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# Transition metal-free domino acyl substitution/ Michael addition of alkenyl Grignard reagents to lactam esters: synthesis of lactam-bearing homoallylic ketones†

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A solvent-controlled protocol for the direct and transition metal-free addition of alkenyl Grignard reagents to vicinally functionalized  $sp^3$ -rich morpholinones has been developed, leading to the chemo and regioselective synthesis of lactam-bearing homoallylic ketones. The addition of lithium chloride proved to be essential. In cases where a new stereocenter is generated, the doubly branched homoallylic ketones are obtained in unexpectedly high diastereoselectivities. Efforts to extend the methodology to other heterosubstituted lactams revealed some important reactivity and selectivity differences.

## Introduction

Primarily due to the continuous search for new therapeutic agents for current difficult-to-cure diseases, the assembly of libraries of nitrogen- and oxygen-containing drug-like cyclic molecules with diversity has become a responsibility entrusted on synthetic organic chemists.<sup>1</sup> However, designing selective, efficient, cost-effective and modular strategies for accessing N-, N,O- and N,S-heterocycles can be quite daunting mainly due to conformational constraints. Meanwhile, the homoallylic ketone motif is an excellent synthon for accessing a plethora of medicinally pertinent entities, including quinolines,<sup>2</sup> isoquinolines,<sup>3</sup> pyrroles,<sup>4</sup> pyridines,<sup>5</sup> dehydropyrrolidines,<sup>6</sup> and homopiperazinones.<sup>7</sup> A synthetic strategy that merges a functionalized lactam and a homoallylic ketone would likely enhance the potential for the discovery of new small molecules with medicinal value given that the lactam topology is prevalent in natural products, ligands, and pharmaceuticals, including antibacterial, antioxidants, antitumor and antibiotics.<sup>8</sup> One way to reduce cost is through the implementation of domino/cascade reactions given that they are inherently step and atom-economical. We previously disclosed the synthesis of vicinally functionalized morpholinones of type **1** (Fig. 1)<sup>9</sup> and demonstrated their synthetic versatility through the preparation of alkenols such as **2**, which smoothly underwent Cu-catalyzed dehydrogenative coupling to furnish dihydropyran-fused morpholinones of type **3**.<sup>10</sup> Following insightful work by Lubell and co-workers,<sup>11</sup> organic chemists are beginning to

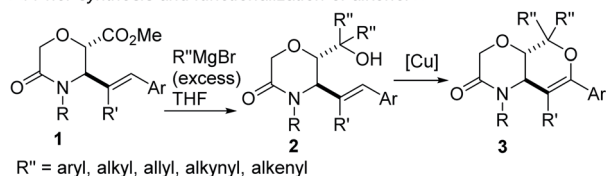
embrace the notion that the direct (*i.e.*, copper-free) addition of excess vinylmagnesium bromide to simple oxoesters can afford the expected 1,2-addition products as well as 1,4-addition products (see **4**) as contaminants. Indeed, during our studies on the preparation and dehydrogenative alkoxylation of **2**, we noticed that the addition of vinylmagnesium bromide to **1** using tetrahydrofuran (THF) as the solvent, yielded very small amounts of the homoallylic ketone side product (<5%).<sup>10</sup> Seeking a transition metal- and directing group-free cascade approach to lactam-bearing homoallylic ketones from ester **1**, we became interested in tuning the selectivity of the aforementioned reaction with the aim of overriding the innate tendency of **1** to form the 1,2-addition product (see **5**). In order to prepare homoallylic ketone **4** in an efficient and selective manner, we recognized that several other obstacles would have to be circumvented. For example, as has been demonstrated by Fleischer and co-workers using inherently more reactive thioesters (Fig. 1C),<sup>12</sup> the displaced methoxide nucleophile could out-compete the C-nucleophile, leading to products of type **12** (Fig. 1D). Additionally, electronically-suitable amides are known to react with excess vinylmagnesium bromide to afford  $\beta$ -aminoketones, following attack of the transient enone by the displaced amine (see **13**).<sup>13</sup> We have surmounted most of these barriers and herein demonstrate that **1** is amenable to transition metal- and directing group-free addition of alkenyl Grignard reagents, under solvent-controlled conditions. The best results are achieved with bulky solvents, consistent with literature reports that steric congestion tends to promote 1,4-addition of vinyl Grignard reagents to esters.<sup>11</sup> The addition of LiCl proved to be beneficial. The homoallylic ketones (**4**) are formed *via* a cascade process whereby conjugate addition of a second equivalent of the alkenyl Grignard reagent to transient

