain Antoniotti, Elisabet Dunach, Malika Trabelsi-Ayadi, and Raja Ben Othman

To be cited as: *Eur. J. Org. Chem.* 10.1002/ejoc.201700530

Link to VoR: http://dx.doi.org/10.1002/ejoc.201700530

Supported by
ACES Asian Chemical Editorial Society

WILEY-VCH

Atom Economical Catalytic Direct Substitution of *N,O*-Acetals with Simple Ketones

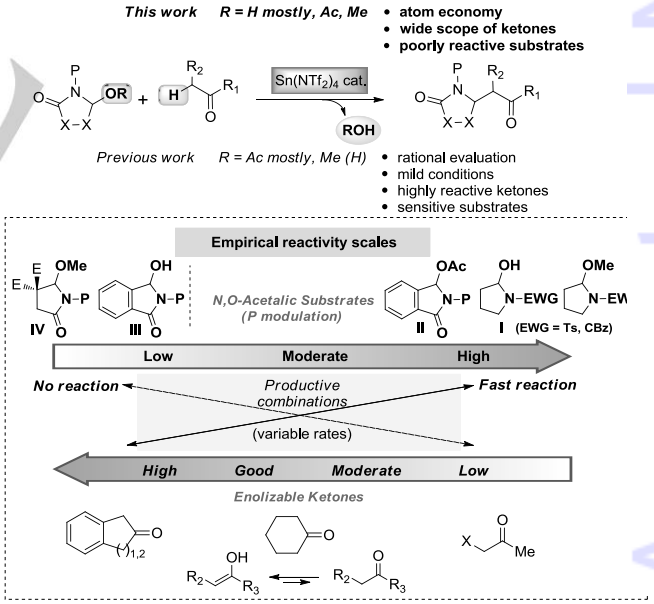
Bahria Touati,[a,c] Abderrahman El Bouakher,[a] Mohamed Salah Azizi,[a,c] CatherineTaillier,[a] Raja Ben Othman,[b] Malika Trabelsi-Ayadi,[c] Sylvain Antoniotti,[d] Elisabet Duñach[d] and Vincent Dalla*[a]

Abstract: A general and powerful catalytic protocol for the direct amidoalkylation of simple enolisable ketones is described using the super Lewis acid $Sn(NTf_2)_4$ as catalyst under thermal conditions. A complete and rational study directed towards the development of efficient conditions for the coupling of a wide range of reaction partner combinations, including the most recalcitrant, is presented. The synthetic potential of the reaction is demonstrated through the use of a large set of both carbonyl and *N,O*-acetalic substrates, providing the corresponding amidoalkylated ketones in 49-99% yields, using very low catalyst loadings (≤ 1 mol %).

Introduction

The direct catalytic amidoalkylation of non pre-activated carbon nucleophiles has been relatively unexplored, mostly with intramolecular arylation (Friedel-Crafts type) reactions and intermolecular couplings with β-keto-esters or β-diketones.[1,2] Besides their synthetic potential for further functionalization, carbonyl motifs are also often encountered in the structure of biologically active compounds. As the need for greener chemical processes increases continuously, the development of efficient, versatile, direct couplings using simple enolisable carbonyl derivatives continues to present a significant synthetic interest. Though major advances have been achieved in recent years for the development of direct catalytic alkylation reactions of ketones and aldehydes,[3-15] most of the contributions that involve racemic or stereoselective S_N1-type processes made use of precursors of highly stabilized carbocations (alcohols or their acetate derivatives or alkyl halides) of carbenium type (*e.g.* benzyl, allyl, indenyl).[5-6] In a number of cases, the use of synergistic catalytic systems intended to promote carbocation formation while simultaneously boosting the nucleophilic character of the carbonyl partner was found to be essential to reach high efficiency and/or selectivity.[5-8] Until recently, only scarce examples of similar reactions involving more reactive carbocations have been described in the literature. [12-15]

In connection with our long-standing interest in catalytic *N*-acyliminium ion chemistry,[16] we have recently started to demonstrate the excellent potential of metallic triflimide-type Lewis superacids,[17] and more particularly of tin(IV) triflimide $Sn(NTf_2)_4$, to promote nucleophilic substitutions of N,O-acetals with a wide range of carbon nucleophiles, including allyltrimethylsilane, silyl enol ethers, active methylene derivatives, and arenes under a remarkably efficient catalytic regime generally requiring ≤ 1 mol % catalyst loading.[16b] Rewardingly, the process was extended even to the most challenging enolisable ketones, which were shown to be suitable nucleophilic partners as illustrated by our description of the first few examples of high temperature (60-70 °C) experiments that were restricted to random combinations of isoindolic hemiaminals and a small set of ketones.



Scheme 1. $Sn(NTf_2)_4$-catalyzed direct α-amidoalkylation reaction of ketones.

We then pursued this study by undertaking a rational design of this transformation at room temperature (rt). This in-depth survey of the reaction under mild reaction conditions was made by a careful individual evaluation of both families of reaction partners, and resulted in the establishment of two orthogonal empirical scales of reactivity, which in turn have

[a] B. Touati, Dr A. El Bouakher, M. S. Azizi, Dr C.Taillier, Dr Pr. V. Dalla, UNIHAVRE, FR 3032 CNRS, URCOM EA3221, 76600 Le Havre, France
25, Rue Philippe Lebon, BP 540, 76058-F. Le Havre (France).
Fax: (+33)2-32-74-43-91
E-mail: vincent.dalla@univ-lehavre.fr
[b] Dr R. Ben Othman,
Ecole supérieure des sciences et de technologie de Hammam Sousse, Rue Lamine Abassi 4011 H. Sousse (Tunisie)
[c] B. Touati, M. S. Azizi, Dr Pr Malika Trabelsi-Ayadi,
Laboratoire d'Application de la Chimie aux Ressources et Substances Naturelles et à l'Environnement-LACReSNE-Faculté des Sciences de Bizerte- 7021, Bizerte
Université de Carthage–Tunisie
[d] Dr S. Antoniotti, Dr E. Duñach
Université Côte d'Azur, C.N.R.S., Institut de Chimie de Nice, Parc Valrose, 06108 - Nice cedex 2, France.
Supporting information for this article is given via a link at the end of the document.

proven to be extremely useful and valuable platforms to develop the reaction in a rational manner (Scheme 1).[16g,18] Considerable advances were thus made during the development of this mild variant of $Sn(NTf_2)_4$-catalyzed direct Mannich-type reaction, not only in terms of selection of the adequate leaving groups to be used inside the various categories of the N,O-acetal substrates, but also in terms of synthetic usefulness. It was indeed found that the reaction had a large number of successful electrophile/nucleophile combinations that could assemble in an efficient way by using only 0.5-2 mol% of catalyst. However, some limitations remained, in particular when dealing with less reactive ketones such as acyclic ones (see reactivity scale in the SI), which were systematically unable to undergo amidoalkylation efficiently. The same held true for the less reactive *N,O*-acetals, a representative example of which being shown in Scheme 1. Moreover, it is worth reminding that only a few atom-economical Mannich couplings making use of hydroxylactams as the electrophilic substrates were effective. This is also a current limitation of the rt protocol that is an additional reason for seeking to improve this tin(IV) triflimidate-based methodology.

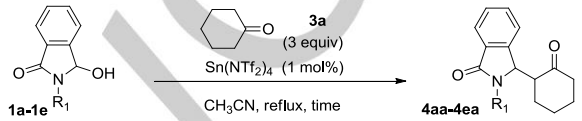
Capitalizing on the valuable information accumulated during our initial study,[16g] we next concentrated on the development of a versatile and powerful direct amidoalkylation protocol, by specifically harnessing the limitations mentioned above, which in turn was expected to push the current limits of the method, *i.e.* ketonic C-nucleophiles of low reactivity and non-activated *N*-acyliminium ion precursors such as hydroxy lactams. We here report the details of the evaluation of a variant of the $Sn(NTf_2)_4$-catalyzed reaction performed under heating that fully fulfilled our expectations. The wide scope of this thermal variant and the complementarity of the two methods were, therefore, firmly established.

Results and Discussion

We started the evaluation of some combinations of reactive partners which were initially found unproductive under mild conditions (Scheme 1).[16g]

The perfect atom-economical α-amidoalkylation of isoindolinic hemiaminals was only possible with 2-indanone and 2-tetralone which appeared outstanding nucleophilic components in our mild variant.[16g,18] Accordingly, we evaluated the same types of ideal coupling with ketones of lower reactivity, paying particular attention to the subunits carried by the nitrogen atom that had shown a propensity to slow down the alkylation process. We started with the amidoalkylation of our model nucleophile cyclohexanone **3a**, which was first examined in refluxing acetonitrile with a range of *N*-substituted isoindolinic hydroxyl lactams **1a-e** of variable reactivities (based on the reactivity trend observed for their acetoxy analogs **2** at rt). Whereas a strong influence of the nitrogen substituent was observed in the reactions at rt, in particular because of the likely interactions of the more metallophilic/Lewis basic of them (*e.g.* isoprenyl, propargyl, 3,4-dimethoxy benzyl, methallyl) with the acidic catalyst, what consequently resulted in significant decrease in reaction output,[16g] rather similar reaction rates were measured in this thermal variant, as shown in Table 1, even with the less reactive substrates **1c-1e** (entries 3-5). In all the cases, every reaction went to completion within 2.5 to 4 h and the corresponding amidoalkylated products **4aa-4ea** were isolated in good to excellent yields (58%-99%) with, in general, either no or modest diastereocontrol.[19]

Table 1. Scope of *N*-protected isoindolinic substrates (from good to low reactivity) in the thermal $Sn(NTf_2)_4$-catalyzed amidoalkylation of cyclohexanone **3a**.



Entry	Substrate	R_1[b]	Product	Time	Yield[a]	d.r.
▪ **More reactive substrates**[b]						
1	**1a**		**4aa**	2.5h	98%	64:36
2	**1b**		**4ba**	4h	99%	54:46
▪ **Less reactive substrates**[b]						
3	**1c**		**4ca**	2.5h	79%[c]	62:38
4	**1d**		**4da**	2.5h	58%[c]	52:48
5	**1e**		**4ea**	2.5h	88%	61:39
6	"	"	"	6h	72%[d]	60:40

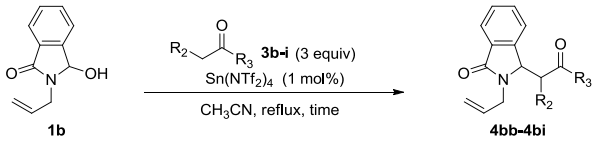
[a] Isolated yields. [b] Based on the reactivity scale established in the room temperature $Sn(NTf_2)_4$-catalyzed amidoalkylation of acetoxy lactam derived from **1b**.[16g] [c] Conversion determined by ^1H NMR analysis of the crude. [d] Reaction run with 0.1 mol% of $Sn(NTf_2)_4$ on a 700 mg scale of **1e**.

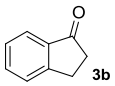
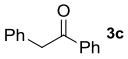
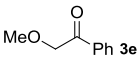
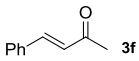
Interestingly, it proved possible to run the reaction with hydroxylactam **1e** on a 700 mg scale, using only 0.1 mol % of catalyst with slightly less erosion of the chemical efficiency and the alkylated cyclohexanone **4ea** was isolated in 72% yield, after 6 h of reaction (entry 6). Since significant differences in ketone reactivity were observed at rt, as anticipated from their respective propensity to equilibrate with their enol form, a set of ketones was next evaluated in the reaction with hydroxylactam **1b** (Table 2). A representative set of results is presented in Table 2.[20]

Ketones with a nucleophilicity close to that of cyclohexanone **3a** were first considered, including the slightly more reactive 1-indanone **3b** or 2-phenylacetophenone **3c**, as well as others slightly weaker ones, such as cyclopentanone **3d**, 2-methoxyacetophenone **1e** and (*E*)-4-phenylbut-3-en-2-one **3f**. All of them gave fast reactions with the corresponding products

4bb-4bf being obtained in yields from 68% to 94% irrespective of their intrinsic reactivity (entries 1-5).

Table 2. Scope of ketones (from good to low reactivity) in the thermal $Sn(NTf_2)_4$-catalyzed amidoalkylation with hydroxy lactam **1b**.

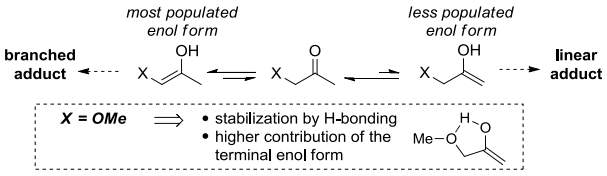


Entry	Ketone	Product	Time	Yield[a]	d.r.
	▪Ketones with good reactivity[b]				
1	 3b	**4bb**	2.5 h	92%	60:40
2	 3c	**4bc**	3 h	68%[c]	68:32
	▪Ketones with moderate reactivity[b]				
3	 3d	**4bd**	2.5 h	94%	60:40
4	 3e	**4be**	3 h	81%	56:44
5	 3f	**4bf**	6 h	93%	
	▪Ketones with low reactivity[b]				
6	 3g	**4bg**	1.5 h	92%	
7	 3h	**4bh**	4 h	95%	
8	 3i	**4bi**	9 h	89%[d],[e]	
9	"	"	16 h	92%[d],[f]	
10	"	"	72 h	80%[f],[g]	

[a] Isolated yield. [b] Based on the reactivity scale established in the room temperature $Sn(NTf_2)_4$-catalyzed amidoalkylation of acetoxy lactam derived from **1b**.[16g] [c] 2 equivalents of ketone **3c** were used. [d] 10 equivalents of acetone **3i** were used to anticipate possible volatility issue. [e] The formation of 10% of the acetamide resulting from a Ritter reaction, was also observed.[21] [f] The reaction was run in toluene. [g] The reaction was run on a half-gram scale of **1b**, in the presence of 0.1 mol% of $Sn(NTf_2)_4$ and 10 equivalents of acetone **3i**.

Gratifyingly, poorly reactive ketones **3g-3i** also underwent smooth reactions affording the coupling product **4bg-4bi** in high yields within short reaction times too (entries 6-8). Even the less reactive acetone **3i** was efficiently amidoalkylated with hydroxylactam **1b** when a longer but still reasonable reaction time (9 h) was applied in the presence of 10 equivalents of acetone, (entry 8).[21] It is worth noting that, in this less favorable case, the formation of a small portion (10%) of the acetamide derived from **1b**, resulting from a Ritter side-reaction with acetonitrile, was also observed.[22] Switching the solvent to toluene was, as expected, found suitable to avoid formation of this side-product, and gave the coupled product in an excellent 92% yield (entry 9).[23] Importantly, this protocol was also successfully applied to the half gram-scale coupling with **3i** under the catalytic influence of only 0.1 mol % of $Sn(NTf_2)_4$ (72 h, 80% isolated yield, entry 10), as a remarkable illustration of the potency of this catalytic direct amidoalkylation methodology.

From this result, we expanded the scope of the reaction to other poorly reactive α-substituted acyclic ketones. To understand the influence of reaction condition parameters on both the efficiency and regiocontrol of the reaction, the catalytic amidoalkylation of 2-chloroacetone **3j** was studied in detail with the model hydroxylactam **1b**. To get a clear comparison, attempts were made over 2 h using 1 mol% of $Sn(NTf_2)_4$. After work-up, conversions and regioselectivities were estimated from ^1H NMR analyses of the crude mixtures by measuring the ratios of adduct formed[24]/**1b** and the proportion of linear and branched regioisomers **4bj** and **5bj**, respectively. As shown in Table 3 (entries 1-5), increasing the temperature from 70 to 90 °C strongly impacted the reaction rate with only a slight influence on the regioselectivity. Conversely, only minor differences were observed when changing the stoichiometry of the ketone from 3 to 2 equivalents.[25] Using the best conditions (3 equiv of ketone **3j**, CH_3CN, heating at 90 °C), only 5 h of reaction time were found necessary to achieve full conversion of the hydroxy lactam **1b** affording the amidoalkylated adducts **4bj** and **5bj** albeit with a slightly lower regioselectivity (ratio **4bj**/**5bj** = 6:1, entry 6). As anticipated, running the reaction in toluene at 110 °C was found to increase the rate of the reaction, which went to completion within only 4 h (entry 7). However, a drop in regiocontrol was again observed, the product being isolated in 91% yield as a 3:1 mixture of regioisomers. We next demonstrated that the alkylation of butan-2-one **3k** and 2-methoxyacetone **3l** was also possible applying these thermal conditions to hydroxy lactam **1b**. Although longer reaction times were required, especially with butan-2-one **3k**, these two reactions led to the formation of the corresponding alkylation products, as mixtures of branched and linear regioisomers **4bj-4bl** and **5bj-5bl**, with a good efficiency and combined isolated yields greater than 85% (entries 8-9). It should be noted that the reaction with ketone **3l** was run at 70 °C with the goal of favoring the formation of the branched regiosiomer **4bl**. A poor regioselectivity of 2.8:1 was however obtained. We interpret this result by a specific and unusual stabilization of the less substituted enol form by H-bonding with the methoxy group. This feature likely contributes in decreasing

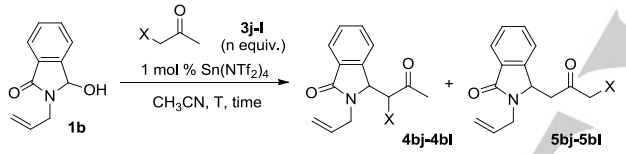


Scheme 2. Proposed rationale of the regiochemical outcome of acyclic ketones as a consequence of the distribution of enol forms.

the energetic gap with the intrinsically more stable trisubstituted enol regioisomer, and thus in influencing the equilibrium position, with, as consequence, delivery of an increased proportion of the linear regioisomer product **5bl** compared with the traditional cases (Scheme 2). To test the limit of the reaction, other challenging transformations also previously beyond our reach were next examined. Scheme 3 outlines a representative selection of results demonstrating the broad applicability and generality of the transformation. We initiated this effort by reinvestigating the reactions of ketones **3m-3p**.

To boost the reactivity of the reaction partners and thus the efficacy of the coupling, the development of more efficient conditions proved in some cases to be essential. On the one hand, the alkylation of the poorly reactive ketones **3m** and **3n** was shown to proceed with good efficiencies, provided that the acetoxylactam **2b** was used (conditions A) instead of its parent heminaminal **1b**, which itself was recognized to be clearly less reactive under general (Brønsted- and Lewis) acid catalysis. The failure of the coupling when using hemiaminal **1b** is somewhat surprising and the reason still remains unclear, given that **1b** gave good results in the reaction with poorly reactive acyclic ketones (see Table 2, entry 8 and Table 3).

