Expanding the Protecting Group Scope for the Carbonyl Olefin Metathesis Approach to 2,5-Dihydropyrroles

Fabian Huck,[1] Lorenzo Catti,[2] Gian Lino Reber,[1] Konrad Tiefenbacher[1,3*]

[1]Department of Chemistry, University of Basel, Mattenstrasse 24a, CH-4058 Basel, Switzerland
[2]Laboratory for Chemistry and Life Science Institute of Innovative Research Tokyo Institute of Technology, 4259-R1-28, Nagatsuta, Midori-ku, Yokohama 226-8503, Japan
[3]Department of Biosystems Science and Engineering, ETH Zurich, Mattenstrasse 26, CH-4058 Basel, Switzerland

KEYWORDS: Supramolecular catalysis, Metathesis, Heterocycles, Acid Catalysis

ABSTRACT: Chiral pyrrolidine derivatives are important building blocks for natural product synthesis. Carbonyl-olefin metathesis has recently emerged as a powerful tool for the construction of such building blocks from chiral amino acid derivatives. Here we demonstrate that the supramolecular resorcinarene catalyst enables access to chiral 2,5-dihydropyrroles under Brønsted acid catalysis. Moreover, this catalytic system even tolerated Lewis-basic protecting groups like mesylates that are not compatible with alternative catalysts. As expected for conversion inside a closed cavity, the product yield and selectivity depended on the size of the substrates.

Introduction

Pyrroles and pyrrolidines are found in many natural products and play an important role as a precursor in drug synthesis.[1-4] However, their synthesis, especially of optically active derivatives, remains challenging.[5-6] Recently, carbonyl olefin metathesis (COM) has emerged as a useful tool to prepare chiral 2,5-dihydropyrroles, also termed 3-pyrrolines (Figure 1).[7-8] The COM reaction is related to the well-established olefin metathesis, but instead of the metathesis of two olefin moieties, it involves one carbonyl and one alkene moiety.[9-10] It has received increasing attention since the discovery of iron(III)chloride as an efficient and rather broadly applicable catalyst by the Schindler group in 2016.[11-12] The Li group presented the first approach to synthesize 2,5-dihydropyrroles via carbonyl olefin metathesis by using 20% iron(III)chloride and an excess of allyl trimethyl silane.[7] The allyl trimethyl silane functions as a scavenger for the formed benzaldehyde (Fig. 1a), which was suggested to inhibit the reaction by catalyst binding. The first catalytic approach without a stoichiometric additive was presented in 2018 by the Schindler group with the introduction of an electron-poor protecting group.[8] It was found that the *p*-toluenesulfonamide group acted as a competitive catalyst binding site, preventing turn-over with substoichiometric amounts of iron(III)chloride. The use of the electron-deficient protecting group 4-trifluoromethyl benzene sulfonyl (trifluorotosyl, ^{F}Ts) reduced the undesired catalyst binding, enabling the use of catalytic amounts of iron(III)chloride (Fig. 1b). Moreover, the Schindler group demonstrated that the use of amino acids as starting materials enables facile access to chiral, optically active, 3-aryl-2,5-dihydropyrroles. In 2020, the Schindler group was able to expand the substrate scope and access tetrahydropyridines.[13] Recent findings in the Nguyen group demonstrated that other catalysts (I_2, NIS, ICl)[14-15] are able to convert regular tosyl-protected substrates with sub-stoichiometric amounts of catalyst (Fig. 1c). Li and Lin reported the use of AuCl3 as catalyst for the COM-approach to pyrrolidines (Fig. 1d).[16]

Lambert and co-worker demonstrated that related N-heterocycles are also accessible by COM via a [3+2] cycloaddition/cycloreversion mechanism.[17] We here present that the catalyst combination of the supramolecular capsule **I** (Figure 2) and HCl is not only able to tolerate the toluenesulfonyl protecting group, but also the more Lewis basic sulfonamide moiety formed from the mesyl protecting group (Fig. 1e). To our knowledge, this is the first report about the successful use of the mesyl protected nitrogen for a COM reaction without the need for (super)stoichiometric additives.[7]