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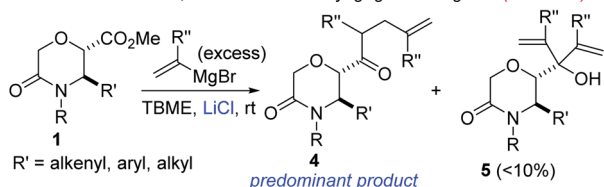
† Electronic supplementary information (ESI) available: Experimental procedures and spectroscopic data. See DOI: 10.1039/d0ra03885g



## A: Prior synthesis and functionalization of alkenol 2



## B: Transition metal-free and solvent-controlled cascade acyl substitution and concomitant 1,4-addition of alkenyl Grignard reagents (this work)



## C: Transition metal-free acyl substitution-Michael addition using thioesters

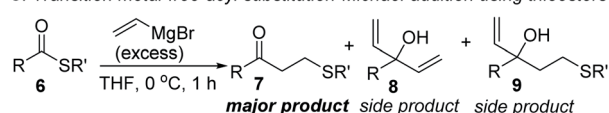
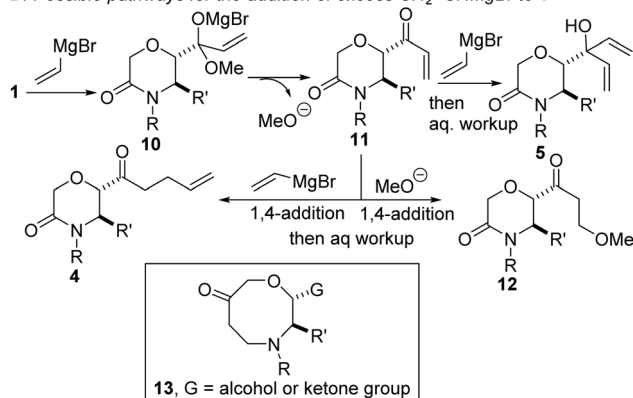
D: Possible pathways for the addition of excess  $\text{CH}_2=\text{CHMgBr}$  to 1

Fig. 1 (A) Prior work on morpholinone esters, (B) proposed plan for the construction of lactam-bearing homoallylic ketones, (C) first detailed report on transition metal-free cascade addition of vinylmagnesium bromide to thioesters, (D) possible reaction pathways.

enone **11** out-competes 1,2-addition as well as 1,4-addition of the displaced methoxide nucleophile.

## Results and discussion

We initiated studies on the selective synthesis of lactam-bearing homoallylic ketones by subjecting model ester **1a** to the reaction conditions described in Table 1. After cooling a solution of **1a** in THF to  $-20\text{ }^{\circ}\text{C}$ , excess vinylmagnesium bromide was introduced over a 1 minute period. Upon warming to room temperature and stirring for 30 min, subsequent hydrolytic workup afforded a 1 : 9 ratio of bis-homoallylic ketone **4a** and trienol **5a** (as judged by NMR and GC-MS, Table 1, entry 1). This result served as a control experiment since we already knew that strongly coordinating and unhindered THF favors the over-addition pathway. Of note, it is necessary to precool the reaction mixture prior to the addition of the Grignard reagent since attack of the lactam moiety is competitive at elevated

Table 1 Optimization of the chemoselective nucleophilic addition of vinylmagnesium bromide to allylic morpholinonate **1a**

Entry	Solvent	Time (h)	Ratio <b>4a</b> : <b>5a</b>	% conversion
1	THF	0.5	~10 : 90	≥99
2	2-MeTHF	0.5	~25 : 75	≥99
3	Et <sub>2</sub> O	3	~40 : 60	<50
4	TBME	3	~80 : 20	<50
5	TBME	12	~80 : 20	80
6	TBME	18	~80 : 20	≥99 (69) <sup>a</sup>
7	TBME	18	>95 : 5	≥99 (78) <sup>a,b</sup>
8	<b>TBME</b>	<b>12</b>	<b>&gt;95 : 5</b>	<b>≥99 (82)<sup>a,b</sup></b>
9	TBME	8	>95 : 5	≥99 (75) <sup>a,b</sup>
10	TBME	12	>95 : 5	≥99 (70) <sup>a,c</sup>
11	TBME	12	>95 : 5	≥99 (82) <sup>a,d</sup>
12	CBME	12	>95 : 5	≥99 (71) <sup>a,b</sup>