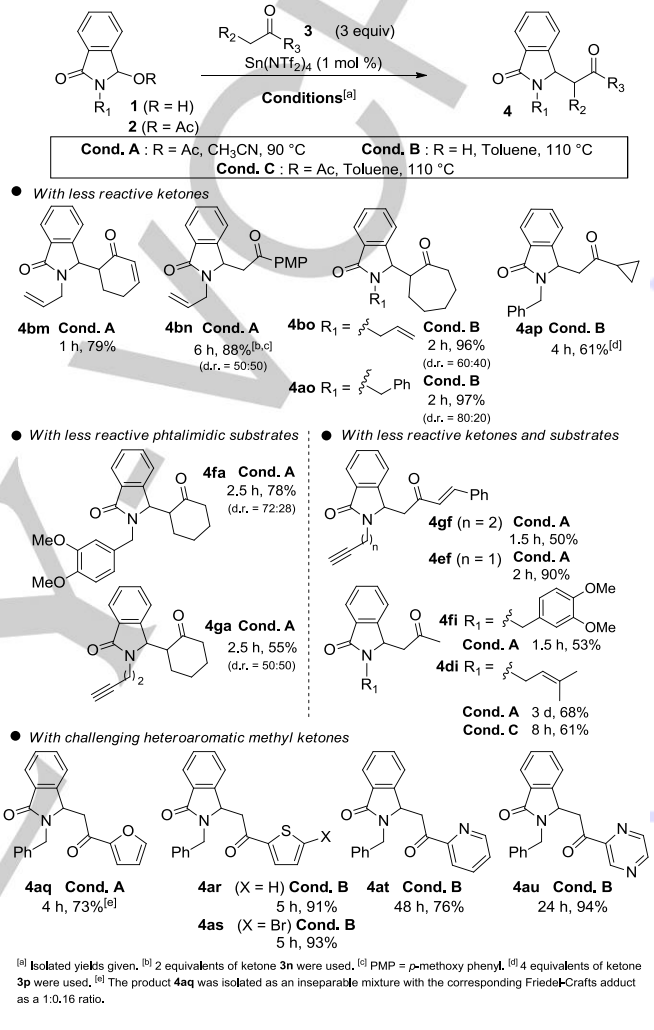
Table 3. $Sn(NTf_2)_4$-catalyzed amidoalkylation of poorly reactive α-substituted acyclic ketones with hydroxy lactam **1b**.



Entry	n	T (°C)[a]	Time	X	Conversion[b]	Ratio **4/5**[b]
1	3	70	2h	Cl (**3j**→**4bj**)	30%[c]	14/1
2	2	80	2h	Cl	38% [c]	12/1
3	3	80	2h	Cl	47% [c]	11/1
4	2	90	2h	Cl	67% [c]	10/1
5	3	90	2h	Cl	71% [c]	11/1
6	3	90	5h	Cl	100% (>99%)	6/1[f],[g]
7[d]	3	110	4h	Cl	100% (91%)[e]	3.1/1[f]
8	3	90	18h	Me (**3k**→**4bk**)	100% (86%)[e]	7.6/1[f],[h]
9	3	70	16h	OMe (**3l**→**4bl**)	100% (98%)[e]	2.8/1[f],[i]

[a] Oil bath temperature. [b] Determined by ^{1}H NMR analysis of the crude product unless otherwise stated. [c] The crude reaction mixture was not purified. [d] Reaction run in toluene. [e] Combined isolated yields. [f] Determined from isolated yields of both regioisomers - the ratio **4/5** on the crude reaction mixtures were not measured. [g] The branched regioisomer was obtained as a mixture of diastereoisomer d_1/d_2 = 72:28. [h] The branched regioisomer was obtained as a mixture of diastereoisomer d_1/d_2 = 66:34. [i] The branched regioisomer was obtained as a mixture of diastereoisomer d_1/d_2 = 55:45.

Conversely and much to our satisfaction, excellent results in terms of reaction rates and yields were obtained when the hemiaminal substrates **1a** or **1b** were engaged with cycloheptanone **3o** and methylcyclopropyl ketone **3p** in refluxing toluene (conditions B), which constitutes a more appealing atom-economical transformation.



[a] Isolated yields given. [b] 2 equivalents of ketone **3n** were used. [c] PMP = *p*-methoxy phenyl. [d] 4 equivalents of ketone **3p** were used. [e] The product **4aq** was isolated as an inseparable mixture with the corresponding Friedel-Crafts adduct as a 1:0.16 ratio.

Scheme 3. Challenging α-amidoalkylation reactions.

Phthalimide-derived acetoxy lactams **2f** and **2g** bearing a 3,4-dimethoxyphenylmethyl and a but-1-ynyl substituent, respectively, featuring the weakest reactivities in standard conditions at room temperature, were also found to be of mandatory use to give coupling products **4fa** and **4ga** with cyclohexanone **3a**, within short reaction times and in satisfactory yields (2.5 h, 55-78% yields, conditions A). Noticeably, the combination of reaction partners displaying both a low reactivity was also found possible as exemplified by the formation of the alkylated ketones resulting from reactions of ketones **3f** and **3i** and *N,O*-acetals **1e** or **2d-2g**. According to the earlier results discussed above, most of these reactions proceeded satisfactorily under conditions A to provide the corresponding

Mannich adducts **4gf**, **4ef** and **4fi** in short reaction times (< 2 h). As anticipated, the alkylation of acetone **3i** with acetate **2d** bearing the "worse" *N*-isoprenyl subunit proved to be even more challenging requiring several days to reach completion. However, running the reaction in refluxing toluene (condition C) turned out to be beneficial with a marked increase in the reaction rate (8 h *versus* 3 d) being observed.

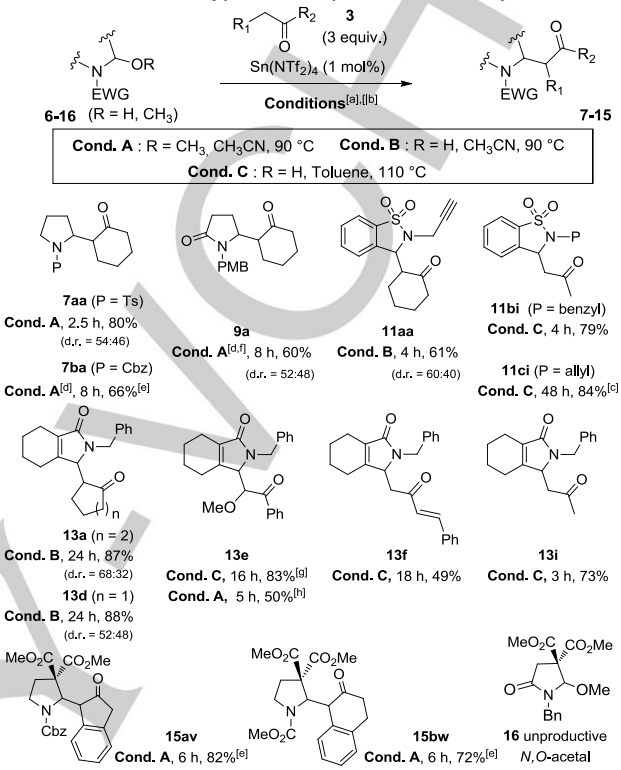
Encouraged by these results, we considered testing whether heteroaromatic methyl ketones could also undergo amidoalkylation in these catalytic conditions. A set of heteroaromatic methyl ketones **3q-u** was then evaluated in the $Sn(NTf_2)_4$-catalyzed alkylation of *N*-benzyl phtalimidic hydroxy and acetoxy substrates **1a** and **2a**. Ketones used appeared to be efficient nucleophiles in the reaction affording the corresponding alkylation products **4aq-4au** in high yields (greater than 73%). Significant differences in reaction rates were however observed, depending on the electronic character of the heteroaromatic ring.

When furane- and thiophene-containing ketones **3q-3s** were used, full conversions of the substrates were obtained in 4 to 5 h, while 48 h and 24 h were respectively required in reactions with the pyridine and pyridazine-derived methylketones **3t** and **3u**. The latter two positive results are quite remarkable and are undoubtedly beyond our expectation, considering the potentially strong coordinating ability of the pyridine and pyridazine rings towards the tin catalyst, with risks of catalyst inhibition. In the coupling of these two ketones **3t-3u**, we observed a counter-intuitive superiority of the *N*-benzyl hydroxylactam **1a** over the generally more reactive acetate **2a**, the latter leading to incomplete conversion whatever the reaction conditions applied, as depicted in Scheme 3.

Besides their increased reactivity towards alkylation, ketones **3q** and **3r** can also undergo competitive Friedel-Crafts (FC) reactions (π-nucleophilic properties of the heteroaromatic ring). No such side-reaction was observed in the thiophene series (as for **3r**) but small proportions of the FC product were repeatedly obtained with 2-acetylfurane **3q**. Optimization (temperature, solvent, substrate, stoichiometry) demonstrated that using conditions A led to an acceptable compromise between α-amidoalkylation and the competitive FC reaction (1:0.16 ratio of alkylated and FC adducts). These results suggest that the FC products increase with the increasing π-nucleophilic properties of the heteroaromatic moiety. Accordingly, when similar reactions were run with 3-acetylindole and 2-acetyl 1-methyl-pyrrole, a poor ketone chemoselectivity was obtained and either formation of a significant amount (the case of NH indole) or formation of the FC product alone (N-Methyl-pyrrole, 88% isolated yield) were respectively observed.[26]

To further evaluate the general applicability of the reaction, we investigated the coupling of non-*iso*-indolinic *N,O*-acetals. In this context, we tried to optimize the coupling involving hemiaminal substrates (hydroxylactams/carbamates) so as to achieve the most atom-economical transformation. In some cases, alkoxy aminals (instead of their hydroxy precursors) were found to be necessary to give a more efficient transformation. Our results are summarized in Scheme 4.

First, the alkylations of cyclohexanone **3a** with *N*-Cbz and *N*-Ts substituted N,O-acetals **6a** and **6b** derived from pyrrolidin-2-one, as well as the succinimidic *N*-PMB N,O-acetal **8** were examined. These substrates are typical examples where alkoxy aminals are



[a] Isolated yields given. [b] Unless otherwise stated, reactions were run on 0.25 mmol scale. [c] Reaction run at 90 °C on 2.5 mmol scale with 0.1 mol% of $Sn(NTf_2)_4$ and 10 equivalents of acetone **3i**. [d] Reaction run at 60 °C. [e] the diasteromeric ration could not be determined. [f] PMB = *p*-methoxy benzyl. [g] The reaction evolved towards the formation of the dienone **13e'** (see SI), resulting from elimination of the methoxy group *E*/*Z* = 62:38. [h] Reaction run from the acetoxy lactam derived from **12**, with 2-methoxy acetophenone **3e** (3 equiv), in the presence of 1 mol% of $Sn(NTf_2)_4$, at 50 °C. Only one diastereoisomer was isolated.

Scheme 4. Generalization to other *N,O*-acetals.

superior to their hydroxy counterparts. Although known to be reactive, this class of *N*-acyliminium precursors was also found to be far less robust than phthalimide derivatives due to their propensity for β-proton loss (E_1 elimination). Consequently, reactions under mild conditions (CH_3CN, rt) were initially run furnishing the corresponding coupled products in variable yields (41-86%).[16g] Interestingly, heating the reactions at 90 °C (for substrate **6a**) and at 60 °C (for substrates **6b** and **8**) was found to increase either the efficiency or the reaction rates of all these reactions without favoring any degradation or side-reaction. Synthetically useful yields ranging from 60% to 80 % were thus obtained within decent reaction times (2.5 h to 8 h). In contrast, most likeky due to a fast β-proton loss in the *N*-acyliminium intermediate, piperidine analogs of **7aa** and **9a** were found to be more difficult substrates (results not shown).[27]

Having found that substrates equipped with a sulfonyl group, as exemplified with the *N*-tosyl pyrrolidine derivative **6b**, were tolerated in this tin(IV) triflimidate-catalyzed direct

amidoalkylation of ketones, we next queried whether the method could also encompass sultam-containing substrates. This was examined by replacing the carbonyl moiety of lactams by a sulfonyl group, giving the opportunity to access a class of valuable products with the sultam pattern in the saccharin series. To our satisfaction, the *N*-propargyl hydroxy sulfonamide **10a** displayed a similar reactivity to its phthalimide analog **1e,** with the reaction of cyclohexanone **3a** being completed in 4 h in refluxing acetonitrile. However, despite full conversion and a clean reaction profile, as confirmed by ^{1}H-NMR analysis of the crude reaction mixture, only 61% of the coupled product **11aa** was obtained after treatment and purification by flash chromatography. We suspect that either the volatility or instability of compound **11aa** accounted for this loss of material. The high reactivity of this class of saccharin derivatives was also demonstrated by the alkylations of substrates**10b** and **10c** with the less reactive acetone **3i**, which proceeded similarly to their phthalimidic analogues (see Table 2 and Scheme 3) in toluene at reflux, to give the corresponding products **11bi** and **11ci** in up to 84 % yields. Satisfyingly, the formation of compound **11ci** was achieved on a 2.5 mmol scale using only 0.1 mol% of the super Lewis acid catalyst, without erosion of the chemical yield.[21]

To push the limit of the reaction further, less reactive *N,O*-acetals as compared to phthalimide-derived substrates were evaluated. The first candidates tested were acetoxy and hydroxy tetrahydrophthalimide derivatives which previously completely failed to react at room temperature with 3 equivalents of cyclohexanone in the presence of 1 mol % of $Sn(NTf_2)_4$.[28] Although the reaction rates were, as anticipated, significantly slower in comparison to the isolindolinic series, this substrate class was adequately tolerated, and even atom-economical reactions of the hemi-aminal substrate **12** provided high yields of the coupling products **12a** and **12d** with cyclohexanone **3a** or cyclopentanone **3d** after 24 h of reaction in refluxing acetonitrile. Having established the feasibility of the reaction with ketones of intermediate reactivity,[18] we continued exploring the scope by varying the carbonyl nucleophile and by choosing some representative examples of poorly reactive partners. The couplings of the tetrahydrophthalimide hemiaminal **12** with 2-methoxyacetophenone **3e**, *trans*-4-phenylbut-2-en-3-one **3f** and acetone **3i** were all found effective when performed in refluxing toluene and the coupled products were isolated in 49% to 83% yield. It should be noted that in the case of α-methoxy acetophenone **3e**, the isolated product was determined to be the conjugated dienone **13'e** resulting from elimination of the methoxy group. However, isolation of the expected coupled product **13e** was shown to be possible when the reaction was run under milder conditions (CH_3CN, 50°C) from the acetoxy lactam **2b** derived from **1b**. Under these conditions, **13e** was isolated in 50% yield.

To complete this investigation and to further highlight the attractive feature of thermal conditions for alkylation, we selected the *N,O*-acetal carbamates **14a** and **14b**, some of the less reactive class of *N,O*-acetals at our disposal. We were delighted to observe that conditions A allowed efficient alkylation of the *N,O*-acetal carbamates **14a** and **14b** that are equipped with two neighboring and deactivating ester groups.[29] However, to circumvent the low reactivity of the electrophilic partners, the use of highly reactive ketones such as 2-indanone **3v** and 2-tetralone **3w** was found to be decisive to afford the corresponding adducts in 72-82% yields. The results presented in this report, and in particular the latter, highlight the complementarity of the thermal alkylative procedure with the previously described mild variant.[16g] We must point out, however, that very challenging transformations continue to resist our method. This is illustrated by the complete lack of reactivity that was observed when combining the two *N,O*-acetal carbamates **14a** and **14b** with less reactive ketones such as cyclohexanone and phenylacetone, or when running the reaction with the pyrrolidinone analog **16** (the least reactive substrate in our collection), whatever the ketones used (see scheme 4).

Conclusions

To summarize, this complete study started from an initial report that presented a few examples of a direct Mannich reaction resulting from the union of a random choice of hydroxylactams and enolisable ketones under Lewis super acid $Sn(NTf_2)_4$ catalysis (1 mol %) in thermal conditions.[16b] Further by going through a comprehensive and rational study of the individual reactivity of each family of reaction partners in mild conditions (at room temperature),[16g] the present paper describes the development of conditions where the combination of Lewis acid catalysis and thermal activation allowed for the effective Mannich coupling of ketones and *N,O*-acetals previously identified as unreactive. The structural requirements of the N,O-acetals (notably the nature of the leaving group being either OAc, OAlkyl or OH) for achieving effective couplings, as well as the best experimental conditions for certain specific and delicate transformations, were determined at catalyst loadings not exceeding 1 mol %. The synthetic benefit of the in-depth study of this direct Mannich-type reaction is a significant increase of an already promising scope, which now accommodates a very wide range of cyclic *N*-acyliminium ion precursors and various ketones with very few limitations. The most prominent results of this study are the execution of highly efficient and atom-economical couplings, with a catalyst loading of only 0.1 mol %, of ketones such as acetone, identified as poorly reactive in our model study[16g] on the one hand, as well as couplings of strongly deactivated *N,O*-acetals by the presence of two electron-withdrawing ester groups nearby to the N,O-acetalic center, on the other hand. The catalytic direct Mannich reactions of N,O-acetals is now well understood, and the potential of the fascinating and easily available $Sn(NTf_2)_4$ Lewis superacid catalyst is also broadened.[30]

Experimental Section

I. General remarks

All reactions were carried out under argon atmosphere in oven-dried glassware with magnetic stirring. Commercially available compounds

were used without further purification. Solvents were distilled prior to use, taking precaution to exclude moisture by refluxing over CaH_2 (CH_3CN, CH_2Cl_2) under inert atmosphere. The tin triflimidate salts were prepared as previously reported[31] and used as such, as solvates. $Sn(NTf_2)_4$ was then used in the form $Sn(NTf_2)_4$.4DMSO or $Sn(NTf_2)_4$.8DMSO.[32] Analytical thin-layer chromatography (TLC) was performed on silica gel 60 with fluorescent indicator UV254 TLC plates. The spots were visualized with UV light (254 nm) and stained with a solution of *p*-anisaldehyde, followed by heating. Flash column chromatography was performed using silica gel 60 (particle size 0.040-0.063 mm) typically using a cyclohexane/ethyl acetate eluent system. FT-IR spectra were recorded with a Perkin-Elmer Frontier. NMR spectra were measured at room temperature on a Bruker Avance 300 spectrometer. 1H NMR spectra were recorded at 300 MHz. Chemical shifts (δ) are reported in ppm using residual solvent peaks as reference ($CHCl_3$: δ 7.26). Data are reported as follows: chemical shift, multiplicity (s: singlet, d: doublet, t: triplet, q: quartet, qui: quintuplet, m: multiplet), coupling constant (J in Hz) and integration. ^{13}C NMR spectra were recorded at 75 MHz using broadband proton decoupling and chemical shifts are reported in ppm using residual solvent peaks as reference ($CHCl_3$: δ 77.0). High resolution mass spectra were recorded on a 6530 Q-TOF (Agilent Technologies). The Q-TOF MS instrument was operated under the following condition: Ion source ESI+ Agilent Jet Stream or APCI both in positive ionization mode. Melting points were measured using open capillary tubes on a Stuart Scientific analyzer and are uncorrected.