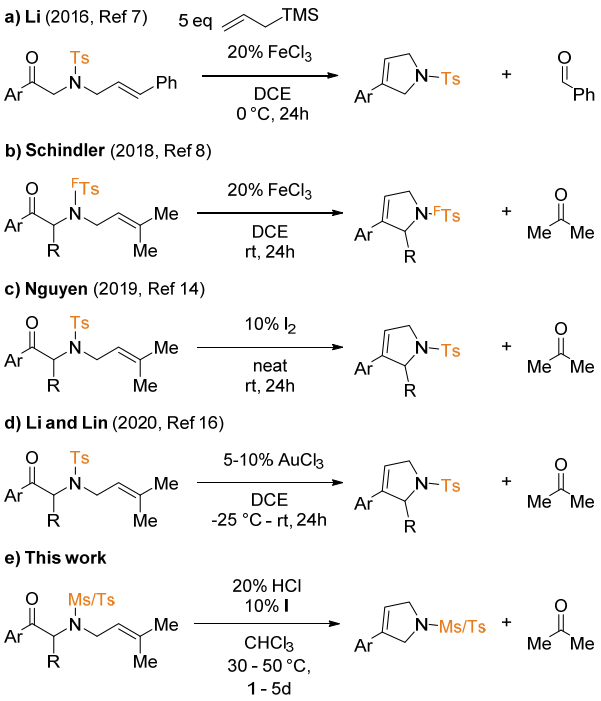


Figure 1: Synthetic routes towards 3-aryl-2,5-dihydropyrroles

In 2018, we reported that the hexameric resorcinarene capsule (**I**) in the presence of HCl, is a competent catalyst for the COM reaction.[18] In apolar solvents, resorcinarene **1** forms a dynamic hexamer interconnected via a hydrogen bond network (Fig. 2).[19-22] This supramolecular capsule has been successfully applied for catalysis of reactions with cationic intermediates/transition states.[23-31] In this work, we present the synthesis of 3-aryl-2,5-dihydropyrroles with three different sulfonamide protecting groups (tosyl, mesyl, trifluorotosyl) catalyzed by **I**/HCl. Mesylates are more electron-rich than tosylates and trifluorotosylates and therefore not suitable for iron(III) catalysis. Moreover, the mesyl group can be removed selectively in the presence of other sulfonamide groups which makes it suitable for the synthesis of more complex target compounds.[32] Therefore, establishing the mesyl group as an orthogonal protecting group for the COM reaction can be considered highly desirable.

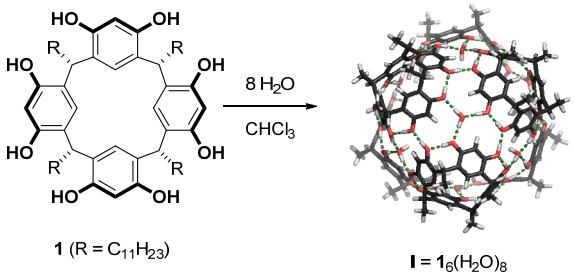
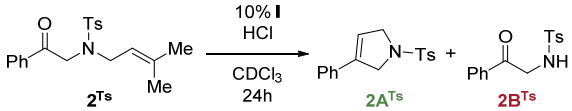


Figure 2: Structure of the self-assembled hexameric resorcinarene capsule **I** and its precursor resorcinarene **1**.

Results and Discussion.

Initially, the established reaction conditions from our previous work on the COM reaction (50 °C, 5% HCl, 10 mol% **I**) were explored.[18] However, these conditions that were optimized for non-nitrogen-containing substrates exclusively resulted in only 30% yield of the desired COM product **2A^{Ts}** (Table 1, entry 1). Mainly deallylation to **2B^{Ts}** was observed (45%). The reduction of the HCl concentration to 2.5% did not improve the outcome, as even more deallylation was observed (entry 2). Subsequently, the reaction was explored at room temperature (entries 5-9). Due to the slow conversion at 2.5% and 5% HCl loadings (entries 8-9), we explored higher concentrations (10-30%, entries 5-7). It was found that 20% HCl produced satisfactory results (85% of the desired COM product **2A^{Ts}** and only 15% of **2B^{Ts}**). However, the fluctuation of the room temperature did lead to reproducibility issues. To establish reproducible reaction conditions, the reaction was carried out at 30 °C (entry 4) which resulted in a good yield of 80% of **2A^{Ts}**. Acid concentrations above 20% lead to a decreased COM product formation, whereas the deallylation seems to be mainly dependent on the temperature.

Table 1 Optimization of HCl-concentration and Temperature



entry	T [°C]	HCl [mol%]	Conversion[a]	Yield[b] 2A^{Ts}	Yield[b] 2B^{Ts}
1	50 °C	5%	100%	30%	45%
2		2.5%	95%	37%	53%
3	30 °C	30%	100%	69%	15%
4		20%	100%	80%	20%
5	rt	30%	100%	75%	17%
6		20%	100%	85%	15%
7		10%	89%	68%	26%
8		5%	48%	30%	4%
9		2.5%	26%	9%	0%
10	4 °C	30%	33%	27%	0%

[a]conversion was determined by ^{1}H NMR, with tetraethylsilane as internal standard after 24h; [b]yields were determined by ^{1}H NMR, with tetraethylsilane as internal standard after 24h

Next, we investigated the influence of the alkene substitution. The unsubstituted olefin **2^{allyl}** (Fig. 3) did not show any reactivity, even at elevated temperature (50 °C) and high HCl loadings (50%; SI ch. 1). The phenyl substituted **2^{styr}** resulted only in deallylation. Thus, all further studies were performed with the dimethyl-substituted olefin moiety.

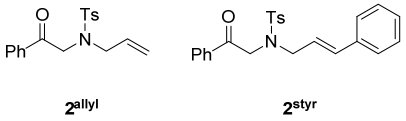
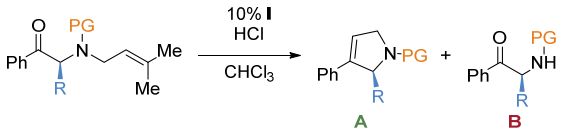


Figure 3. Substrates investigated concerning the influence of the alkene substitution.