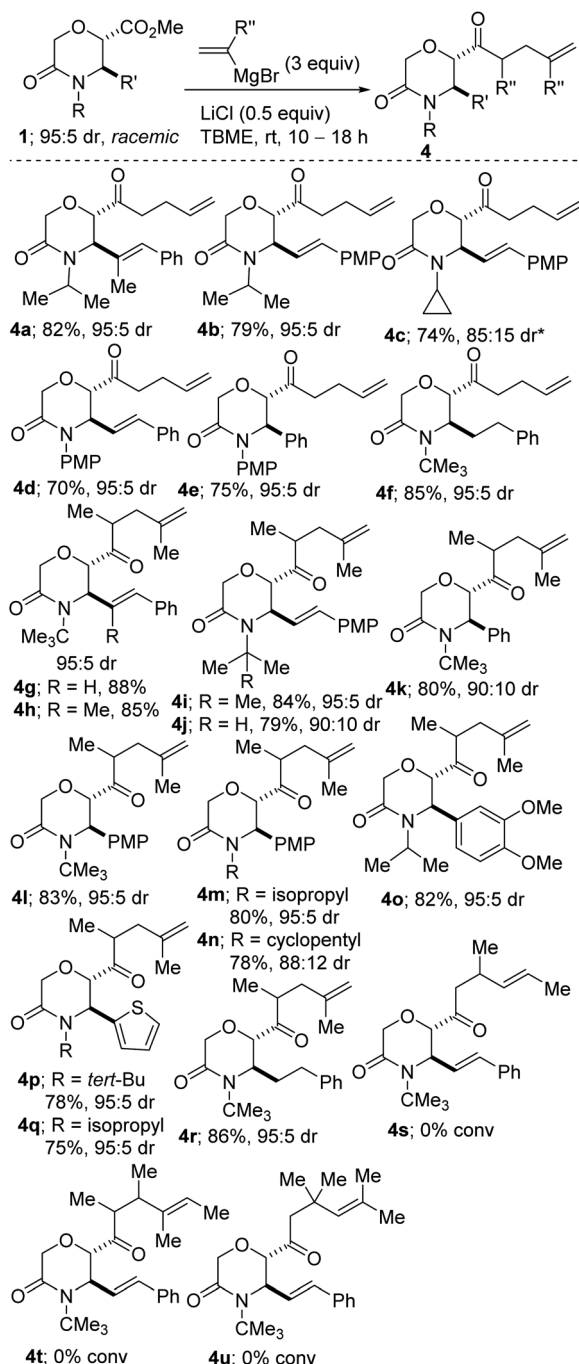
<sup>a</sup> Isolated yield of **4a** in parentheses. <sup>b</sup> 0.5 equiv. LiCl added. <sup>c</sup> 0.2 equiv. LiCl added. <sup>d</sup> 1 equiv. LiCl added.

temperatures. When environmentally benign 2-methyltetrahydrofuran (2-MeTHF)<sup>14</sup> was employed as the solvent, the reaction proceeded smoothly and the product ratio changed (entry 2). The nucleophilic addition proceeded recalcitrantly when less coordinating ethereal solvents such as diethyl ether (Et<sub>2</sub>O) and tert-butylmethyl ether (TBME) were employed (entries 3 & 4). Importantly, in the case of TBME, a reversal in selectivity was observed and the desirable 1,4-addition product was mostly obtained. This outcome is probably a reflection of the significant steric encumbrance of TBME since steric effects are known to influence the regio and chemoselectivity of addition of vinyl Grignard reagents to esters.<sup>11</sup> Ultimately, we found that when the reaction is aged for 12 h at room temperature in the presence of 0.5 equivalents of LiCl,<sup>15</sup> **4a** is isolated in 82% yield (entry 8). This level of efficiency is noteworthy for a cascade reaction. Another hindered solvent, cyclopentylmethyl ether (CPME), was evaluated but it did not perform as well as TBME. Such a solvent-controlled addition of Grignard reagents to carbonyl compounds has previously been observed.<sup>16</sup> Mechanistically speaking, two equivalents of vinylmagnesium bromide suffice for this transformation, but the third equivalent aided to maximize efficiency.