General procedure for the $Sn(NTf_2)_4$-Catalyzed direct α-amidoalkylation reactions of ketones: To a solution of *N,O*-acetal in dry solvent (2 mL/mmol of substrate) were successively added a ketone (3 equiv) and $Sn(NTf_2)_4$.xDMSO (x = 4 or 8, 0.1 to 1 mol %) under argon atmosphere. The reaction mixture was then heated at the indicated temperature (*see* also reaction time specified for each compound). The reaction mixture was next allowed to cool to room temperature and directly purified by flash-column chromatography on silica gel, eluting with cyclohexane and ethyl acetate, to afford the corresponding α-amidoalkylated ketone.

2-Benzyl-3-(2-oxocyclohexyl)isoindolin-1-one (4aa): Prepared from hydroxy lactam **1a** (0.25 mmol) and cyclohexanone **3a** (3 equiv) following the general procedure at 90°C in acetonitrile with 1 mol % of $Sn(NTf_2)_4$.4DMSO. Reaction time: 2.5 h. The product was isolated after purification by flash chromatography on silica gel (eluting with Cyclo/EtOAc = 70:30) as a white solid. Yield: 98% (78 mg, mixture of diastereoisomers d_1/d_2 = 64:36). R_f = 0.34 (cyclohexane/EtOAc = 70/30); ^1H NMR (300 MHz, $CDCl_3$, 20°C) δ 0.66 (m, 0.64H, 1H d_1), 0.99-2.06 (m, 5.36H), 2.13-2.54 (m, 2H), 2.73 (m, 0.36H, 1H d_2), 2.88 (m, 0.64H, 1H d_1), 4.43 (d, *J* = 15.3 Hz, 0.64H, 1H d_1), 4.47 (d, *J* = 14.7 Hz, 0.36H, 1H d_2), 4.84 (d, *J* =14.7 Hz, 0.36H, 1H d_2), 5.03 (d, *J* = 15.3 Hz, 0.64H, 1H d_1), 5.18 (s, 0.64H, 1H d_1), 5.43 (s, 0.36H, 1H d_2), 7.15-7.56 (m, 8H), 7.80-7.92 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 20°C) mixture of diastereoisomers δ 24.2, 24.2, 25.3, 25.4, 26.4, 41.6, 42.1, 44.5, 46.0, 50.3, 53.8, 57.9, 58.8, 121.2, 123.6, 123.8, 124.5, 127.3, 127.7, 127.9, 128.2, 128.2, 128.3, 128.8, 128.9, 131.6, 131.8, 132.6, 137.0, 137.7, 143.6, 145.2, 169.0, 169.9, 209.4, 210.6; Data analyses were identical in all respects with our previously reported data.[16g]

2-Allyl-3-(2-oxocyclohexyl)isoindolin-1-one (4ba): Prepared from hydroxy lactam **1b** (0.25 mmol) and cyclohexanone **3a** (3 equiv) following the general procedure at 90°C in acetonitrile with 1 mol % of $Sn(NTf_2)_4$.4 DMSO. Reaction time: 4 h. The product was isolated after purification by flash chromatography on silica gel (eluting with Cyclohexane/EtOAc = 70:30) as a white solid. Yield: 99% (67 mg, mixture of diastereoisomers d_1/d_2 = 46:54). *Rf* = 0.21 (cyclohexane/EtOAc: 70/30); ^1H NMR (300 MHz, $CDCl_3$, 20°C) mixture of diastereoisomers δ 0.76 (m, 0.54H, 1H d_2), 1.20-1.89 (m, 4.46H), 1.98-2.16 (m, 1H), 2.24-2.46 (m, 1H), 2.50-2.66 (m, 1H), 2.82 (m, 0.46H, 1H d_1), 3.01 (m, 0.54H, 1H d_2), 3.72 (dd, *J* = 5.9 and 15.7 Hz, 0.46H, 1H d_1), 3.81 (dd, *J* = 7.0 and 15.8 Hz, 0.54H, 1H d_2), 4.45 (dd, *J* = 6.0 and 15.3 Hz, 0.46 H, 1H d_1), 4.57 (dd, *J* = 5.2 and 15.7 Hz, 0.54H, 1H d_2), 5.08-5.34 (m, 2.54H), 5.47 (s, 0.46H, 1H d_1), 5.78-6.00 (m, 1H), 7.30-7.59 (m, 3H), 7.79-7.88 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 20°C) mixture of diastereoisomers δ 24.3, 24.4, 24.5, 25.2, 26.1, 26.5, 26.9, 41.8, 42.2, 43.1, 44.4, 50.1, 53.9, 57.1, 58.6, 117.7, 118.0, 121.3, 123.5, 123.7, 124.5, 128.2, 128.3, 131.6, 131.7, 132.7, 133.0, 133.2, 143.6, 145.1, 169.2, 169.3, 209.5, 210.7; Data analyses were identical in all respects with our previously reported data.[33]

2-(2-Methylallyl)-3-(2-oxocyclohexyl)isoindolin-1-one (4ca): Prepared from hydroxy lactam **1c** (0.25 mmol) and cyclohexanone **3a** (3 equiv) following the general procedure at 90°C in acetonitrile with 1 mol % of $Sn(NTf_2)_4$.4DMSO. Reaction time: 2.5 h. The product was isolated after purification by flash chromatography on silica gel (eluting with Cyclohexane/EtOAc = 70:30) as a colorless viscous oil. Yield: 79% (56 mg, mixture of diastereoisomers d_1/d_2 = 62:38). R_f = 0.45 (cyclohexane/EtOAc : 70/30); ^1H NMR (300 MHz, $CDCl_3$, 20°C) mixture of diastereoisomers δ 0.66 (m, 0.38H, 1H d_2), 1.08-2.60 (m, 7.62H),1.61 (s, 1.14H, 3H d_2), 1.68 (s, 1.86H, 3H d_1), 2.75 (m, 0.62H, 1H d_1), 2.92 (m, 0.38H, 1H d_2), 3.38 (d, *J* = 15.8 Hz, 0.62H, 1H d_1), 3.51 (d, *J* = 15.4 Hz, 0.38H, 1H d_2), 4.41 (d, *J* = 15.8 Hz, 0.62H, 1H d_1), 4.56 (d, *J* = 15.4 Hz, 0.38H, 1H d_2), 4.59 (s, 0.38H, 1H d_2), 4.77 (s, 0.62H, 1H d_1), 4.81 (s, 0.62H, 1H d_1), 4.84 (s, 0.38H, 1H d_2), 5.17 (s, 0.38H, 1H d_2), 5.36 (s, 0.62H, 1H d_1), 7.36-7.91 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$, 20°C) mixture of diastereoisomers δ 19.9, 20.6, 24.3, 24.5, 24.7, 25.3, 26.1, 26.4, 41.7, 42.1, 46.2, 47.1, 50.0, 53.9, 57.1, 58.1, 111.6, 113.4, 121.3, 123.6, 123.7, 124.5, 128.1, 128.2, 131.5, 131.7, 132.5, 132.6, 140.5, 140.9, 143.5, 145.1, 168.8, 169.3, 209.1, 210.5; Data analyses were identical in all respects with our previously reported data.[16g]

2-(3-Methylbut-2-enyl)-3-(2-oxocyclohexyl)isoindolin-1-one (4da): Prepared from hydroxy lactam **1d** (0.25 mmol) and cyclohexanone **3a** (3 equiv) following the general procedure at 90°C in acetonitrile with 1 mol % of $Sn(NTf_2)_4$.4 DMSO. Reaction time: 2.5 h. The product was isolated after purification by flash chromatography on silica gel (eluting with Cyclohexane/EtOAc = 70:30) as a colorless viscous oil. Yield: 58% (43 mg, mixture of diastereoisomers d_1/d_2 = 52:48). R_f = 0.37 (cyclohexane/EtOAc : 70/30); ^1H NMR (300 MHz, $CDCl_3$, 20°C) mixture of diastereoisomers δ 0.74 (m, 0.48H, 1H d_2), 1.22-1.95 (m, 4.52H), 1.72 (s, 1.44H, 6H d_2), 1.75 (s, 1.56H, 6H d_1), 2.01-2.14 (m, 1H), 2.30-2.47 (m 1H), 2.52-2.64 (m, 1H), 2.80 (dd, *J* = 7.2 and 11.5 Hz, 0.52H, 1H d_1), 2.98 (m, 0.48H, 1H d_2), 3.71 (dd, *J* = 4.6 and 15.4 Hz, 0.52H, 1H d_1), 3.80 (dd, *J* = 7.1 and 15.4 Hz, 0.48H, 1H d_2), 4.43 (dd, *J* = 7.7 and 15.4 Hz, 0.52H, 1H d_1), 4.53 (dd, *J* = 7.1 and 15.4 Hz, 0.48H, 1H d_2), 5.24 (t, *J* = 7.0 Hz, 0.48H, 1H d_2), 5.30 (d, *J* = 2.6 Hz, 0.48H, 1H d_2), 5.35 (m, 0.52H, 1H d_1), 5.47 (s, 0.52H, 1H d_1), 7.30-7.64 (m, 3H), 7.77-7.86 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 20°C) mixture of diastereoisomers δ 18.0 18.1, 24.4, 24.4, 25.4, 25.7, 25.8, 25.8, 26.5, 38.1, 40.1, 41.6, 42.2, 50.4, 53.7, 57.4, 58.4, 119.1, 119.8, 121.1, 123.4, 123.5, 124.4, 128.0, 128.1, 131.3, 131.4, 133.0, 133.1, 135.5, 136.6, 143.5, 145.1, 168.4, 169.0, 209.0, 210.7; Data analyses were identical in all respects with our previously reported data.[16g]

3-(2-Oxocyclohexyl)-2-(prop-2-ynyl)isoindolin-1-one (4ea): Prepared from hydroxy lactam **1e** (0.25 mmol) and cyclohexanone **3a** (3 equiv) following the general procedure at 90°C in acetonitrile with 1 mol % of $Sn(NTf_2)_4$.4 DMSO. Reaction time: 2.5 h. The product was isolated after purification by flash chromatography on silica gel (eluting with Cycloehxane/EtOAc = 70:30) as a yellow viscous oil. Yield: 88% (59 mg, mixture of diastereoisomers d_1/d_2 = 61:39). R_f = 0.18 (cyclohexane/EtOAc : 70/30); ^1H NMR (300 MHz, $CDCl_3$, 20°C) mixture

of diastereoisomers δ 0.76 (m, 0.61H, 1H d_1), 1.21-2.72 (m, 8.39H), 2.88 (m, 0.39H, 1H d_2), 3.23 (m, 0.61H, 1H d_1), 4.18 (d, *J* = 17.9 Hz, 0.61H, 1H d_1), 4.3 (d, *J* = 17.9 Hz, 0.39H, 1H d_2), 4.37 (d, *J* = 17.9 Hz, 0.39H, 1H d_2), 4.61 (d, *J* = 17.9 Hz, 0.61H, 1H d_1), 5.48 (s, 1H), 7.32-7.98 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$, 20°C) mixture of diastereoisomers δ 24.1, 24.5, 25.5, 25.9, 26.5, 26.8, 30.0, 32.2, 41.6, 42.1, 50.3, 53.8, 58.3, 59.0, 71.7, 72.3, 77.8, 79.5, 121.2, 123.5, 123.8, 124.5, 128.2, 128.2, 131.8, 132.0, 132.1, 143.4, 145.0, 168.1, 169.0, 209.4, 210.4; Data analyses were identical in all respects with our previously reported data.[16g]

2-Allyl-3-(2,3-dihydro-1-oxo-1*H*-inden-2-yl)isoindolin-1-one (4bb): Prepared from hydroxy lactam **1b** (0.25 mmol) and 1-indanone **3b** (3 equiv) following the general procedure at 90°C in acetonitrile with 1 mol % of $Sn(NTf_2)_4$.4 DMSO. Reaction time: 2.5 h. The product was isolated after purification by flash chromatography on silica gel (eluting with Cyclohexane/EtOAc = 70:30) as a colorless viscous oil. Yield: 92% (70 mg, mixture of diastereoisomers d_1/d_2 = 60:40). R_f = 0.35 (cyclohexane/EtOAc : 70:30); ^{1}H NMR (300 MHz, $CDCl_3$, 20°C) mixture of diastereoisomers δ 2.07 (dd, *J* = 4.4 and 17.7 Hz, 0.60H, 1H d_1), 2.48 (dd, *J* = 4.8 and 17.7 Hz, 0.40 H, 1H d_2), 2.76 (dd, *J* = 8.0 and 17.7 Hz, 0.40H, 1H d_2), 2.93 (dd, *J* = 8.0 and 17.7 Hz, 0.60H, 1H d_1), 3.20 (dd, *J* = 6.6 and 15.8 Hz, 0.40H, 1H d_2), 3.36 (m, 0.40H, 1H d_2), 3.52 (m, 0.60H, 1H d_1), 3.96 (dd, *J* = 6.6 and 15.6 Hz, 0.60H, 1H d_1), 4.35 (dd, *J* = 5.4 and 15.6 Hz, 0.40H, 1H d_2), 4.65 (dd, *J* = 5.4 and 15.6 Hz, 0.60H, 1H d_1), 4.95-5.07 (m, 1H), 5.25-5.49 (m, 2H), 5.61 (m, 0.40H, 1H d_2), 5.93 (m, 0.60H, 1H d_1), 7.00 (d, *J* = 7.2 Hz, 0.60H, 1H d_1), 7.21-7.90 (m, 7.40H); ^{13}C NMR (75 MHz, $CDCl_3$, 20°C) mixture of diastereoisomers δ 25.5, 26.7, 43.2, 43.9, 47.8, 50.5, 58.6, 59.9, 118.1, 118.4, 121.8, 122.7, 123.4, 123.6, 123.8, 123.9, 123.9, 126.6, 126.8, 127.6, 127.8, 128.5, 128.6, 131.6, 131.8, 132.0, 132.0, 132.7, 132.9, 135.2, 135.4, 136.2, 136.9, 141.5, 144.7, 153.4, 153.7, 168.1, 169.0, 205.2, 205.7; Data analyses were identical in all respects with our previously reported data.[16g]

2-Allyl-3-(2-oxo-1,2-diphenylethyl)isoindolin-1-one (4bc): Prepared from hydroxy lactam **1b** (0.25 mmol) and 2-phenylacetophenone **3c** (2 equiv) following the general procedure at 90°C in acetonitrile with 1 mol % of $Sn(NTf_2)_4$.4 DMSO. Reaction time: 3 h. The product was isolated after purification by flash chromatography on silica gel (eluting with Cyclohexane/EtOAc = 70:30). Yield: 67% (61.5 mg, two diastereoisomers d_1/d_2 = 68:32). Major diastereoisomer d_1 (62 mg, 68%), white solid; mp = 134°C, R_f = 0.27 (cyclohexane/EtOAc : 70:30); ^{1}H NMR (300 MHz, $CDCl_3$, 20°C) δ 2.57 (dd, *J* = 7.6 and 15.7 Hz, 1H), 4.50 (m, 1H), 4.74 (d, *J* = 8.4 Hz, 1H), 4.85 (d, *J* = 17.4 Hz, 1H), 5.08 (d, *J* = 9.9 Hz, 1H), 5.50 (d, *J* = 8.4 Hz, 1H), 5.59 (m, 1H), 7.21-7.54 (m, 11H), 7.84-7.96 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 20°C) δ 44.5, 59.2, 61.2, 117.7, 123.3, 123.9, 128.4, 128.5, 128.7, 128.7, 129.3, 131.7, 132.0, 132.9, 133.5, 135.1, 136.2, 145.5, 169.6, 198.1; Minor diastereoisomer d_2 (29 mg, 32%), white solid; mp = 156°C, R_f = 0.48 (cyclohexane/EtOAc : 70:30); ^{1}H NMR (300 MHz, $CDCl_3$, 20°C) δ 3.85 (dd, *J* = 6.4 and 15.8 Hz, 1H), 4.72 (m, 1H), 4.80 (d, *J* = 6.4 Hz, 1H), 5.12-5.24 (m, 2H), 5.55 (d, *J* = 6.4 Hz, 1H), 5.84 (m, 1H), 6.64 (d, *J* = 7.6 Hz, 1H), 7.03-7.56 (m, 11H), 7.93-7.99 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, 20°C) δ 43.8, 56.9, 60.8, 62.6, 117.9, 123.3, 125.0, 128.1, 128.2, 128.8, 128.8, 128.9, 129.3, 129.3, 129.5, 130.7, 132.4, 132.8, 133.5, 134.2, 135.8, 143.4, 143.7, 197.7, 214.7; Data analyses were identical in all respects with our previously reported data.[16g]

2-Allyl-3-(2-oxocyclopentyl)isoindolin-1-one (4bd): Prepared from hydroxy lactam **1b** (0.25 mmol) and cyclopentanone **3d** (3 equiv) following the general procedure at 90°C in acetonitrile with 1 mol % of $Sn(NTf_2)_4$.4 DMSO. Reaction time: 2.5 h. The product was isolated after purification by flash chromatography on silica gel (eluting with Cyclohexane/EtOAc = 70:30) as a yellow viscous oil. Yield: 94% (60 mg, mixture of diastereoisomers d_1/d_2 = 60:40). R_f = 0.27 (cyclohexane/EtOAc : 70:30); ^{1}H NMR (300 MHz, $CDCl_3$, 20°C) mixture of diastereoisomers δ 0.96 (m, 0.60H, 1H d_1), 1.37-2.55 (m, 5.40H), 2.73 (t, *J* = 10.4 Hz, 0.40H, 1H d_2), 2.98 (m, 0.60H, 1H d_1), 3.44 (dd, *J* = 6.2 and 15.6 Hz, 0.40H, 1H d_2), 3.75 (dd, *J* = 7.2 and 15.7 Hz, 0.60H, 1H d_1), 4.54 (dd, *J* = 5.7 and 15.6 Hz, 0.40H, 1H d_2), 4.70 (dd, *J* = 4.9 and 15.6 Hz, 0.60H, 1H d_1), 5.13-5.33 (m, 3H), 5.72-5.99 (m, 1H), 7.20 (m, 0.60H, 1H d_1), 7.36-7.63 (m, 2.40H), 7.85-7.93 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 20°C) mixture of diastereoisomers δ 20.1, 20.2, 21.8, 22.7, 38.4, 39.6, 42.9, 44.0, 49.9, 52.8, 57.7, 58.9, 118.2, 118.3, 121.4, 122.9, 123.8, 128.4, 128.6, 131.7, 131.9, 132.3, 132.9, 142.6, 145.1, 167.9, 169.1, 218.0, 219.0; Data analyses were identical in all respects with our previously reported data.[16g]

2-Allyl-3-(1-methoxy-2-oxo-2-phenylethyl)isoindolin-1-one (4be): Prepared from hydroxy lactam **1b** (0.25 mmol) and 2-methoxyacetophenone **3e** (3 equiv) following the general procedure at 90°C in acetonitrile with 1 mol % of $Sn(NTf_2)_4$.4 DMSO. Reaction time: 3 h. The product was isolated after purification by flash chromatography on silica gel (eluting with Cyclohexane/EtOAc = 70:30) as a colorless viscous oil. Yield: 81% (65 mg, mixture of diastereoisomers d_1/d_2 = 56:44). R_f = 0.38 (cyclohexane/EtOAc : 50:50); ^{1}H NMR (300 MHz $CDCl_3$, 20°C) mixture of diastereoisomers δ 3.36 (s, 1.32H, 3H d_2), 3.39 (s, 1.68H, 3H d_1), 3.83-4.02 (m, 1H), 4.08 (m, 0.44H, 1H d_2), 4.65-4.83 (m 1.56H), 5.02-5.39 (m, 3H), 5.71-5.97 (m, 1H), 7.16-7.68 (m, 6H); 7.69-7.98 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 20°C) mixture of diastereoisomers δ 43.5, 44.4, 58.7, 58.8, 60.6, 61.1, 76.6, 76.7, 77.0, 77.2, 77.4, 82.5, 85.6, 117.8, 118.1, 123.2, 123.6, 127.5, 128.3, 128.4, 128.5, 128.6, 128.7, 128.8, 129.5, 130.3, 131.3, 131.3, 132.3, 132.5, 132.9, 133.5, 133.7, 133.8, 133.8, 133.9, 135.8, 136.1, 140.9, 141.3, 168.5, 198.0; Data analyses were identical in all respects with our previously reported data.[16g]

(*E*)-2-Allyl-3-(2-oxo-4-phenylbut-3-en-1-yl)isoindolin-1-one (4bf): Prepared from hydroxy lactam **1b** (0.25 mmol) and (*E*)-4-phenylbut-3-en-2-one **3f** (3 equiv) following the general procedure at 90°C in acetonitrile with 1 mol % of $Sn(NTf_2)_4$.4 DMSO. Reaction time: 6 h. The product was isolated after purification by flash chromatography on silica gel (eluting with Cyclohexane/EtOAc = 60:40) as a white solid. Yield: 93% (74 mg). R_f = 0.34 (cyclohexane/EtOAc : 60/40); ^{1}H NMR (300 MHz, $CDCl_3$, 20°C) δ 2.95 (dd, *J* = 7.5 and 17.1 Hz, 1H), 3.30 (dd, *J* = 5.1 and 17.1 Hz, 1H), 3.91 (dd, *J* = 6.4 and 15.8 Hz, 1H), 4.56 (dd, *J* = 5.1 and 15.8 Hz, 1H), 5.20-5.28 (m, 3H), 5.81-5.94 (dddd, *J* = 5.1, 6.4, 10.6 and 16.8 Hz, 1H), 6.77 (d, *J* = 16.2 Hz, 1H), 7.42-7.62 (m, 9H), 7.88 (d, *J* = 6.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 20°C) δ 43.3, 43.9, 55.8, 117.9, 122.8, 123.8, 125.7, 128.4, 128.5, 129.1, 129.1, 131.0, 131.0, 131.7, 131.8, 133.1, 133.9, 144.0, 145.7, 168.1, 196.9; Data analyses were identical in all respects with previously reported data.[16b]

2-Allyl-3-(2-oxo-2-phenylethyl)isoindolin-1-one (4bg): Prepared from hydroxy lactam **1b** (0.25 mmol) and acetophenone **3g** (3 equiv) following the general procedure at 90°C in acetonitrile with 1 mol % of $Sn(NTf_2)_4$.4 DMSO. Reaction time: 1.5 h. The product was isolated after purification by flash chromatography on silica gel (eluting with Cyclohexane/EtOAc = 60:40) as a colorless oil. Yield: 92% (67 mg). *Rf* = 0.27 (cyclohexane/EtOAc: 60/40); ^{1}H NMR (300 MHz, $CDCl_3$, 20°C) δ 3.22 (dd *J* = 7.8 and 17.2 Hz, 1H), 3.60 (dd, *J* = 5.4 and 17.2 Hz, 1H), 3.92 (dd, *J* = 6.3 Hz, 16.4 Hz, 1H), 4.55 (dd, *J* = 4.7 Hz, 16.4 Hz, 1H), 5.10-5.20 (m, 2H), 5.30-5.35 (m, 1H), 5.70-5.95 (m, 1H), 7.40-7.65 (m, 6H), 7.85-7.95 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 20°C) δ 42.3, 43.6, 56.1, 118.1, 123.2, 134.1, 136.6, 146.1, 168.4, 197.5; Data analyses were identical in all respects with our previously reported data.[33]

2-Allyl-3-(2-oxobut-3-yn-1-yl)isoindolin-1-one (4bh): Prepared from hydroxy lactam **1b** (0.25 mmol) and but-3-yn-2-one **3h** (3 equiv) following

the general procedure at 90°C in acetonitrile with 1 mol % of $Sn(NTf_2)_4$.4 DMSO. Reaction time: 4 h. The product was isolated after purification by flash chromatography on silica gel (eluting with Cyclohexane/EtOAc = 60:40) as a white solid. Yield: 95% (57 mg). *R*f = 0.45 (cyclohexane/EtOAc: 60/40); mp = 88°C; ^{1}H NMR (300 MHz, $CDCl_3$, 20°C) δ 2.90 (dd, *J* = 7.0 and 17.6 Hz, 1H), 3.20 (dd, *J* = 4.7 and 17.6 Hz, 1H), 3.35 (s, 1H), 3.87 (dd, *J* = 6.2 and 16.4 Hz, 1H), 4.50 (dd, *J* = 5.4 and 16.4 Hz, 1H), 5.00 (t, *J* = 6.2 Hz, 1H), 5.15-5.25 (m, 2H), 5.70-5.90 (m, 1H), 7.03-7.50 (m, 3H), 7.80 (d, *J* = 7.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 20°C) δ 43.5, 48.4, 55.3, 81.2, 118.4, 122.8, 124.1, 128.9, 132.1, 133.1, 144.8, 168.2, 183.8; Data analyses were identical in all respects with our previously reported data.[33]

2-Allyl-3-(2-oxopropyl)isoindolin-1-one (4bi): Prepared from hydroxy lactam **1b** (0.25 mmol) and propan-2-one **3i** (10 equiv) following the general procedure at 90°C in acetonitrile with 1 mol % of $Sn(NTf_2)_4$.4DMSO. Reaction time: 9 h. The product was isolated after purification by flash chromatography on silica gel (eluting with Cyclohexane/EtOAc = 70:30) as a colorless oil. Yield: 89% (51 mg). *Rf* = 0.15 (cyclohexane/EtOAc: 70/30); IR (neat) υ 1625, 1617, 1404, 1353, 1161, 755 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, 20°C) δ 2.18 (s, 3H), 2.72 (dd, *J* = 7.3 and 17.8 Hz, 1H), 3.05 (dd, *J* = 5.1 and 17.9 Hz, 1H), 3.89 (dd, *J* = 6.2 and 15.9 Hz, 1H), 4.43 (dd, *J* = 5.2 and 15.9 Hz, 1H), 5.07 (t, *J* = 5.8 Hz, 1H), 5.17 (d, *J* = 12.6 Hz, 2H), 5.67-5.94 (m, 1H), 7.37-7.53 (m, 3H), 7.82 (d, *J* = 7.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 20°C) δ 30.7, 43.3, 46.4, 55.5, 117.7, 122.6, 123.7, 128.4, 131.6, 131.8, 133.1, 145.5, 168.2, 205.8; HRMS (ESI) m/z calculated for $C_{14}H_{16}NO_2$ $[M+H]^+$: 230.1181, found: 230.1183.

2-Allyl-3-(1-chloro-2-oxopropyl)isoindolin-1-one (4bj) and 2-Allyl-3-(3-chloro-2-oxopropyl)isoindolin-1-one (5bj): Prepared from hydroxy lactam **1b** (0.25 mmol) and 1-chloropropan-2-one **3j** (3 equiv) following the general procedure at 90°C in acetonitrile with 1 mol % of $Sn(NTf_2)_4$.4 DMSO. Reaction time: 5 h. The product was isolated after purification by flash chromatography on silica gel (eluting with Cyclohexane/EtOAc = 70:30) as a separable mixture of branched and linear regioisomers (ratio **4bj**/**5bj** = 6 : 1). Combined isolated yield: 100%. **Branched regioisomer 4bj** (57 mg, 86%, mixture of diastereoisomers d_1/d_2 = 72:28), yellow viscous oil; *Rf* = 0.32 (cyclohexane/EtOAc: 50/50); IR ($CHCl_3$) υ 1728, 1670 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, 20°C) mixture of diastereoisomers δ 2.16 (s, 0.84H, 3H d_2), 2.39 (s, 2.16H, 3H d_1), 3.63 (dd, *J* = 6.8 and 15.8 Hz, 0.28H, 1H d_2), 3.72 (dd, *J* = 7.4 and 16.0 Hz, 0.72H, 1H d_1), 4.51-4.68 (m, 1.28H), 4.77 (m, 0.72H), 5.09-5.34 (m, 3H), 5.66-5.90 (m, 1H), 7.08-7.19 (m, 0.72 H), 7.40-7.58 (m, 2.28H), 7.77-7.85 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 20°C) mixture of diastereoisomers δ 28.0, 29.2, 43.0, 43.7, 60.1, 60.4, 63.1, 64.2, 118.4, 118.6, 122.3, 122.9, 123.4, 123.8, 124.0, 129.1, 129.2, 131.7, 131.9, 132.5, 132.8, 133.1, 134.2, 140.3, 141.7, 168.2, 168.4, 201.6, 203.5; HRMS (ESI) m/z: calculated for $C_{14}H_{15}NO_2Cl$ $[M+H]^+$: 264.0786, found: 264.0782. **Linear regioisomer 5bj** (9 mg, 14%), yellow viscous oil; *Rf* = 0.17 (cyclohexane/EtOAc: 50/50); IR ($CHCl_3$) υ 1732, 1668 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, 20°C) δ 2.92 (dd, *J* = 7.1 and 18.0 Hz, 1H), 3.25 (dd, *J* = 5.2 and 18.1 Hz, 1H), 3.96 (dd, *J* = 6.3 and 15.9 Hz, 1H), 4.09 (s, 2H), 4.46 (dd, *J* = 5.4 and 16.0 Hz, 1H), 5.12 (dd, *J* = 5.3 and 7.1 Hz, 1H), 5.18-5.27 (m, 2H), 5.86 (m, 1H), 7.40 (d, *J* = 7.3 Hz, 1H), 7.46-7.61 (m, 2H), 7.88 (d, *J* = 7.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 20°C) δ 41.6, 48.2, 55.2, 81.3, 118.0, 122.4, 123.4, 124.0, 129.9, 131.4, 132.3, 132.7, 143.8, 167.1, 208.3; HRMS (ESI) m/z: calculated for $C_{14}H_{15}NO_2Cl$ $[M+H]^+$: 264.0786, found: 264.0784.

2-Allyl-3-(3-oxobutan-2-yl)isoindolin-1-one (4bk) and 2-Allyl-3-(2-oxobutyl)isoindolin-1-one (5bk): Prepared from hydroxy lactam **1b** (0.25 mmol) and butan-2-one **3k** (3 equiv) following the general procedure at 110°C in toluene with 1 mol % of $Sn(NTf_2)_4$.4 DMSO. Reaction time: 18 h. The product was isolated after purification by flash chromatography on silica gel (eluting with Cyclohexane/EtOAc = 70:30) as an inseparable mixture of branched and linear regiosiomers (ratio **4bk**/ **5bk** = 7.3 : 1). Colorless oil. Global Yield: 86% (52 mg, mixture of regioisomers **4bk** (as a mixture of diastereoisomers d_1/d_2 = 66:34) and **5bk** (ratio **4bk**/**5bk** = 7.3 : 1). *Rf* = 0.27 (cyclohexane/EtOAc: 70/30); IR ($CHCl_3$) υ 1704, 1676 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, 20°C) mixture of regioisomers and diastereoisomers δ 0.66 (d, *J* = 7.4 Hz, 1.56H, 3H d_1 **4bk**), 0.86 (d, *J* = 7.2 Hz, 0.90H, 3H d_2 **4bk**), 1.08 (t, *J* = 7.3 Hz, 0.33H, 3H **5bk**), 2.22 (s, 0.90H, 3H d_2 **4bk**), 2.30 (s, 1.56H, 3H d_1 **4bk**), 2.38-2.50 (m, 0.22H, 2H **5bk**), 2.68 (dd, *J* = 7.4 and 17.5 Hz, 0.11H, 1H **5bk**), 2.96-3.10 (m, 0.41 H, 1H d_2 **4bk** + 1H **5bk**), 3.15 (qd, *J* = 2.9 and 7.2 Hz, 0.52H, 1H d_1 **4bk**), 3.56 (dd, *J* = 6.9 and 15.7 Hz, 0.30H, 1H d_2 **4bk**), 3.70 (dd, *J* = 7.4 and 15.7 Hz, 0.52H, 1H d_1 **4bk**), 3.88 (m, 0.11H, 1H **5bk**), 4.43 (m, 0.11H, 1H **5bk**), 4.56-4.73 (m, 0.82H, 1H **4bk**), 5.06-5.32 (m, 3H), 5.72-5.93 (m, 1H), 7.25-7.62 (m, 3H), 7.68-7.86 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 20°C) mixture of regioisomers and diastereoisomers δ 7.6, 8.6, 9.1, 28.6, 29.0, 36.7, 42.9, 43.3, 43.5, 45.4, 46.7, 49.9, 55.5, 59.1, 59.3, 117.6, 117.9, 118.3, 121.8, 122.5, 123.6, 123.7, 123.8, 128.4, 128.4, 128.5, 131.5, 131.7, 131.8, 132.4, 132.8, 132.9, 133.1, 133.2, 142.5, 144.4, 145.6, 168.0, 168.4, 168.8, 208.4, 208.6, 209.1; HRMS (ESI) m/z: calculated for $C_{15}H_{17}NaNO_2$ $[M+Na]^+$: 266.1157, found: 266.1156.

2-Allyl-3-(1-methoxy-2-oxopropyl)isoindolin-1-one (4bl) and 2-Allyl-3-(3-methoxy-2-oxopropyl)isoindolin-1-one (5bl): Prepared from hydroxy lactam **1b** (0.25 mmol) and 1-methoxypropan-2-one **3l** (3 equiv) following the general procedure at 70°C in acetonitrile with 1 mol % of $Sn(NTf_2)_4$.4 DMSO. Reaction time: 16 h. The product was isolated after purification by flash chromatography on silica gel (eluting with Cyclohexane/EtOAc = 50:50) as a separable mixture of branched (d_1/d_2 = 55:45) and linear regioisomers (ratio **4bl**/ **5bl** = 2.8 : 1). Combined isolated yield: 98%. **Branched regioisomer 4bl** (42 mg, 74%), colorless viscous oil; *Rf* = 0.30 (cyclohexane/EtOAc: 50/50); IR ($CHCl_3$) υ 1692, 1616 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, 20°C) mixture of diastereoisomers δ 1.85 (s, 1.65H, 3H d_1), 2.07 (s, 1.35H, 3H d_2), 3.35 (s, 1.35H, 3H d_2), 3.41 (s, 1.65H, 3H d_1), 3.75 (dd, *J* = 7.7 and 15.8 Hz, 0.55H, 1H d_1), 3.79 (dd, *J* = 7.3 and 15.6 Hz, 0.45H, 1H d_2), 4.07 (d, *J* = 4.3 Hz, 0.55H, 1H d_1), 4.09 (d, *J* = 2.7 Hz, 0.45H, 1H d_2), 4.68 (dd, *J* = 4.7 and 15.6 Hz, 0.45H, 1H d_2), 4.80 (m, 1H), 4.95 (d, *J* = 4.3 Hz, 0.55H, 1H d_1), 4.96 (d, *J* = 2.6 Hz, 0.45H, 1H d_2), 5.15-5.36 (m, 2H), 5.74-5.92 (m, 1H), 7.22 (m, 1H d_2), 7.38-7.89 (m, 4.55H); ^{13}C NMR (75 MHz, $CDCl_3$, 20°C) mixture of diastereoisomers δ 27.0, 27.9, 39.6, 43.6, 43.6, 46.1, 49.1, 59.3, 59.7, 59.9, 61.1, 85.7, 85.8, 118.3, 122.5, 123.4, 123.8, 123.8, 123.9, 128.7, 128.9, 131.5, 131.6, 132.3, 132.6, 132.8, 132.9, 134.2, 141.1, 142.0, 168.3, 168.7, 207.6, 208.7; HRMS (ESI) m/z: calculated for $C_{15}H_{17}NaNO_3$ $[M+Na]^+$: 282.1106, found: 282.1108. **Linear regioisomer 5bl** (14 mg, 25%), colorless viscous oil; *Rf* = 0.17 (cyclohexane/EtOAc: 50/50); IR ($CHCl_3$) υ 1715, 1687 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, 20°C) δ 2.70 (dd, *J* = 7.4 and 17.9 Hz, 1H), 3.05 (dd, *J* = 5.1 and 18.0 Hz, 1H), 3.33 (s, 3H), 3.83 (dd, *J* = 6.5 and 15.9 Hz, 1H), 3.92 (s, 2H), 4.44 (dd, *J* = 5.2 and 15.9 Hz, 1H), 5.05 (dd, *J* = 5.1 and 7.4 Hz, 1H), 5.10-5.18 (m, 2H), 5.77 (m, 1H), 7.27-7.50 (m, 3H), 7.79 (d, *J* = 7.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 20°C) δ 42.2, 43.4, 55.2, 59.4, 117.8, 122.6, 123.9, 128.6, 131.9, 133.1, 145.4, 206.1; HRMS (ESI) m/z: calculated for $C_{15}H_{17}NaNO_3$ $[M+Na]^+$: 282.1106, found: 282.1107.