With satisfactory conditions for transition metal-free cascade acyl substitution and 1,4-addition of vinylmagnesium bromide to **1a** in hand (entry 8), the scope of the transformation with respect to the steric and electronic effects of the

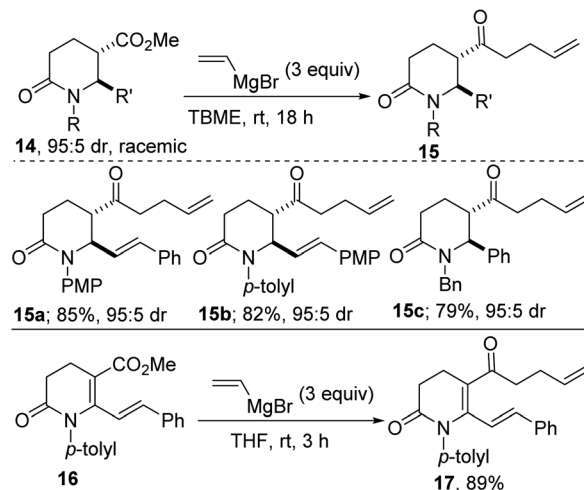


morpholinone ester was next explored (Scheme 1). Morpholinones bearing *N*-alkyl and aryl substituents were surveyed as were those harboring  $\alpha$ -amino alkenyl, aryl, and alkyl groups. Pleasingly, several homoallylic ketones were obtained in



PMP = *para*-methoxyphenyl; Isolated yields are reported. Performed on 1.0 mmol scale, using 5 mL TBME. Reaction times ranged from 10 to 18 h. Diastereomeric ratios were determined by GC-MS analysis of the crude mixtures. Representative traces are shown in ESI. Spectroscopic data are of the diastereomeric mixtures. \*The dr of the ester precursor was 85:15.

Scheme 1 Synthesis of homoallylic ketones by solvent-controlled direct 1,4-addition of vinyl Grignard reagents to morpholinonates.



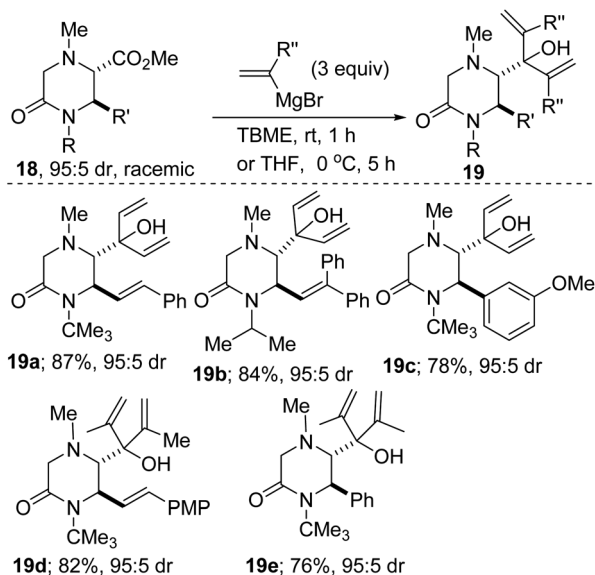
Scheme 2 Synthesis of  $\delta$ -valerolactam-bearing homoallylic ketones.

synthetically attractive yields when vinylmagnesium bromide was added to diversely functionalized lactam esters (see 4a–f).

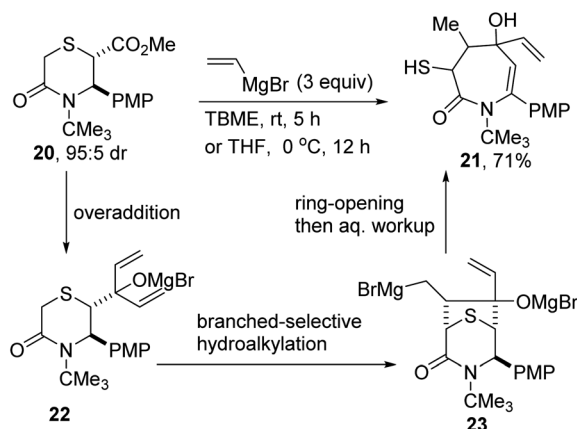
It is a testament to the mitigated reactivity of alkenyl Grignard reagents that they react with highly activated *N*-aryl-substituted lactam esters exclusively at the ester terminus to afford products such as 4e given that alkyl and allyl Grignard reagents react non-chemoselectively. Prior studies on the cascade acyl substitution-conjugate addition of alkenyl Grignard reagents to oxoesters<sup>11</sup> and thioesters<sup>12</sup> have mostly been centered around vinylmagnesium bromide.<sup>17</sup> We were therefore pleased to find that the addition of excess isopropenylmagnesium bromide to these vicinally functionalized morpholinonates proceeds highly stereoselectively and furnishes predominantly a single diastereomer (see 4g–r). The relative configurations of these doubly branched homoallylic ketones are yet to be fully established at this point (mainly due to overlap of signals in the <sup>1</sup>H NMR spectrum). As with all existing synthetic methodologies, limitations are bound to exist. In our case, we find that due to steric encumbrance, alkenyl Grignard reagents bearing an external substituent fail to participate in this cascade process, even at elevated temperatures (see 4s–u). The mass balance in these cases is mostly accounted for by the recovered ester precursors. Heteroaryl groups are well tolerated as exemplified through the synthesis of branched homoallylic ketones 4p/q.