2-Allyl-3-(2-oxocyclohex-3-en-1-yl)isoindolin-1-one (4bm): Prepared from acetoxy lactam **2b** (0.25 mmol) and cyclohex-2-enone **3m** following the general procedure at 90°C with 1 mol % of $Sn(NTf_2)_4$.4 DMSO. Reaction time: 1 h. The product was isolated after purification by flash chromatography on silica gel (eluting with Cyclohexane/EtOAc = 60:40) as a colorless oil. Yield: 79% (53 mg, mixture of diastereoisomers d_1/d_2 = 50:50). *Rf* = 0.37 (d_1) and 0.30 (d_2) (cyclohexane/EtOAc: 70/30);

^{1}H NMR (300 MHz, $CDCl_3$, 20°C) mixture of diastereoisomers δ 1.02 (ddd, J = 5.8, 10.9 and 13.6 Hz, 0.50H, 1H, d_1), 1.40-1.60 (m, 1H), 1.95 (m, 0.50H, 1H d_2), 2.10-2.35 (m, 2H), 2.77 (dd, J = 4.0 and 14.1 Hz, 0.50H, 1H d_1), 3.0 (ddd, J = 3.0, 3.9 and 14.0 Hz, 0.50H, 1H d_2), 3.41 (dd, J = 5.6 and 15.5 Hz, 0.50H, 1H, d_1), 3.75 (dd, J = 7.0 and 15.6 Hz, 0.50H, 1H d_2), 4.38 (dd, J = 6.0 and 15.5 Hz, 0.50H, 1H d_1), 4.51 (dd, J = 5.3 and 15.6 Hz, 0.50H, 1H d_2), 5.05-5.35 (m, 2H), 5.46 (d, J = 3.0 Hz, 0.50H, 1H d_2), 5.57 (s, 0.50H, 1H d_1), 5.70-5.90 (m, 1H), 6.09 (dd, J = 3.0 and 10.0 Hz, 1H), 6.9-7.02 (m, 1H), 7.30-7.55 (m, 3H), 7.78 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 20°C) mixture of diastereoisomers δ 20.3, 20.8, 25.3, 25.6, 43.1, 44, 46.7, 50.1, 57.1, 58.6, 117.9, 118.2, 121.3, 123.5, 123.6, 123.7, 128.3, 129.6, 130.0, 131.6, 131.8, 132.2, 132.7, 132.7, 132.7, 133.0, 143.1, 144.9, 151.1, 151.2, 168.5, 169, 197.4, 198.7; Data analyses were identical in all respects with our previously reported data.[16b]

2-Allyl-3-(2-(4-methoxyphenyl)-2-oxoethyl)isoindolin-1-one (4bn): Prepared from acetoxy lactam **2b** (0.25 mmol) and *p*-methoxyacetophenone **3n** (2 equiv) in toluene following the general procedure at 90°C with 1 mol % of $Sn(NTf_2)_4$.8DMSO. Reaction time: 6 h. The crude material was purified by flash chromatography on silica gel (eluting with Cyclohexane/EtOAc = 70:30) as a colorless oil. Yield: 88 % (71 mg). *Rf* = 0.21 (cyclohexane/EtOAc: 60/40); IR ($CHCl_3$) υ 1681, 1600, 755 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, 20°C) δ 3.22 (dd, J = 7.5 and 17.4 Hz, 1H), 3.51 (dd, J = 5.1 and 17.4 Hz, 1H), 3.90 (s, 3H), 3.91 (dd, J = 6.6 and 15.9 Hz, 1H), 4.51 (dd, J = 4.8 and 15.9 Hz, 1H), 5,15-5,22 (m, 2H), 5.33-5.37 (m, 1H), 5.85 (m, 1H), 6.97 (d, J = 8.7 Hz, 2H), 7.49-7.51 (m, 3H), 7.85-8.08 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 20°C) δ 41.6, 43.3, 55.5, 56.0, 113.9, 117.7, 122.9, 123.7, 128.3, 129.5, 130.4, 131.7, 131.8, 133.1, 146.0, 164.0, 168.1, 195.6; LRMS (ESI) m/z 321 ($M^{+\cdot}$, 2), 280 (97), 158 (100); HRMS (ESI) m/z: calculated for $C_{20}H_{20}NO_3$ $[M+H]^+$: 322.1443, found: 322.1441.

2-Allyl-3-(2-oxocycloheptyl)isoindolin-1-one (4bo): Prepared from hydroxy lactam **2b** (0.25 mmol) and cycloheptanone **3o** (3 equiv) in toluene following the general procedure at 110°C with 1 mol % of $Sn(NTf_2)_4$.8DMSO. Reaction time: 2 h. The crude material was purified by flash chromatography on silica gel (eluting with Cyclohexane/EtOAc = 70:30) to give the title compound as colorless viscous oil. Yield: 96 % (68 mg, mixture of diastereoisomers d_1/d_2 = 60:40). R_f = 0.27 (cyclohexane/EtOAc: 70:30); IR ($CHCl_3$) υ 1772, 1615 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, 20°C) mixture of diastereoisomers δ 0.60-2.76 (m, 10H), 2.82 (d, J = 10.6 Hz, 0.40H, 1Hd_2), 3.03 (d, J = 10.6 Hz, 0.60H, 1Hd_1), 3.49 (dd, J = 6.0 and 15.5 Hz, 0.40H, 1Hd_2), 3.76 (dd, J = 6.8 and 15.8 Hz, 0.60H, 1Hd_1), 4.36-4.52 (m, 1 H), 5.00-5.27 (m, 3H), 5.67-5.87 (m, 1H), 7.18-7.58 (m, 2.60H), 7.61-7.86 (m, 1.40H); ^{13}C NMR (75 MHz, $CDCl_3$, 20°C) mixture of diastereoisomers δ 21.9, 22.2, 23.2, 23.4, 28.6, 29.2, 29.5, 29.7, 42.3, 43.2, 43.3, 43.9, 51.1, 54.7, 58.9, 59.6, 75.6, 76.1, 76.3, 76.5, 116.6, 117.1, 120.6, 122.4, 122.6, 122.7, 122.8, 127.3, 127.3, 130.5, 130.8, 131.7, 131.8, 131.8, 132.2, 133.1, 142.2, 144.0, 167.8, 168.1, 212.3, 213.3; LRMS (ESI) m/z 283 ($M^{+\cdot}$, 0.7), 242 (48), 172 (100); HRMS (ESI) m/z: calculated for $C_{18}H_{21}NaNO_2$ $[M+Na]^+$: 306.1470, found: 306.1464.

2-Benzyl-3-(2-oxocycloheptyl)isoindolin-1-one (4ao): Prepared from hydroxy lactam **2a** (0.25 mmol) and cycloheptanone **3o** (3 equiv) in toluene following the general procedure at 110°C with 1 mol % of $Sn(NTf_2)_4$.8DMSO. Reaction time: 2 h. The crude material was purified by flash chromatography on silica gel (eluting with Cyclohexane/EtOAc = 70:30) to give the title compound as a white solid. Yield: 97 % (81 mg, mixture of diastereoisomers d_1/d_2 = 80:20). R_f = 0.34 (cyclohexane/EtOAc : 70:30); IR ($CHCl_3$) υ 1681, 1520 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, 20°C) mixture of diastereoisomers δ 0.64-1.90 (m, 7.6H), 2.18-2.51 (m, 2.4H), 2.52-2.74 (m, 1H), 2.87 (m, 0.20H, 1H d_2), 3.01 (m, 0.80H, 1H d_1), 4.31 (d, J = 15 Hz, 0.20H, 1H d_2), 4.61 (m, J = 15.2 Hz, 0.80H, 1H d_1), 4.91 (m, J = 15.2 Hz, 0.80H, 1H d_1), 4.97 (d, J = 15 Hz, 0.20H, 1H d_2), 5.14 (bs, 0.80H, 1H d_1), 5.25 (bs, 0.20H, 1H d_2), 7.20-7.40 (m, 6H), 7.41-7.62 (m, 2H), 7.86-7.95 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 20°C) mixture of diastereoisomers δ 23.1, 23.4, 24.1, 24.3, 29.3, 30.3, 30.4, 30.7, 44.2, 44.9, 44.9, 45.8, 52.2, 55.8, 60.4, 61.2, 121.6, 123.7, 123.9, 123.9, 127.4, 127.7, 128.1, 128.3, 128.4, 128.5, 128.9, 131.5, 131.8, 132.8, 137.3, 137.4, 143.3, 169.2, 213.2, 214.3; LRMS (ESI) m/z 333 ($M^{+\cdot}$, 10), 242 (42), 222 (100); HRMS (ESI) m/z: calculated for $C_{22}H_{23}NaNO_2$ $[M+Na]^+$: 356.1626, found: 356.1622.

2-Benzyl-3-(2-cyclopropyl-2-oxoethyl)isoindolin-1-one (4ap): Prepared from hydroxy lactam **2a** (0.25 mmol) and cyclopropylethanone **3p** (3 equiv) in toluene following the general procedure at 110°C with 1 mol % of $Sn(NTf_2)_4$.8DMSO. Reaction time: 4 h. The crude material was purified by flash chromatography on silica gel (eluting with Cyclohexane/EtOAc = 60:40) to give the title compound as a white solid. Yield: 61% (46 mg). *Rf* = 0.37 (cyclohexane/EtOAc: 60/40); mp = 119°C; IR (neat) υ 1679, 1646, 1411, 1296, 985, 723 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, 20°C) δ 0.81-0.94 (m, 2H), 1.01-1.07 (m, 2H), 1.71-1.79 (m, 1H), 2.85 (dd, J = 7.1 and 17.3Hz, 1H), 3.12 (dd, J = 5.2 and 17.3 Hz, 1H), 4.48 (d, J = 15.4 Hz, 1H), 5.02 (dd, J = 5.5 and 6.8 Hz, 1H), 5.11 (d, J = 15.4 Hz, 1H), 7.26-7.38 (m, 6H), 7.47-7.57 (m, 2H), 7.92 (dd, J = 1.8 and 6,3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 20°C) δ 11.4, 11.6, 21.2, 44.5, 46.3, 55.6, 122.6, 123.9, 127.5, 127.9, 128.4, 128.7, 131.8, 137.2, 145.7, 168.5, 207.7; HRMS (ESI) m/z: calculated for $C_{20}H_{20}NO_2$ $[M+H]^+$: 306.1503, found: 306.1503.

2-(3,4-Dimethoxybenzyl)-3-(2-oxocyclohexyl)isoindolin-1-one (4fa): Prepared from acetoxy lactam **2f** (0.25 mmol) and cyclohexanone **3a** (3 equiv) in acetonitrile following the general procedure at 90°C with 1 mol % of $Sn(NTf_2)_4$.4 DMSO. Reaction time: 2.5 h. The crude material was purified by flash chromatography on silica gel (eluting with Cyclohexane/EtOAc = 60:40) to give the title compound as a yellow viscous oil. Yield: 78% (74 mg, mixture of diastereosiomers d_1/d_2 = 72:28). R_f = 0.25 (cyclohexane/EtOAc: 60/40); ^{1}H NMR (300 MHz, $CDCl_3$, 20°C) mixture of diastereoisomers δ 0.69 (m, 0.72H, 1H d_1), 1.02-1.74 (m 3.28H), 1.82-2.10 (m, 2H), 2.22-2.37 (m, 1H), 2.44-2.55 (m, 1H), 2.77 (dd J = 6.1 and 12.5 Hz, 0.28H, 1H d_2), 2.94 (m, 0.72H, 1H d_1), 3.83 (s, 2.16H, 3H d_1), 3.85 (s, 0.84H, 3H d_2), 3.86 (s, 2.16H, 3H d_1), 3.88 (s, 0.84H, 3H d_2), 4.40 (d, J = 15.1 Hz, 0.72H, 1H d_1), 4.43 (d, J = 14.3 Hz, 0.28H, 1H d_2), 4.77 (d, J = 14.3 Hz, 0.28H, 1H d_2), 4.97 (d, J = 15.1 Hz, 0.72H, 1H d_1), 5.21 (s, 0.72H, 1H d_1), 5.45 (s, 0.28H, 1H d_2), 6.74-7.14 (m, 3H), 7.29-7.57 (m, 3H), 7.82-7.90 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 20°C) mixture of diastereoisomers δ 22.3, 22.7, 24.2, 24.2, 24.2, 24.8, 25.2, 25.3, 25.5, 26.4, 27.2, 27.6, 29.6, 31.8, 41.7, 42.0, 44.3, 45.6, 50.3, 53.9, 55.8, 55.8, 55.9, 57.8, 58.7, 58.8, 76.6, 77.0, 77.0, 77.2, 77.4, 110.6, 110.9, 111.0, 112.4, 120.1, 121.2, 121.4, 123.5, 123.6, 124.4, 128.1, 128.1, 129.5, 130.4, 131.5, 131.7, 132.6, 143.6, 145.2, 148.2, 148.5, 148.7, 149.3, 168.9, 169.7, 209.5, 210.5; Data analyses were identical in all respects with our previously reported data.[16g]

2-(But-3-ynyl)-3-(2-oxocyclohexyl)isoindolin-1-one (4ga): Prepared from acetoxy lactam **2g** (0.25 mmol) and cyclohexanone **3a** (3 equiv) in acetonitrile following the general procedure at 90°C with 1 mol % of $Sn(NTf_2)_4$.4 DMSO. Reaction time: 2.5 h. The crude material was purified by flash chromatography on silica gel (eluting with Cyclohexane/EtOAc = 70:30) to give the title compound as a yellow viscous oil. Yield: 55% (39 mg, mixture of diastereosiomers d_1/d_2 = 50:50). R_f = 0.18 (cyclohexane/EtOAc : 80/20); ^{1}H NMR (300 MHz, $CDCl_3$, 20°C) mixture of diastereoisomers δ 0.76 (m, 0.50H, 1H d_1), 1.15-1.88 (m, 4.50H), 1.96 (t, J = 2.7 Hz, 0.50H, 1H d_1), 2.03 (t, J = 2.7 Hz, 0.50H, 1H d_2), 2.03-2.21 (m, 1H), 2.37-2.75 (m, 4H), 2.80-3.01 (m, 1H), 3.10 (m, 0.50H, 1H d_2), 3.29 (dt, J = 7.2 and 13.5 Hz, 0.50H, 1H d_1), 4.15 (dt, J = 7.2 and 13.5 Hz,

0.50H, 1H d_2), 4.30 (dt, *J* = 7.7 and 13,5 Hz, 0.50H, 1H d_1), 5.47 (s, 0.50H, 1H d_1), 5.51 (s, 0.50H, 1H d_2), 7.33-7.85 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$, 20°C) mixture of diastereoisomers *δ* 17.6, 18.5, 24.2, 24.4, 24.7, 25.2, 26.4, 39.1, 39.9, 41.7, 42.1, 50.1, 53.8, 56.2, 58.9, 69.7, 70.3, 81.1, 81.4, 121.3, 123.4, 123.7, 124.4, 128.1, 128.2, 131.6, 131.7, 132.4, 132.5, 143.6, 144.8, 169.0, 169.1, 209.8, 210.5; LRMS (ESI) m/z 281 ($M^{+\bullet}$, 6), 184 (12), 228 (38), 170 (100); Data analyses were identical in all respects with our previously reported data.[16g]

(*E*)-2-(But-3-yn-1-yl)-3-(2-oxo-4-phenylbut-3-en-1-yl)isoindolin-1-one (4gf): Prepared from acetoxy lactam **2g** (0.25 mmol) and (*E*)-4-phenylbut-3-en-2-one **3f** (3 equiv) in acetonitrile following the general procedure at 90°C with 1 mol % of $Sn(NTf_2)_4$.4 DMSO. Reaction time: 1.5 h. The crude material was purified by flash chromatography on silica gel (eluting with Cyclohexane/EtOAc = 70:30) to give the title compound as a yellow viscous oil. Yield: 50% (41 mg). R_f = 0.38 (cyclohexane/EtOAc : 70/30); IR (neat) *υ* 1637, 1520 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, 20°C) *δ* 2.00 (t, *J* = 2.7 Hz, 1H), 2.62 (m, 2H), 3.01 (dd, *J* = 7.3 and 17.3 Hz, 1H), 3.24-3.44 (m, 2H), 4.17 (m, 1H), 5.41 (dd, *J* = 5.2 and 7.3 Hz, 1H), 6.80 (d, *J* = 16.2 Hz, 1H), 7.36-7.65 (m, 9H), 7.86 (d, *J* = 7.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 20°C) *δ* 18.4, 39.4, 44.0, 55.9, 70.3, 81.4, 122.8, 123.7, 125.6, 128.5, 128.5, 129.1, 131.1, 131.6, 131.9, 133.9, 144.2, 145.7, 197.0; LRMS (ESI) m/z 329 ($M^{+\cdot}$, 5), 251 (21), 160 (100); HRMS (ESI) calculated for $C_{22}H_{19}NaNO_2$ $[M+Na]^+$: 352.1313, found: 352.1311.

(*E*)-3-(2-Oxo-4-phenylbut-3-en-1-yl)-2-(prop-2-yn-1-yl)isoindolin-1-one (4ef): Prepared from hydroxy lactam **1e** (0.25 mmol) and (*E*)-4-phenylbut-3-en-2-one **3f** (3 equiv) in toluene following the general procedure at 110°C with 1 mol % of $Sn(NTf_2)_4$.4 DMSO. Reaction time: 2 h. The crude material was purified by flash chromatography on silica gel (eluting with Cyclohexane/EtOAc = 70:30) to give the title compound as a yellow viscous oil. Yield: 90% (71 mg). R_f = 0.54 (cyclohexane/EtOAc: 70/30); IR ($CHCl_3$) *υ* 1973, 1685 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, 20°C) *δ* 2.15 (bs, 1H), 2.94 (dd, *J* = 7.3 and 17.3Hz, 1H), 3.36 (dd, *J* = 5.2 and 17.3Hz, 1H), 4.12 (dd, *J* = 2.6 and 17.9Hz, 1H), 4.55 (dd, *J* = 2.6 and 17.8Hz, 1H), 5.28 (t, *J* = 6.3 Hz, 1H), 6.69 (d, *J* = 16.1 Hz, 1H), 7.22-7.61 (m, 12H), 7.75 (d, *J* = 7.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 20°C) *δ* 30.4, 43.8, 55.9, 72.4, 78.5, 122.9, 123.8, 125.6, 128.5, 128.5, 129.1, 131.0, 131.3, 132.1, 134.0, 143.9, 145.6, 167.7, 196.7; HRMS (ESI) *m/z* 315 ($M^{+\cdot}$, 5), 145 (40), 170 (100); HRMS (ESI) calculated for $C_{21}H_{17}NaNO_2$ $[M+Na]^+$: 358.1157, found: 338.1157.

2-(3,4-Dimethoxybenzyl)-3-(2-oxopropyl)isoindolin-1-one (4fi): Prepared from acetoxy lactam **2f** (0.25 mmol) and acetone **3i** (3 equiv) in acetonitrile following the general procedure at 90°C with 1 mol % of $Sn(NTf_2)_4$.8DMSO. Reaction time: 1.5 h. The crude material was purified by flash chromatography on silica gel (eluting with Cyclohexane/EtOAc = 70:30) to give the title compound as a colorless oil. Yield: 53 % (45 mg). *Rf* = 0.15 (cyclohexane/EtOAc: 60/40); IR (neat) *υ* 1675, 1615, 1514, 1258, 1024, 755 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, 20°C) *δ* 1.99 (s, 3H), 2.71 (dd, *J* = 6.6 and 17.8 Hz, 1H), 2.94 (dd, *J* = 5.6 and 17.8Hz, 1H), 3.84 (s, 3H), 3.86 (s, 3H), 4.53 (d, *J* = 15.1 Hz, 1H), 4.87 (d, *J* = 15.2 Hz, 1H), 5.03 (t, *J* = 6.1 Hz, 1H), 6.79 (d, *J* = 8.4 Hz, 1H), 6.82 (d, *J* = 8.4 Hz, 1H), 6.83 (s, 1H), 7.36 (d, *J* = 7.2 Hz, 1H), 7.46-7.56 (m, 2H), 7.90 (dd, *J* = 1.1 and 6.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 20°C) *δ* 30.6, 44.6, 46.6, 55.6, 55.9, 55.9, 111.0, 111.2, 120.3, 122.4, 123.9, 128.5, 129.7, 131.6, 131.9, 145.6, 148.5, 149.2, 168.5, 205.6; HRMS (ESI) calculated for $C_{20}H_{21}NaNO_4$ $[M+Na]^+$: 362.1368, found: 362.1364.

2-(3-Methylbut-2-enyl)-3-(2-oxopropyl)isoindolin-1-one (4di): Prepared from hydroxy lactam **1d** (0.25 mmol) and acetone **3i** (3 equiv) in toluene following the general procedure at 110°C with 1 mol % of $Sn(NTf_2)_4$.8DMSO. Reaction time: 8 h. The crude material was purified by flash chromatography on silica gel (eluting with Cyclohexane/EtOAc = 70:30) to give the title compound as a colorless oil. Yield: 61% (39 mg). *Rf* = 0.22 (cyclohexane/EtOAc: 70/30); IR (neat) *υ* 1710, 1626, 1396, 1364, 695 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, 20 °C) *δ* 1.65 (s, 6H), 2.11 (s, 3H), 2.62 (dd, *J* = 7.7 and 17.7 Hz, 1H), 2.99 (dd, *J* = 4.8 and 17.7, 1H), 3.79 (dd, *J* = 7.0 and 15.4 Hz, 1H), 4.39 (dd, *J* = 6.6 and 15.5 Hz, 1H), 4.98 (dd, *J* = 4.9 and 7.5 Hz, 1H), 5.11 (t, *J* = 6.8 Hz, 1H), 7.31 (d, *J* = 7.2 Hz, 1H), 7.29-7.43 (m, 2H), 7.76 (d, *J* = 7.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 20°C) *δ* 18.0, 25.7, 30.8, 38.4, 46.4, 55.2, 119.5, 122.5, 123.7, 128.4, 131.6, 134.1, 136.6, 145.6, 167.9, 205.7; HRMS (ESI) calculated for $C_{16}H_{20}NO_2$ $[M+H]^+$: 258.1494, found: 258.1499.

2-Benzyl-3-(2-oxo-2-(thiophen-2-yl)ethyl)isoindolin-1-one (4aq): Prepared from hydroxylactam **1a** (0.25 mmol) and 2-acetyl-furane **3r** (2 equiv) in toluene following the general procedure at 90°C with 1 mol % of $Sn(NTf_2)_4$.8DMSO. Reaction time: 4 h. The crude material was purified by flash chromatography on silica gel (eluting with Cyclohexane/EtOAc = 60:40) to give an inseparable mixture of the title compound **4aq** and the related Friedel-crafts adduct **4aq'** as a pale solid; Yield: 73 % (61 mg, ratio **4aq**/**4aq'** = 82/18). *Rf* = 0.35 (cyclohexane/EtOAc: 60/40); ^{1}H NMR (300 MHz, $CDCl_3$, 20°C) δ 2.41 (s, 0.54H, 3H **4aq'**), 3.07 (dd, *J* = 7.0 and 17.0 Hz, 0.82H, 1H **4aq**), 3.36 (dd, *J* = 5.8 and 17.0 Hz, 0.82H, 1H **4aq**), 4.19 (d, *J* = 15.0 Hz, 0.18H, 1H **4aq'**), 4.53 (d, *J* = 15.4 Hz, 0.82H, 1H **4aq**), 5.10 (d, *J* = 15.4 Hz, 0.82H, 1H **4aq**), 5.19 (t, *J* = 6.4 Hz, 0.82H, 1H **4aq**), 5.31 (d, *J* = 15.0 Hz, 0.18H, 1H **4aq'**), 5.51 (s, 0.18H, 1H **4aq'**), 6.33 (d, *J* = 3.5 Hz, 0.18H, 1H **4aq'**), 6.53 (dd, *J* = 1.7 and 3.6 Hz, 0.82H, 1H **4aq**), 6.98-7.72 (m, 11H), 7.84-8.10 (m, 1H).

2-Benzyl-3-(2-oxo-2-(thiophen-2-yl)ethyl)isoindolin-1-one (4ar): Prepared from hydroxylactam **1a** (0.25 mmol) and 2-acetyl-thiophene **3r** (2 equiv) in toluene following the general procedure at 110°C with 1 mol % of $Sn(NTf_2)_4$.8DMSO. Reaction time: 5 h. The crude material was purified by flash chromatography on silica gel (eluting with Cyclohexane/EtOAc = 60:40) to give the title compound as a white solid. Yield: 91 % (79 mg). *Rf* = 0.39 (cyclohexane/EtOAc: 60/40); mp = 129°C; IR (neat) *υ* 1677, 1649, 1410, 721 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, 20°C) *δ* 3.12 (dd, *J* = 6.9 and 17.0 Hz, 1H), 3.41 (dd, *J* = 5.8 and 17.0 Hz, 1H), 4.57 (d, *J* = 15.4 Hz, 1H), 5.06 (d, *J* = 15.4 Hz, 1H), 5.23 (t, *J* = 6.3 Hz, 1H), 7.08 (dd, *J* = 3.9 and 4.9 Hz, 1H), 7.18-7.27 (m, 5H), 7.40-7.43 (m, 1H), 7.46 (dd, *J* = 1.0 and 3.8 Hz, 1H), 7.50-7.53 (m, 2H), 7.68 (dd, *J* = 1.0 and 4.9 Hz, 1H), 7.91-7.95 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 20°C) *δ* 42.8, 44.7, 55.9, 122.8, 123.9, 127.5, 128.0, 128.3, 128.5, 128.6, 131.7 131.9, 132.4, 134.6, 137.0, 143.5, 145.5, 168.5, 189.7; HRMS (ESI) m/z: calculated for $C_{21}H_{18}NO_2S$ $[M+H]^+$: 348.1058, found: 348.1060.

2-Benzyl-3-(2-(5-bromothiophen-2-yl)-2-oxoethyl)isoindolin-1-one (4as): Prepared from hydroxy lactam **1a** (0.25 mmol) and 2-acetyl-5-bromothiophene **3s** (2 equiv) in toluene following the general procedure at 110°C with 1 mol % of $Sn(NTf_2)_4$.8DMSO. Reaction time: 5 h. The crude material was purified by flash chromatography on silica gel (eluting with Cyclohexane/EtOAc = 70:30) to give the title compound as a white solid. Yield: 93% (99 mg). *Rf* = 0.41 (cyclohexane/EtOAc: 60/40); mp = 145°C; IR (neat) *υ* 1678, 1646, 1411, 1340, 984, 736 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, 20°C) *δ* 3.03 (dd, *J* = 6.7 and 16.9 Hz, 1H), 3.30 (dd, *J* = 5.9 and 16.9 Hz, 1H), 4.61 (d, *J* = 15.4 Hz, 1H), 4.99 (d, *J* = 15.4 Hz, 1H), 5.20 (t, *J* = 6.3 Hz, 1H), 7.03 (d, *J* = 4.1 Hz, 1H), 7.13 (d, *J* = 4.1 Hz, 1H), 7.20-7.26 (m, 5H), 7.37-7.34 (m, 1H), 7.48-7.56 (m, 2H), 7.92-7.95 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 20°C) *δ* 42.2, 44.8, 55.9, 122.6, 123.9, 124.0, 127.6, 128.0, 128.6, 128.7, 131.4, 131.7, 131.9, 132.5, 137.0, 144.9, 145.3, 168.5, 188.6; HRMS (ESI) m/z: calculated for $C_{42}H_{32}Br_2$ $NaN_2O_4S_2$ $[2M+Na]^+$: 875.0036, found: 875.0041.

2-Benzyl-3-(2-oxo-2-(pyridin-2-yl)ethyl)isoindolin-1-one (4at): Prepared from hydroxy lactam **1a** (0.25 mmol) and 2-acetylpyridine **3t** (2 equiv) in toluene following the general procedure at 110°C with 1 mol %

of $Sn(NTf_2)_4$.8DMSO. Reaction time: 48 h. The crude material was purified by flash chromatography on silica gel (eluting with Cyclohexane/EtOAc = 70:30) to give the title compound as a white solid. Yield: 76% (65 mg). *Rf* = 0.33 (cyclohexane/EtOAc: 60/40); mp = 122°C; IR (neat) υ 1682, 1410, 1360, 992, 725 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, 20°C) δ 3.52 (dd, *J* = 7.0 and 17.8 Hz, 1H), 3.87 (dd, *J* = 5.4 and 17.8 Hz, 1H), 4.47 (d, *J* = 15.4 Hz, 1H), 5.18 (t, *J* = 6.7 Hz, 1H), 5.23 (d, *J* = 15.4 Hz, 1H), 7.16-7.28 (m, 5H), 7.41-7.51 (m, 4H), 7.85 (td, *J* = 1.7 and 7.7 Hz, 1H), 7.91-7.93 (m, 1H), 8.03 (dt, *J* = 1.0 and 7.9 Hz, 1H), 8.60 (ddd, *J* = 0.9, 1.6 and 4.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 20°C) δ 41.0, 44.4, 55.6, 121.9, 122.8, 123.8, 127.4, 127.5, 128.0, 128.3, 128.6, 131.6, 131.8, 136.9, 137.1, 145.9, 148.9, 152.6, 168.5, 198.8; HRMS (ESI) m/z: calculated for $C_{22}H_{19}N_2O_2$ $[M+H]^+$: 343.1446, found: 343.1444.

2-Benzyl-3-(2-oxo-2-(pyrazin-2-yl)ethyl)isoindolin-1-one (4au): Prepared from hydroxy lactam **1a** (0.25 mmol) and 2-acetylpyrazine **3u** (2 equiv) in toluene following the general procedure at 110°C with 1 mol % of $Sn(NTf_2)_4$.8DMSO. Reaction time: 24 h. The crude material was purified by flash chromatography on silica gel (eluting with Cyclohexane/EtOAc = 70:30) to give the title compound as a white solid. Yield: 94% (81 mg). *Rf* = 0.23 (cyclohexane/EtOAc: 60/40); mp = 163°C; IR (neat) υ 1677, 1647, 1411, 985, 736 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, 20°C) δ 3.45 (dd, *J* = 6.2 and 18.1 Hz, 1H), 3.80 (dd, *J* = 6.1 and 18.1 Hz, 1H), 4.65 (d, *J* = 15.5 Hz, 1H), 5.03 (d, *J* = 15.5 Hz, 1H), 5.20 (t, *J* = 6.1 Hz, 1H), 7.06-7.11 (m, 1H), 7.15-7.25 (m, 4H), 7.41-7.45 (m, 1H), 7.47-7.57 (m, 2H), 7.92-7.95 (m, 1H), 8.52 (dd, *J* = 1.5 and 2.4 Hz, 1H), 8.74 (d, *J* = 2.5 Hz, 1H), 9.16 (d, *J* = 1.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 20°C) δ 41.2, 44.7, 55.6, 122.6, 124.0, 127.3, 127.9, 128.5, 128.6, 131.7, 131.8, 136.9, 143.4, 143.6, 145.5, 146.7, 148.0, 168.6, 198.1; HRMS (ESI) m/z: calculated for $C_{21}H_{18}N_3O_2$ $[M+H]^+$: 344.1399, found: 344.1397.

***N*-Tosyl-2-(2-oxocyclohexyl)pyrrolidine (7aa):** Prepared from methoxy compound **6a** (0.25 mmol) and cyclohexanone **3a** (3 equiv) in acetonitrile following the general procedure at 90°C with 1 mol % of $Sn(NTf_2)_4$.8DMSO. Reaction time: 2.5 h. The crude material was purified by flash chromatography on silica gel (eluting with Cyclohexane/EtOAc = 80:20) to give the title compound as a white solid. Yield: 80% (64 mg); The adduct was obtained as a mixture of two diastereoisomers (d_1/d_2 = 54:46). *Rf* = 0.45 (cyclohexane/EtOAc: 70/30); IR ($CHCl_3$) υ 1703, 1339, 1155 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, 20°C) mixture of diastereomers δ 1.22-1.90 (m, 7H), 1.91-2.16 (m, 2H), 2.21-2.50 (m, 3.46H), 2.43 (s, 3H), 3.09 (s, 0.54H), 3.17-3.44 (m, 2H), 3.98-4.08 (m, 1H), 7.29-7.35 (m, 2H), 7.67-7.74 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, 20°C) mixture of diastereomers δ 21.5, 23.8, 24.6, 24.8, 25.1, 26.5, 27.3, 28.2, 28.2, 30.5, 32.0, 42.2, 43.0, 48.6, 49.8, 54.8, 55.4, 58.6, 60.2, 127.6, 127.7, 129.7, 133.3, 135.0, 143.4, 143.5, 211.9, 212.3; Data analyses were identical in all respects with our previously reported data.[16g]

***N*-Benzylcarboxy-2-(2-oxocyclohexyl)pyrrolidine (7ba):** Prepared from methoxy compound **6b** (0.25 mmol) and cyclohexanone **3a** (3 equiv) in acetonitrile following the general procedure at 60°C with 1 mol % of $Sn(NTf_2)_4$.8DMSO. Reaction time: 8 h. The crude material was purified by flash chromatography on silica gel (eluting with Cyclohexane/EtOAc = 80:20) to give the title compound as a colorless oil. Yield: 66% (50 mg). The adduct was obtained as an inseparable mixture of two diastereoisomers, the ratio of which could not be determined due to complication of both ^1H and ^{13}C NMR spectra by the presence of rotamers. *R*f = 0.20 (cyclohexane/EtOAc : 80/20); ^1H NMR (300 MHz, CDCl3, 20°C) δ 1.19-2.02 (m, 9H), 2.04-2.43 (m, 3H), 2.63-2.74 (m, 0.25H), 2.83-2.97 (m, 0.25H), 3.14-3.58 (m, 2.5H), 3.97-4.37 (m, 1H), 4.93-5.22 (m, 2H), 7.22-7.35 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$, 20°C) δ 24.6, 24.9, 26.7, 27.2, 27.9, 29.7, 31.1, 42.1, 42.7, 46.6, 47.1, 51.9, 53.3, 56.9, 66.6, 127.8, 127.9, 128.4, 128.5, 136.9, 154.8, 155.5, 211.8, 212; Data analyses were identical in all respects with literature data.[33]

***N*-(4-Methoxybenzyl)-5-(2-Oxo-cyclohexyl)pyrrolidin-2-one (9a):** Prepared from methoxy lactam **8** (0.25 mmol) and cyclohexanone **3a** (3 equiv) in acetonitrile following the general procedure at 60°C with 1 mol % of $Sn(NTf_2)_4$.8DMSO. Reaction time: 8 h. The crude material was purified by flash chromatography on silica gel (eluting with Cyclohexane/EtOAc = 20:80) to give the title compound as a colorless oil. Yield: 60% (45 mg). The adduct was obtained as a mixture of two diastereoisomers (d_1/d_2 = 52:48). *Rf* = 0.26 (d_1) and 0.15 (d_2) (cyclohexane/EtOAc: 80/20); IR ($CHCl_3$) υ 1703, 1667, 1611 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, 20°C) mixture of diastereoisomers (deliberately not separated) δ 1.15-2.53 (m, 12H), 2.53-2.77 (m, 1H), 3.80 (s, 1.56H, 3H d_1), 3.81 (s, 1.44H, 3H d_2), 3.95 (dt, *J* = 3.4 and 9.6Hz, 0.52 H), 3.99-4.14 (m, 1.48H), 4.63 (d, *J* = 14.9 Hz, 0.52H, 1H d_1), 4.70 (d, *J* = 14.9 Hz, 0.48 H, 1H d_2), 6.81-6.88 (m, 2H), 7.13-7.24 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, 20°C) mixture of diastereoisomers δ 20.8, 22.5, 24.5, 25.0, 25.7, 26.9, 27.0, 28.8, 30.3, 30.5, 42.2, 44.2, 45.2, 51.4, 53.2, 55.3, 55.3, 56.3, 57.1, 113.9, 114.1, 128.6, 129.2, 129.3, 129.6, 158.9, 159.1, 175.6, 176.3, 210.2, 210.7; Data analyses were identical in all respects with previously reported data.[16b]

2-(1,1-Dioxido-2-(prop-2-yn-1-yl)-2,3-dihydrobenzo[d]isothiazol-3-yl) cyclohexanone (11aa): Prepared from hydroxy sultam **10a** (0.25 mmol) and cyclohexanone **3a** (3 equiv) in acetonitrile following the general procedure at 90°C with 1 mol % of $Sn(NTf_2)_4$.8DMSO. Reaction time: 4 h. The crude material was purified by flash chromatography on silica gel (eluting with Cyclohexane/EtOAc = 70:30) to give the title compound as a white solid. Yield: 61% (46 mg). The adduct was obtained as a mixture of two diastereoisomers (d_1/d_2 = 60:40). *Rf* = 0.34 (Cyclohexane/EtOAc : 60/40), mp = 156°C; IR ($CHCl_3$) υ 1696 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, 20°C) mixture of diastereoisomers δ 1.02 (m, 0.6H, 1H d_1), 1.21-2.63 (m, 8.4H), 2.81 (m, 0.4H, 1H d_2), 3.13 (m, 0.6H, 1H d_1), 4.18 (s, 1.2H, 2H d_1), 4.27 (s, 1.2H, 2H d_2), 5.44 (d, *J* = 2.0 Hz, 0.6H, 1H d_1), 5.48 (bs, 0.4H, 1H d_2), 7.37-7.69 (m, 3H), 7.74-7.84 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 20°C) mixture of diastereoisomers δ 24.6, 24.7, 26.8, 27.1, 27.5, 27.5, 34.1, 36.9, 42.1, 42.3, 53.5, 56.5, 60.0, 60.5, 73.0, 73.8, 77.3, 78.2, 121.3, 121.4, 123.9, 126.3, 129.3, 129.4, 132.9, 133.3, 135.4, 135.5, 136.1, 138.1, 210.4, 211.2; HRMS (ESI) calculated for $C_{16}H_{18}NO_3S$ $[M+H^+]$: 304.1007, found: 304.1007.