Congruent with morpholinonates, the transition metal-free addition of vinylmagnesium bromide to sp<sup>3</sup>-rich piperidinonates<sup>9</sup> proceeds efficiently and furnishes homoallylic ketones (Scheme 2, see 15a–c). The LiCl additive was not necessary in these cases. Indeed, these valerolactam esters display a strong preference for 1,4-addition even when THF is employed as the solvent. Under the THF conditions, dienolate 16 reacts satisfactorily to afford trienone 17. Although in TBME, vicinally functionalized morpholinonates and piperidinonates display 1,4-selectivity when treated with excess alkenyl Grignard reagents, we have found that piperazinonates<sup>18</sup> instead undergo exclusive 1,2-addition (Scheme 3). Substrate-dependent





Scheme 3 Overaddition of alkenyl Grignard reagents to ketopiperazine esters in TBME or THF.



Scheme 4 Overaddition of vinylmagnesium bromide to 20 and concomitant intramolecular hydroalkylation-elimination.

regioselectivities of the type described herein have also been observed on trifluoromethylated  $\alpha$ -bromo enones.<sup>19</sup> These  $\alpha$ -amino esters react much faster than their  $\alpha$ -alkoxy congeners (*i.e.*, morpholinonates). Presumably, coordination of the proximal nitrogen to magnesium brings the carbonyl group in close proximity and facilitates 1,2-addition.

Primarily due to conformational differences, it is now fully appreciated that extending reactivity trends from one class of N-heterocycle to another can be quite daunting and even foolhardy at times. This salient point is highlighted by observations that thiomorpholinone 20 (ref. 20) undergoes a novel domino reaction featuring overaddition of vinylmagnesium bromide, branch-regioselective intramolecular hydroalkylation,<sup>21</sup> and concomitant deconstructive elimination to arrive at highly functionalized unsaturated caprolactam 21. Three new contiguous stereocenters are generated with impeccable stereocontrol

and the two pre-existing stereocenters are obliterated. A full investigation of the scope and mechanistic underpinnings of this formal one-carbon homologation process is underway.

Finally, we note in passing that when electronically diverse  $\alpha$ -alkoxy esters and  $\alpha$ -amino esters of types 1 and 18 were exposed to alkynyl Grignard reagents (*e.g.*, ethynylmagnesium bromide), only the overaddition products were obtained (see the ESI† for details).

## Conclusions

In summary, a solvent-controlled and transition metal-free addition of alkenyl Grignard reagents to vicinally functionalized morpholinonates and piperidinonates has been successfully implemented, leading to the selective synthesis of lactam-bearing branched homoallylic ketones. The transformation involves a tandem two-step process featuring acyl substitution of esters and concomitant conjugate addition of vinyl or isopropenylmagnesium bromide to the transient enone. The heteroatom proximal to the ester group appears to influence the selectivity of this domino process as highlighted by observations that  $\alpha$ -amino esters (*i.e.*, piperazinonates) deliver exclusively the overaddition products whereas  $\alpha$ -thioalkoxy esters (*i.e.*, thiomorpholinonates) undergo a one-pot four-step cascade process to furnish unsaturated caprolactams. The divergent nature of the transformation bodes well for future late-stage assembly of complex azaheterocycles. Efforts to expand the scope of the ring expansion of thiomorpholinonates to caprolactams are underway.