1-(2-Benzyl-1,1-dioxido-2,3-dihydrobenzo[d]isothiazol-3-yl)propan-2-one (11bi): Prepared from hydroxy sultam **10b** (0.25 mmol) and acetone **3i** (3 equiv) in toluene following the general procedure at 110°C with 1 mol % of $Sn(NTf_2)_4$.8DMSO. Reaction time: 4 h. The crude material was purified by flash chromatography on silica gel (eluting with Cyclohexane/EtOAc = 70:30) to give the title compound as a white solid. Yield: 79 % (62 mg). *Rf* = 0.25 (cyclohexane/EtOAc: 70/30); mp = 89°C; IR (neat) υ 1716, 1279, 1164, 1135, 1062, 709 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, 20°C) δ 1.92 (s, 3H), 2.79 (dd, *J* = 6.2 and 18.1 Hz, 1H), 2.98 (dd, *J* = 5.6 and 18.1 Hz, 1H), 4.44 (d, *J* = 15.6 Hz, 1H), 4.59 (d, *J* = 15.6 Hz, 1H), 5.01 (t, *J* = 5.9 Hz, 1H), 7.28-7.43 (m, 6H), 7.52-7.61 (m, 2H), 7.84 (dd, *J* = 1.4 and 6.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 20°C) δ 30.3, 47.2, 48.2, 56.4, 121.3, 124.3, 128.0, 128.5, 128.8, 129.4, 133.0, 134.7, 135.7, 138.1, 205.4; HRMS (ESI) m/z: calculated for $C_{17}H_{18}NO_3S$ $[M+H]^+$: 316.1007, found: 316.1005.

1-(2-Allyl-1,1-dioxido-2,3-dihydrobenzo[d]isothiazol-3-yl)propan-2-one (11ci): Prepared from hydroxy sultam **10c** (2.5 mmol) and acetone **3i** (10 equiv) in toluene following the general procedure at 90°C with 0.1 mol % of $Sn(NTf_2)_4$.8DMSO. Reaction time: 48 h. The crude material was purified by flash chromatography on silica gel (eluting with Cyclohexane/EtOAc = 70:30) to give the title compound as colorless oil.

Yield: 84 % (557 mg). *Rf* = 0.25 (cyclohexane/EtOAc: 70/30); IR (neat) υ 1716, 1455, 1281, 1134, 1062, 709 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, 20°C) δ 2.22 (s, 3H), 2.90 (dd, *J* = 6.5 and 17.9 Hz, 1H), 3.18 (dd, *J* = 5.8 and 17.9 Hz, 1H), 3.91 (ddt, *J* = 1.1, 7.3 and 15.7 Hz, 1H), 4.04 (ddt, *J* = 1.4, 5.4 and 15.7 Hz, 1H), 5.06 (t, *J* = 6.2 Hz, 1H), 5.28 (ddd, *J* = 1.2, 2.4 and 10.1 Hz, 1H), 5.39 (ddd, *J* = 1.1, 7.3 and 10.1 Hz, 1H), 5.83-5.95 (m, 1H), 7.37-7.40 (m, 1H), 7.52-7.63 (m, 2H), 7.78-7.81 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 20°C) δ 30.7, 47.2, 48.6, 56.2, 119.5, 121.3, 124.4, 129.4, 132.5, 133.0, 135.2, 138.5, 205.7; HRMS (ESI) m/z: calculated for $C_{13}H_{15}NaNO_3S$ $[M+Na]^+$: 288.0671, found: 288.0676.

2-Benzyl-3-(2-oxocyclohexyl)-2,3,4,5,6,7-hexahydro-1H-isoindol-1-one (13a): Prepared from hydroxy lactam **12** (0.25 mmol) and cyclohexanone **3a** (3 equiv) in acetonitrile following the general procedure at 90°C with 1 mol % of $Sn(NTf_2)_4.8DMSO$. Reaction time: 24 h. The crude material was purified by flash chromatography on silica gel (eluting with Cyclohexane/EtOAc = 70:30) to give the title compound as colorless oil. Yield: 87 % (70 mg). The adduct was obtained as a mixture of two diastereoisomers (d_1/d_2 = 68:32). *Rf* = 0.25 (cyclohexane/EtOAc: 70/30); IR (neat) υ 1728, 1672, 1160 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, 20°C) mixture of diastereoisomers δ 0.80-2.50 (m, 16.68 H), 2.63 (m, 0.32H, 1H d_2), 4.33 (d, *J* = 15.4 Hz, 0.32H, 1H d_2), 4.43 (d, *J* = 15.0 Hz, 0.68H, 1H d_1), 4.58 (d, *J* = 15.0 Hz, 0.68H, 1H d_1), 4.61 (s, 0.32H, 1H d_2), 4.81 (s, 0.68H, 1H d_1), 4.82 (d, *J* = 15.4 Hz, 0.32H, 1H d_2), 7.18-7.40 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$, 20°C) mixture of diastereoisomers δ 20.4, 20.5, 21.7, 21.9, 22.3, 23.1, 23.6, 24.1, 24.2, 25.0, 25.1, 25.6, 26.2, 41.6, 41.8, 44.2, 45.8, 48.8, 50.2, 60.8, 61.0, 127.0, 127.5, 127.8, 128.2, 128.7, 129.0, 132.7, 133.0, 137.8, 138.4, 152.5, 152.5, 172.2, 173.2, 209.6, 209.8; HRMS (ESI) m/z: calculated for $C_{21}H_{25}NaNO_2$ $[M+Na]^+$: 346.1783, found: 346.1782.

2-Benzyl-3-(2-oxocyclopentyl)-2,3,4,5,6,7-hexahydro-1*H*-isoindol-1-one (13d): Prepared from hydroxy lactam **12** (0.25 mmol) and cyclopentanone **3d** (3 equiv) in acetonitrile following the general procedure at 90°C with 1 mol % of $Sn(NTf_2)_4.8DMSO$. Reaction time: 24 h. The crude material was purified by flash chromatography on silica gel (eluting with Cyclohexane/EtOAc = 70:30) to give the title compound as colorless oil. Yield: 88 % (68 mg). The adduct was obtained as a mixture of two diastereoisomers (d_1/d_2 = 52:48). *Rf* = 0.23 (cyclohexane/EtOAc: 70/30); IR (neat) υ 1733, 1670, 1408, 1160, 729 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, 20°C) mixture of diastereoisomers δ 0.88 (m, 0.48H, 1H d_2), 1.07-2.44 (m, 11.04H), 2.61 (m, 0.48H, 1H d_2), 4.16 (d, *J* = 8.0 Hz, 0.48H, 1H d_2), 4.21 (d, *J* = 8.1 Hz, 0.52H, 1H d_1), 4.35 (bs, 0.52H, 1H d_1), 4.45 (bs, 0.48H, 1H d_2), 4.60 (d, *J* = 15.3 Hz, 0.52H, 1H d_1), 4.94 (d, *J* = 15.3 Hz, 0.48H, 1H d_2), 7.19-7.35 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$, 20°C) mixture of diastereoisomers δ 20.0, 20.1, 20.3, 20.4, 21.4, 21.7, 21.8, 22.2, 22.2, 23.1, 23.1, 24.9, 38.0, 39.0, 43.9, 45.7, 49.1, 49.9, 61.3, 61.5, 127.2, 127.5, 127.9, 128.4, 128.5, 128.7, 132.2, 133.5, 137.5, 137.8, 151.2, 153.5, 171.5, 173.3, 218.2, 219.0; HRMS (ESI) m/z: calculated for $C_{20}H_{24}NO_2$ $[M+H]^+$: 310.1813, found: 310.1815.

2-Benzyl-3-(1-methoxy-2-oxo-2-phenylethyl)-2,3,4,5,6,7-hexahydro-1*H*-isoindol-1-one (13e): Prepared from hydroxy lactam **12** (0.25 mmol) and 2-methoxyacetophenone **3e** (3 equiv) in acetonitrile following the general procedure at 50°C with 1 mol % of $Sn(NTf_2)_4.8DMSO$. Reaction time: 5 h. The crude material was purified by flash chromatography on silica gel (eluting with Cyclohexane/EtOAc = 70:30) to give the title compound as a colorless oil. Yield: 50 % (47 mg). The adduct was obtained as a single diastereoisomer. *Rf* = 0.20 (cyclohexane/EtOAc: 70/30); IR (neat) υ1672, 1447, 1416, 1104, 727 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, 20°C) δ 1.43-1.85 (m, 8H), 4.24 (t, *J* = 5.4 Hz, 1H), 4.31 (d, *J* = 15.4 Hz, 1H), 4.84 (d, *J* = 2.3 Hz, 1H), 5.29 (d, *J* = 15.4 Hz, 1H), 7.30-7.42 (m, 7H), 7.48-7.55 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 20°C) δ 20.3, 21.3, 22.0, 24.2, 44.5, 58.7, 63.6, 81.5, 127.6, 127.8, 128.3, 128.8, 128.9, 133.3, 133.4, 136.3, 137.6, 150.0, 172.0, 197.7; HRMS (ESI) m/z: calculated for $C_{24}H_{26}NO_3$ $[M+H]^+$: 376.1924, found: 376.1926.

2-Benzyl-3-(2-oxo-2-phenylethylidene)-2,3,4,5,6,7-hexahydro-1*H*-isoindol-1-one (13e'): Prepared from hydroxy lactam **12** (0.25 mmol) and 2-methoxyacetophenone **3e** (3 equiv) in toluene following the general procedure at 110°C with 1 mol % of $Sn(NTf_2)_4.8DMSO$. Reaction time: 16 h. The crude material was purified by flash chromatography on silica gel (eluting with Cyclohexane/EtOAc = 70:30) to give the title compound as a yellow solid. Yield: 83% (71 mg). The adduct was obtained as a mixture of two diastereoisomers (*E*/*Z* = 62:38). *Rf* = 0.63 (cyclohexane/EtOAc: 70/30); mp = 101°C; IR (neat) υ 1698, 1647, 1615, 1222, 767 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, 20°C) mixture of diastereoisomers δ 1.67-1.83 (m, 4H), 2.23-2.52 (m, 4H), 4.92 (s, 1.24H, 2H *E*), 5.14 (s, 0.76H, 2H *Z*), 6.05 (s, 0.38H, 1H *Z*), 6.31 (s, 0.62H, 1H *E*) 6.87-6.90 (m, 7H), 6.95-6.98 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 20°C) mixture of diastereoisomers δ 20.5, 21.0, 21.1, 21.2, 21.7, 22.1, 22.5, 25.0, 43.0, 44.2, 103.6, 107.0, 126.8, 127.0, 127.4, 127.5, 128.1, 128.2, 128.4, 128.5, 128.9, 132.7, 132.8, 133.1, 135.7, 136.7, 136.8, 137.9, 138.1, 143.6, 146.1, 146.5, 147.8, 169.9, 171.9, 190.1, 190.8; HRMS (ESI) m/z: calculated for $C_{23}H_{22}NO_2$ $[M+H]^+$: 344.1652, found: 344.1654.

(*E*)-2-Benzyl-3-(2-oxo-4-phenylbut-3-enyl)-2,3,4,5,6,7-hexahydro-1*H*-isoindol-1-one (13f): Prepared from hydroxy lactam **12** (0.25 mmol) and (*E*)-4-phenylbut-3-en-2-one **3f** (3 equiv) in toluene following the general procedure at 110°C with 1 mol % of $Sn(NTf_2)_4.8DMSO$. Reaction time: 18 h. The crude material was purified by flash chromatography on silica gel (eluting with Cyclohexane/EtOAc = 70:30) to give the title compound as a colorless oil. Yield: 49% (46 mg). *Rf* = 0.2 (cyclohexane/EtOAc: 70/30); IR (neat) υ 1668, 1607, 1089, 730 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, 20°C) δ 1.57-1.74 (m, 4H), 2.08-2.29 (m, 4H), 2.73 (dd, *J* = 6.0 and 16.9 Hz, 1H), 2.87 (dd, *J* = 6.0 and 16.9 Hz, 1H), 4.42 (d, *J* = 15.5 Hz, 1H), 4.51 (m, 1H), 4.81 (d, *J* = 15.4 Hz, 1H), 6.55 (d, *J* = 16.2 Hz, 1H), 7.11-7.58 (m, 11H); ^{13}C NMR (75 MHz, $CDCl_3$, 20°C) δ 20.4, 21.8, 22.2, 23.6, 41.8, 44.5, 58.6, 125.5, 127.3, 128.0, 128.4, 128.6, 129.0, 130.9, 131.6, 134.0, 137.8, 143.5, 154.0, 171.8, 196.8; HRMS (ESI) m/z: calculated for $C_{25}H_{26}NaNO_2$ $[M+Na]^+$: 394.1783, found: 394.1782.

2-Benzyl-3-(2-oxopropyl)-2,3,4,5,6,7-hexahydro-1*H*-isoindol-1-one (13i): Prepared from hydroxy lacatam **12** (0.25 mmol) and acetone **3i** (3 equiv) in toluene following the general procedure at 110°C with 1 mol % of $Sn(NTf_2)_4.8DMSO$. Reaction time: 3 h. The crude material was purified by flash chromatography on silica gel (eluting with Cyclohexane/EtOAc = 70:30) to give the title compound as a white solid. Yield: 73 % (52 mg). *Rf* = 0.25 (cyclohexane/EtOAc: 70/30); mp = 90°C; IR (neat) υ 1719, 1666, 1429, 1407, 737 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, 20°C) δ 1.60-1.78 (m, 4H), 1.84 (s, 3H), 2.07-2.17 (m, 2H), 2.22-2.35 (m, 2H), 2.50 (dd, *J* = 6.3 and 18.2 Hz, 1H), 2.58 (dd, *J* = 5.6 and 18.0 Hz, 1H), 3.39 (t, *J* = 6.0 Hz, 1H), 4.52 (d, *J* = 15.5 Hz, 1H), 4.64 (d, *J* = 15.5 Hz, 1H), 7.20-7.33 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$, 20°C) δ 20.3, 21.8, 22.2, 23.3, 30.2, 44.5, 44.6, 58.2, 127.2, 127.9, 128.6, 131.7, 138.1, 153.4, 171.7, 205.5; HRMS (ESI) m/z: calculated for $C_{18}H_{22}NO_2$ $[M+H]^+$: 284.1654, found: 284.1655.

1-Benzyl 3,3-dimethyl 2-(2-oxo-2,3-dihydro-1*H*-inden-1-yl)pyrrolidine-1,3,3-tricarboxylate (15av): Prepared from 1-benzyl 3,3-dimethyl 2-methoxypyrrolidine-1,3,3-tricarboxylate **14a** (0.25 mmol) and 2-indanone **3v** (3 equiv) in acetonitrile following the general procedure at 90°C with 1 mol % of $Sn(NTf_2)_4.8DMSO$. Reaction time: 6 h. The crude material was purified by flash chromatography on silica gel (eluting with Cyclohexane/EtOAc = 70:30) to give the title compound as a colorless oil. Yield: 82 % (92 mg). The adduct was obtained as an inseparable mixture of two diastereoisomers, the ratio of which could not be determined due to complication of both ^1H and ^{13}C NMR spectra by the presence of

rotamers. *Rf* = 0.33 (cyclohexane/EtOAc: 70/30); IR (neat) υ 1734, 1695, 1409, 1265, 1217, 1111, 1070, 730 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, 20°C) mixture of diastereoisomers δ 2.36-3.18 (m, 3.74H), 3.18-3.90 (m, 9H), 4.47 (d, *J* = 12.1 Hz, 0.26H), 4.82-5.02 (m, 1H), 5.04-5.19 (m, 1H), 5.21-5.44 (m, 1H), 6.94-7.43 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$, 20°C) mixture of diastereoisomers δ 27.6, 27.8, 29.5, 31.0, 32.2, 37.1, 37.5, 37.8, 43.4, 43.5, 44.0, 44.3, 52.5, 52.7, 52.9, 53.0, 53.1, 53.4, 53.4, 54.2, 54.9, 56.0, 57.3, 61.2, 61.2, 61.7, 62.1, 62.5, 62.7, 63.2, 66.7, 66.9, 67.0, 67.3, 124.7, 124.8, 126.2, 126.5, 127.1, 127.4, 127.5, 127.6, 127.6, 127.7, 127.7, 127.8, 127.9, 128.0, 128.1, 128.2, 128.3, 128.3, 128.4, 128.4, 128.7, 129.5, 130.0, 130.1, 133.7, 133.8, 135.9, 136.6, 137.8, 138.3, 154.2, 154.3, 154.4, 167.5, 167.9, 170.0, 170.2, 210.2, 210.4, 214.4, 214.9; HRMS (ESI) m/z: calculated for $C_{25}H_{26}NO_7$ $[M+H]^+$: 452.1722, found: 452.1722.

Trimethyl 2-(2-oxo-1,2,3,4-tetrahydronaphthalen-1-yl)pyrrolidine-1,3,3-tricarboxylate (15bw): Prepared from trimethyl 2-methoxypyrrolidine-1,3,3-tricarboxylate **14b** (0.25 mmol) and 2-tetralone **3w** (3 equiv) in acetonitrile following the general procedure at 90°C with 1 mol % of $Sn(NTf_2)_4.8DMSO$. Reaction time: 6 h. The crude material was purified by flash chromatography on silica gel (eluting with Cyclohexane/EtOAc = 70:30) to give the title compound as colorless oil. Yield: 72 % (70 mg). The adduct was obtained as an inseparable mixture of two diastereoisomers, the ratio of which could not be determined due to complication of both ^1H and ^{13}C NMR spectra by the presence of rotamers. *Rf* = 0.2 (cyclohexane/EtOAc: 70/30); IR (neat) υ 1734, 1702, 1449, 1385, 1019, 1176, 729 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, 20°C) mixture of diastereoisomers δ 2.11-3.06 (m, 5H), 3.07-3.87 (m, 13H), 5.18 (m, 0.72H), 5.31 (m, 0.28H), 6.94-7.18 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$, 20°C) mixture of diastereoisomers δ 27.6, 27.9, 29.5, 30.1, 31.1, 37.3, 37.5, 37.9, 42.6, 43.4, 43.4, 52.3, 52.5, 52.7, 52.8, 52.9, 53.4, 53.4, 54.5, 56.0, 57.4, 61.1, 61.6, 61.9, 62.0, 62.4, 63.1, 63.4, 100.0, 126.1, 126.2, 126.6, 127.3, 127.6, 127.7, 127.8, 127.9, 128.4, 129.3, 130.0, 130.2, 133.7, 133.8, 137.8, 138.2, 138.9, 154.8, 154.9, 155.4, 167.4, 167.5, 168.0, 170.0, 170.3, 209.8, 210.2, 210.3; HRMS (ESI) m/z: calculated for $C_{20}H_{23}NaNO_7$ $[M+Na]^+$: 412.1372, found: 412.1380.

Acknowledgements

B.T. and M.S.A. are grateful to the Tunisian government for scholarships. A. E. B. thanks the University of Le Havre for an ATER position. Dr Radouane Affani and Ms Nabawia Mechi are acknowledged for their contribution at the early stage of this study. We are grateful to Dr Nicolas Hucher and Ms Marie-José Tranchant for their analytical assistance.

Keywords: Direct S_N1 α-amidoalkylation • Lewis superacid catalysis • N,O-acetals • Enolisable ketones

[1] a) N. Soares Camilo, R. A. Pilli, *Tetrahedron Lett.* **2004**, *45*, 2821. b) O. Onomura, Y. Kanda, Y. Nakamura, T. Maki, Y. Matsumara, *Tetrahedron Lett.* **2002**, *43*, 3229. c) O. Onomura, Y. Kanda, M. Imai, Y. Matsumura, *Electrochim. Acta* **2005**, *50*, 4926. d) Y. Matsumura, T. Ikeda, O. Onomura, *Heterocycles* **2006**, *67*, 113.

[2] a) S. S. Kinderman, M. M. T. Wekking, J. H. van Maarseveen, H. E. Schoemaker, H. Hiemstra, F. P. J. T. Rutjes, *J. Org. Chem.* **2005**, *70*, 5519. b) F. Pin, S. Comesse, B. Garrigues, Š. Marchalín, A. Daïch, *J. Org. Chem.* **2007**, *72*, 1181. c) I. T. Raheem, P. S. Thiara, E. A. Peterson, E. N. Jacobsen, *J. Am. Chem. Soc.* **2007**, *129*, 13404; d) I. T. Raheem, P. S. Thiara, E. N. Jacobsen, *Org. Lett.* **2008**, *10*, 1577.

[3] For reviews and features articles: a) P. Melchiorre, *Angew. Chem. Int. Ed.* **2009**, *48*, 1360; *Angew. Chem.* **2009**, *121*, 1386. b) A. Gualandi, P. G. Cozzi, *Synlett*, **2013**, 281. c) D. M. Hodgson, A. Charlton, *Tetrahedron*, **2014**, *70*, 2207.

[4] For asymmetric organocatalytic S_N2 α-alkylations of aldehydes: B. List, I. Čorić, O. O. Grygorenko, P. S. J. Kaib, I. Komarov, A. Lee, M. Leutzsch, S. Chandra Pan, A. V. Tymtsunik, M. van Gemmeren, *Angew. Chem. Int. Ed.* **2014**, *53*, 282; *Angew. Chem.* **2014**, *126*, 286 and references cited therein.

[5] For selected key examples of asymmetric organocatalytic S_N1 α-alkylations of aldehydes, see: a) R. R. Shaikh, A. Mazzanti, M. Petrini, G. Bartoli, P. Melchiorre, *Angew. Chem. Int. Ed.* **2008**, *47*, 8707; *Angew. Chem.* **2008**, *120*, 8835. b) P.-G. Cozzi, F. Benfatti, L. Zoli, *Angew. Chem. Int. Ed.* **2009**, *48*, 1313; *Angew. Chem.* **2009**, *121*, 1339. c) A. R. Brown, W.-H. Kuo, E. N. Jacobsen, *J. Am. Chem. Soc.* **2010**, *132*, 9286. d) B. Xu, Z. –L. Guo, W.-Y. Jin, Z.-P. Wang, Y.-G. Peng, Q.-X. Guo,; *Angew. Chem. Int. Ed.* **2012**, *51*, 1059; *Angew. Chem.* **2012**, *124* 1083.

[6] For some examples of asymmetric organocatalytic S_N1 α-alkylations of aldehydes involving stable carbenium ions: a) A. Gualandi, E. Emer, M. G. Capdevila, P. G. Cozzi, *Angew. Chem. Int. Ed.* **2011**, *50*, 7842; *Angew. Chem.* **2011**, *123*, 7988. b) A. Gualandi, D. Petruzziello, E. Emer, P. G. Cozzi, *Chem. Commun*. **2012**, 3614. For a cascade reaction including an organocatalytic stereoselective S_N1 α-alkylation, see: c) J. Stiller, A. J. Vorholt, K. A. Ostrowski, A. Behr, M. Christmann, *Chem. Eur. J.* **2012**, *18*, 9496.

[7] For selected key examples of asymmetric dual-catalytic α-alkylation of aldehydes, see: a) A. Gualandi, L. Mengozzi, C. M. Wilson, P. G. Cozzi, *Synthesis* **2014**, 1321. b) M. G. Capdevila, F. Benfatti, L. Zoli, M. Stenta P. G. Cozzi, *Chem. Eur. J.* **2010**, *16*, 11237. c) K. Motoyama, M. Ikeda, Y. Miyake, Y. Nishibayashi, *Eur. J. Org. Chem.* **2011**, 2239.

[8] For selected key examples of dual-catalytic α-allylation of aldehydes and references cited, see: a) S. Afewerki, I. Ibrahem, J. Rydfjord, P. Breistein, A. Cordova, *Chem. Eur. J.* **2012**, *18*, 2972. b) M. Yoshida, E. Masaki, T. Terumine, S. Hara, *Synthesis* **2014**, *46*, 1367. c) M. Chiarucci, M. di Lillo, A. Romaniello, P. G. Cozzi, G. Cera, M. Bandini, *Chem. Sci.* **2012**, *3*, 2859. d) S. Krautwald, D. Sarlah, M. A. Schrafroth, E. M. Carreira, *Science* **2013**, *340*, 1065. e) G. Jiang. B. List, *Angew. Chem. Int. Ed.* **2011**, *50*, 9471; *Angew. Chem.* **2011**, *123*, 9643. f) P.-S. Wang, H.-C. Lin, Y.-J. Zhai, Z.-Y. Han, L.-Z. Gong, *Angew. Chem. Int. Ed.* **2014**, *53*, 12218; *Angew. Chem.* **2014**, *126*, 12414.

[9] For selected key examples of asymmetric organocatalytic dehydrogenative α-alkylation of aldehydes, see a) F. Benfatti, M. G. Capdevila, L. Zoli, E. Benedetto, P. G. Cozzi, *Chem. Commun.* **2009**, 5919. b) B. Zhang, S.-K. Xiang, L.-H. Zhang, Y. Cui, N. Jiao, *Org. Lett.* **2011**, *13*, 5212.

[10] For selected key examples of asymmetric organocatalytic α-alkylation of aldehydes involving radical and electron transfer processes: a) T. D. Beeson, A. Mastracchio, J.-B. Hong, K. Ashton, D. W. C. MacMillan, *Science* **2007**, *316*, 582. b) D. A. Nicewicz, D. W. C. MacMillan, *Science* **2008**, *322*, 77. c) E. Arceo, A. Bahamonde, G. Bergonzini, P. Melchiorre, *Chem. Sci.* **2014**, *5*, 2438. d) A. Gualandi, M. Marchini, L. Mengozzi, M. Natali, M. Lucarini, P. Ceroni, P. G. Cozzi, *ACS. Catal.* **2015**, *5*, 5927. e) E. R. Welin, A. A. Warkentin, J. C. Conrad, D. W. C. MacMillan, *Angew. Chem. Int. Ed.* **2015**, *54*, 9668; *Angew. Chem.* **2015** *127*, 9804.

[11] For selected examples of asymmetric organocatalytic S_N1 α-alkylation of ketones: a) L. Song, Q. X. Guo, X. C. Li, J. Tian, Y. G. Peng, *Angew. Chem. Int. Ed.* **2012**, *51*, 1899; *Angew. Chem.* **2012**, *124*, 1935. b) Reference 11c. c) L. Zhang, L. Cui, X. Li, J. Li, S. Luo, J.-P. Cheng, *Eur. J. Org. Chem.* **2010**, 4876. d) M. Trifonidou, C. G. Kotokos, *Eur. J. Org. Chem.* **2012**, 1563. e) X. Huo, M. Quan, G. Yang, X. Zhao, D. Liu, Y. Liu, W. Zhang, *Org. Lett.* **2014**, *16*, 1570.

[12] For selected examples of racemic direct catalytic α-alkylation of aldehydes and ketones involving highly reactive carbenium ions: a)

C. Xing, H. Sun, J. Zhang, G. Li, R. Y. Chi, *Chem. Eur. J.* **2011**, *17*, 12272. b) X. Pan, M. Li, Y. Gu, *Chem. Asian J.* **2014**, *9*, 268. c) N. Naveen, S. R. Koppolu, R. Balamurugan *Adv. Synth. Catal.* **2015**, *357*, 1463. d) K. V. Wagh, B. M. Bhanage *ACS Sustainable Chem. Eng.* **2016**, *4*, 445. e) Y. Inada, Y. Nishibayashi, S. Uemura,; *Angew. Chem. Int. Ed.* **2005**, *44*, 7715; *Angew. Chem.* **2005**, 117, 7893. For a stoichiometric direct α-alkylation of ketones: f) S. R. Koppolu, N. Naveen, R. Balamurugan, *J. Org. Chem.* **2014**, *79*, 6069.

[13] For a recent review on enantioselective organocatalytic transformations involving *N*-acyliminium ions, see : a) Y.-S. Lee, Md. M. Alam, R. S Keri, *Chem. Asian J.* **2013**, *8*, 2906. For a recent review on stereoselective organocatalytic transformations involving isoquinolinium and related ions : b) A. Gualandi, L. Mengozzi, E. Manoni, P. G. Cozzi, *Catal. Lett.* **2015**, *145*, 398. For seminal contributions in catalytic asymmetric amidoalkylations, see: c) M. Takamura, K. Funabashi, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* **2000**, *122*, 6327. d) O. Onomura, Y. Kanda, Y. Nakamura, T. Maki, Y. Matsumura, *Tetrahedron Lett.* **2002**, *43*, 3229. e) see ref. 2c. f) M. C. Muratore, C. A. Holloway, A. W. Pilling, R. I. Storer, G. Trevitt, D. J. Dixon, *J. Am. Chem. Soc.* **2009**, *131*, 10796.

[14] For seminal examples of asymmetric organocatalytic direct α-amidoalkylations of aldehydes involving *N*-acyliminium ions, see: a) L. Mengozzi, A. Gualandi, P. G. Cozzi, *Chem. Sci.* **2014**, *5*, 3915. b) S. Sun, Y. Mao, H. Lou, L. Liu, *Chem. Commun*. **2015**, 10691. c) F. Berti, F. Malossi, F. Marchetti, M. Pineschi, *Chem. Commun.* **2015**, 13694. d) C. M. R. Volla, E. Fava, I. Atodiresei, M. Rueping *Chem. Commun.* **2015**, *51*, 15788. e) L. Mengozzi, A. Gualandi, P. G. Cozzi, *Eur. J. Org. Chem.* **2016**, 3200.

[15] For selected examples of direct α-amidoalkylations of ketones which, except reference 15b, do not proceed catalytically, see : a) R. T. Sawant, M. Y. Stevens, L. R. Odell, *Eur. J. Org. Chem.* **2015**, 7743. b) B. Schweitzer-Chaput, M. Klussmann, *Eur. J. Org. Chem.* **2013**, 666. c) T. Fujita, H. Nagasawa, Y. Uto, T. Hashimoto, Y. Asakawa, H. Hori, *Org. Lett.* **2004**, *6*, 827. d) W. G. Earley, T. Oh, L. E. Overman, *Tetrahedron Lett.* **1988**, *29*, 3785. e) I. H. Sánchez, F. J. López, H. J. Flores, M. I. Larraza, *Heterocycles* **1983**, *20*, 247.

[16] a) R. Ben Othman, T. Bousquet, M. Othman, V. Dalla, *Org. Lett.* **2005**, *7*, 5335. b) R. Ben Othman, R. Affani, M. J. Tranchant, S. Antoniotti, V. Dalla, E. Duñach, *Angew. Chem., Int. Ed.* **2010**, *49*, 776; *Angew. Chem.* **2010***, 122,* 788. c) A. Devineau, G. Pousse, C. Taillier, J. Rouden, J. Blanchet, V. Dalla, *Adv. Synth. Catal.* **2010**, *352*, 2881. d) M. Hamon, N. Dickinson, A. Devineau, D. Bolien, M. J. Tranchant, C. Taillier, I. Jabin, D.-C. Harrowven, R. Whitby, A. Ganesan, V. Dalla, *J. Org. Chem.* **2014**, *79*, 1900. e) M. Michalska, O. Songis, C. Taillier, S. P. Bew, V. Dalla *Adv. Synth. Catal.* **2014**, *356*, 2040. f) L. Boiaryna, M.S. Azizi, A. El Bouakher, B. Picard, C. Taillier, M. Othman, M. Trabelsi-Ayadi, V. Dalla, *Org. Lett.*, **2015**, *17*, 2130. g) B. Touati, A. El Bouakher, C. Taillier, R. Ben Othman, M. Trabelsi-Ayadi, S. Antoniotti, E. Duñach, V. Dalla, *Chem. Eur. J.* **2016**, *22*, 6012.

[17] S. Antoniotti, V. Dalla, E. Duñach, *Angew. Chem., Int. Ed.* **2010**, *49*, 7860; *Angew. Chem.* **2010**, *122*, 8032.

[18] Scheme 1 shows simplified pictures of our two reactivity scales which are fully presented in the SI.

[19] It is worth noting that, for a given combination of substrate and ketone, no significant differences in terms of diastereoselectivity were observed between the room-temperature and thermal experiments.

[20] A lot more examples involving more favorable combinations of reaction partners, that are ketones and phthalimide-derived *N,O*-acetals identified as more reactive than the compounds used in table 2 (see reactivity scales in SI) were also obtained, yielding in every cases the corresponding coupled products in high yields.

[21] 10 equivalents of acetone were used in this case to prevent incomplete conversion due to possible loss of acetone by evaporation in refluxing toluene.

[22] Structure of the minor by-product thus formed in 10% yield was shown to be  resulting from condensation of acetonitrile on the *N*-acyliminium intermediate (Ritter-type reaction).

[23] Provided that solid $Sn(NTf_2)_4.xDMSO$ was added in the reaction vessel. When the reaction was carried out in toluene using a stock solution of tin catalyst in CH_3CN, the Ritter product was also fomed in the same proportion as when the reaction was run in acetonitrile.

[24] The ratio of adduct formed was estimated from combination of the ratios of branched and linear regioisomers measured on the ^1H NMR spectrum of the crude reaction mixture.

[25] This result also suggests that this catalytic Mannich process might operate in the presence of only 2 equivalents of the ketone, whilst we have mostly used 3 equivalents in a non optimized way throughout this work.

[26] Results not shown.

[27] Reactions of these class of substrates with 2-indanone were not selective and gave several products. Chromatography purification enabled collection of several fractions, the ^1H NMR spectra of which were too complicated to ascertain the presence of the desired Mannich adducts, which, if formed, resulted in rather low yields. With the less reactive cyclohexanone the desired products could be isolated as separable diastereoisomers in 25-33% yield and 17% yield, respectively.

[28] In comparison, the reaction of the *N*-benzyl phthalimidic acetoxy lactam **2b** in identical conditions (3 equiv. cyclohexanone **3a**, 1 mol % $Sn(NTf_2)_4$, rt, 24 h) gave approximately 80 % of conversion.

[29] S. Moussa, S. Comesse, V. Dalla, P. Netchitaïlo, A. Daïch, *Synlett* **2011**, 2425.

[30] Tin tetrakis(trifluoromethanesulfonimide)-DMSO complex is now commercially available from Sigma-Aldrich – CAS number 919356-21-1.

[31] S. Antoniotti, E. Duñach, *Chem. Commun.* **2008**, 993.

[32] Control experiments using *N*-allyl acetoxy lactam **2a** and cyclohexanone **3a** as reaction partners were run over 24 hours to compare the catalytic efficiency of $Sn(NTf_2)_4.x$ DMSO (with x = 4 or 8) batches. Since very similar conversions were obtained irrespective of the catalyst used, both catalysts were used indifferently in our study.

[33] R. Ben Othman, T. Bousquet, A. Fousse, M. Othman, V. Dalla, *Org. Lett.* **2005***, 7*, 2825.

Entry for the Table of Contents (Please choose one layout)

Layout 1:

FULL PAPER

Text for Table of Contents

((Insert TOC Graphic here: max. width: 5.5 cm; max. height: 5.0 cm; NOTE: the final letter height should not be less than 2 mm.))

Key Topic*

*Author(s), Corresponding Author(s)**

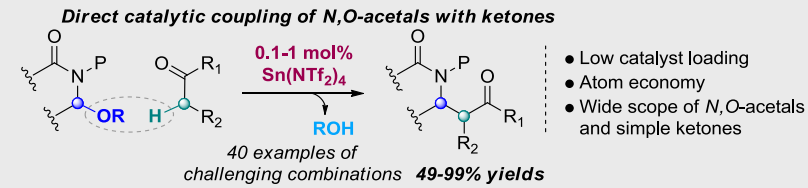
Page No. – Page No.

Title

*oneortwowordsthathighlighttheemphasisofthepaperorthefieldofthestudy

Layout 2:

FULL PAPER



Lewis superacid catalysis*

*B. Touati, A. El Bouakher, M. S. Azizi, C. Taillier, R. Ben Othman, M. Trabelsi-Ayadi, S. Antoniotti, E. Duñach, V. Dalla**

Page No. – Page No.

Atom Economical Catalytic Direct Substitution of *N,O*-Acetals with Simple Ketones

A general and powerful catalytic protocol for the direct amidoalkylation of simple enolisable ketones is described using the super Lewis acid $Sn(NTf_2)_4$ as catalyst. The synthetic potential of the reaction was demonstrated through the coupling of a large set of both carbonyl and *N,O*-acetalic substrates (mostly the simplest OH-hemi aminals), with very low catalyst loadings (≤ 1 mol%), providing the corresponding amidoalkylated ketones in high yields (up to 99%).