## Experimental

All experiments involving air and moisture sensitive reagents were carried out under an inert atmosphere of nitrogen and using freshly distilled solvents. Column chromatography was performed on silica gel (230–400 mesh). Thin-layer chromatography (TLC) was performed using Silicycle Siliplate™ glass backed plates (250  $\mu$ m thickness, 60 Å porosity, F-254 indicator) and visualized using UV (254 nm) or KMnO<sub>4</sub> stain. Unless otherwise indicated, <sup>1</sup>H, <sup>13</sup>C, and DEPT-135 NMR, and NOESY spectra were acquired using CDCl<sub>3</sub> solvent at room temperature. Chemical shifts are quoted in parts per million (ppm). HRMS-EI<sup>+</sup> data were obtained using either electrospray ionization (ESI) or electron impact (EI) techniques. High-resolution ESI was obtained on an LTQ-FT (ion trap; analyzed using Excalibur). High resolution EI was obtained on an Autospec (magnetic sector; analyzed using MassLynx). Representative GC-MS traces are provided to substantiate the diastereomeric ratios.

### General procedure A: direct addition of alkenyl Grignard reagents

To the lactamoyl ester (1.0 mmol) dissolved in freshly purchased TBME (5 mL), LiCl (0.5 mmol, 0.5 equiv.) was added vinylmagnesium bromide or isopropenylmagnesium bromide (3 mmol, 3 equiv.) under nitrogen at –20 °C (over a 1 minute





period). The mixture was warmed slowly to room temperature. After complete consumption of the ester (as indicated by TLC and GC-MS), the mixture was cooled to 0 °C, diluted with Et<sub>2</sub>O and quenched by slow addition of sat. aq NH<sub>4</sub>Cl. The layers were separated and the aqueous layer was extracted twice with EtOAc. The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub> for 30 min, filtered, and concentrated under reduced pressure to give the desired product. Purification: flash chromatography on silica eluting with hexane/EtOAc.

### Synthesis of ketone 4a

Prepared in 1 mmol scale using General procedure A. Purification: flash chromatography on silica eluting with hexane/EtOAc (80 : 20). Oily substance. Yield = 280 mg, 82%, 95 : 5 dr. <sup>1</sup>H NMR (400 MHz, Chloroform-*d*) δ 7.35–7.24 (m, 5H), 6.47 (s, 1H), 5.80 (ddt, *J* = 16.9, 10.2, 6.6 Hz, 1H), 5.03 (dd, *J* = 19.8, 13.5 Hz, 2H), 4.47 (d, *J* = 7.0 Hz, 2H), 4.38–4.27 (m, 3H), 2.82 (dt, *J* = 18.0, 7.3 Hz, 1H), 2.64 (dt, *J* = 18.0, 7.3 Hz, 1H), 2.36 (p, *J* = 9.3, 8.2 Hz, 2H), 1.96 (s, 3H), 1.25 (d, *J* = 6.3 Hz, 3H), 1.20 (d, *J* = 6.3 Hz, 3H). <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 208.40, 165.76, 136.73, 136.57, 129.41, 128.96, 128.77, 128.47, 128.37, 127.13, 115.96, 80.85, 65.28, 58.61, 47.66, 38.37, 27.36, 19.71, 19.58, 15.41. FTIR (KBr): 2976.0754, 2927.2335, 1721.7979, 1650.1792, 1492.0415, 1438.4625, 1362.2698, 1320.5399, 1290.1484, 1206.364, 1180.3512, 1146.7618, 1132.397, 995.8166, 918.8793, 700.1334. HRMS calc. for C<sub>21</sub>H<sub>27</sub>NO<sub>3</sub> 341.1991, found 341.1996.

Note: all other homoallylic ketones depicted in Scheme 1 were prepared as described above. Spectroscopic data can be found in the ESI.†

### Synthesis of ketone 15a

Prepared in 1 mmol scale using General procedure A but without LiCl. Purification: flash chromatography on silica eluting with hexane/EtOAc (60 : 40). Oily substance. Yield = 331.1 mg, 85%, 95 : 5 dr. <sup>1</sup>H NMR (400 MHz, Chloroform-*d*) δ 7.32–7.18 (m, 7H), 6.86 (d, *J* = 8.3 Hz, 2H), 6.31 (d, *J* = 15.8 Hz, 1H), 6.15 (dd, *J* = 15.8, 7.2 Hz, 1H), 5.82–5.75 (m, 1H), 5.05–4.96 (m, 2H), 4.82–4.67 (m, 1H), 3.75 (s, 3H), 2.97 (dt, *J* = 7.3, 4.7 Hz, 1H), 2.79–2.46 (m, 4H), 2.42–2.33 (m, 2H). <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 208.77, 169.48, 158.44, 136.71, 135.93, 134.80, 134.35, 133.32, 129.05, 128.71, 128.17, 128.01, 126.52, 115.80, 114.41, 63.33, 55.39, 51.56, 40.75, 30.62, 27.54, 21.49. HRMS calc. for C<sub>25</sub>H<sub>27</sub>NO<sub>3</sub> 389.1991, found 389.1996.

Note: all homoallylic ketones depicted in Scheme 2 were prepared as described above. Spectroscopic data can be found in the ESI.†

### Synthesis of alcohol 19a

Prepared in 1 mmol scale using General procedure A but without LiCl. Purification: flash chromatography on silica eluting with hexane/EtOAc (50 : 50). Oily substance. Yield = 308.4 mg, 87%, 95 : 5 dr. <sup>1</sup>H NMR (400 MHz, Chloroform-*d*) δ 7.42–7.28 (m, 5H), 6.42 (d, *J* = 16.0 Hz, 1H), 6.18–6.04 (m, 3H), 5.48 (d, *J* = 17.2 Hz, 1H), 5.37 (d, *J* = 17.2 Hz, 1H), 5.27 (d, *J* = 10.8 Hz, 1H), 5.18 (d, *J* = 10.6 Hz, 1H), 4.74 (d, *J* = 6.6 Hz, 1H), 3.44 (d, *J* = 15.1 Hz, 1H), 3.33 (d, *J* = 15.0 Hz, 1H), 3.02 (s, 1H),

2.83 (s, 1H), 2.49 (s, 3H), 1.45 (s, 9H). <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 169.14, 141.88, 139.72, 136.24, 132.01, 130.92, 130.56, 128.81, 128.03, 126.62, 126.39, 114.37, 113.78, 78.66, 72.22, 58.88, 58.12, 55.58, 47.54, 28.88. FTIR (KBr): 3384.5506, 2924.8333, 1642.2515, 1494.9545, 1448.8548, 1427.0419, 1393.4602, 1361.6968, 1328.7144, 1289.7737, 1223.6425, 1198.9141, 1130.0001, 1074.1578, 1030.4745, 988.561, 966.1662, 925.5022, 741.6755, 693.4562. HRMS calc. for C<sub>22</sub>H<sub>30</sub>N<sub>2</sub>O<sub>2</sub> 354.2307, found 354.2304.

Note: all other alcohols depicted in Scheme 3 were prepared as described above. Spectroscopic data can be found in the ESI.†

### Synthesis of unsaturated caprolactam 21

Prepared in 1 mmol scale using General procedure A but without LiCl. Purification: flash chromatography on silica eluting with hexane/EtOAc (80 : 20). Oily substance. Yield = 256.7 mg, 71%, 95 : 5 dr. <sup>1</sup>H NMR (400 MHz, Chloroform-*d*) δ 7.35 (d, *J* = 8.4 Hz, 2H), 6.88 (d, *J* = 8.4 Hz, 2H), 6.52 (s, 1H), 6.03 (s, 1H), 5.93 (s, 1H), 5.81–5.62 (m, 2H), 5.43–5.34 (m, 1H), 3.83–3.76 (m, 4H), 2.34 (p, *J* = 7.2 Hz, 1H), 1.43–1.24 (m, 10H), 1.09 (d, *J* = 7.0 Hz, 3H). <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 171.77, 158.78, 140.29, 131.72, 129.87, 120.84, 116.15, 114.13, 113.75, 85.69, 55.76, 55.37, 55.32, 52.50, 47.40, 28.62, 9.54. FTIR (KBr): 3391.475, 2971.495, 2923.9815, 1644.4038, 1491.4705, 1446.8961, 1429.3142, 1391.6056, 1362.4703, 1318.9377, 1292.671, 1268.871, 1223.0439, 1199.5844, 1151.3831, 1117.7388, 993.1353, 905.3314, 744.2027, 699.8784. HRMS calc. for C<sub>20</sub>H<sub>27</sub>NO<sub>3</sub>S 361.1712, found 361.1718.

Note: all other methyl ethers depicted in Scheme 4 were prepared as described above. Spectroscopic data can be found in the ESI.†

## Conflicts of interest

There are no conflicts of interest to declare.

## Acknowledgements

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