The main part of the investigation focused on the exploration of the substrate scope with three different protecting groups: tosyl, mesyl, and trifluorotosyl.

Table 2 Evaluation of the Protecting Group Influence



20% HCl, 30 °C, 24h	40% HCl, 50 °C, 14d	20% HCl, 50 °C, 48h
2^{Ts} A: 74±2%[a] B:25±3%[a] Iso. yield: 62% (A)[b]	**2^{FTs}** A: 9±1%[a] B: 22±0.6%[a] Iso. yield: 6% (A)[b,c]	**2^{Ms}** A: 27±2%[a] B: 43±5%[a] Iso. yield: 25% (A)[b]
3^{Ts} A: 84±0.8%[a] B: 11±0.5%[a] Iso. yield: 79% (A)[b]	**3^{FTs}** A: 58±3%[a] B: 35±2%[a] Iso. yield: 50% (A)[b]	**3^{Ms}** A: 54±0.2%[a] B:30±0.1%[a] Iso. yield: 55% (A)[b]
4^{Ts} A: 31±0.8%[a] B: 30±5%[a] Iso. yield: 34% (A)[b]	**4^{FTs}** A: 18±0.5%[a] B 52±0.9%[a] Iso. yield: 17% (A)[b]	**4^{Ms}** A: 45±0.4%[a] B: 38±0.3%[a] Iso. yield: 41% (A)[b]
5^{Ts} A: 24±0.4%[a] B: 66±0.6%[a] Iso. yield: 17% (A)[b]	**5^{FTs}** A: 32±2%[a] B: 16±1%[a] Iso. yield: 35% (A)[b]	**5^{Ms}** A: 83±2%[a] B:12±2%[a] Iso. yield: 62% (A)[b]

[a]reactions run in triplicate and analyzed by ^{1}H NMR with tetraethylsilane as internal standard (std. deviation reported). [b]isolated yield [c] addition of HCl to the olefin was observed.

The smallest Ts-protected substrates **2^{Ts}** and **3^{Ts}** were converted to the respective COM products in good yields. Based on chiral HPLC analysis of **3^{Ts}**, the stereoinformation of the substrate was efficiently transferred onto the product (SI, ch. 3, pp. 28-30). Interestingly, increasing the size of the substrate by only one methylene unit (**4^{Ts}**) resulted in a greatly reduced yield of the COM product (34%). This trend continued with the largest substrate investigated, the phenylalanine-derived substrate (**5^{Ts}**), which produced only 17% isolated yield. To estimate the reproducibility of this trend of decreasing yield with increasing substrate size, all reactions were run in triplicate and the yield was determined via a ^{1}H NMR (internal standard) to exclude an influence of the purification procedure. Indeed, the trend was confirmed by these studies. Additionally, it revealed that deallylation was the dominating reaction for larger substrates. The unsubstituted, glycine-derived substrate **2^{Ts}** performs slightly worse than the methyl-substituted **3^{Ts}**. The Thorpe-Ingold effect might be responsible for this observation, as also discussed by the Schindler group in their studies with iron(III)chloride.[8] This influence was even more pronounced for the other protecting group (**2^{FTs}** vs. **3^{FTs}** and **2^{Ms}** vs. **3^{Ms}**, see below). To demonstrate the scalability of the procedure, one gram of substrate **3^{Ts}** was converted and delivered product **3ATs** in comparable yield to the small scale reaction (77% vs. 79%; see the end of the experimental section). Furthermore, more readily available HCl sources than HCl-saturated chloroform, and alternative Brønsted acids were explored with substrate **3^{Ts}** (SI ch. 2). Several acids can be utilized in combination with capsule **I**. The best alternative performance was observed with HCl (37%, aq.) that resulted in nearly the same yield as the standard condition (82% vs. 84%).

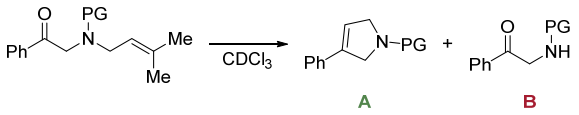
Interestingly, ^{F}Ts-protected substrates performed, on average, worse. They required much harsher reaction conditions (40% HCl, 50 °C vs. 20% HCl, 30 °C) and still converted extremely sluggishly (14d vs. 24h). This is in contrast to iron(III)-catalysis and is likely a result of the decreased uptake of fluorinated substrates inside capsule **I** that we have observed before. As a side reaction, the addition of HCl to the olefin was observed in the cyclization of **2^{FTs}**.

Most interestingly, Ms-protected substrates were converted efficiently inside capsule **I** at slightly elevated temperatures (50 °C) but with the original acid loading (20% HCl). Surprisingly, the largest substrate, **5^{Ms}** produced the highest yield (83±2% NMR-yield, 62% isolated yield) of the mesyl-series. This is in contrast to the tosyl and trifluorotosyl-protected substrates where the smaller, alanine-derived substrate displayed the highest yield.

Control experiments were carried out to learn more about the origin of the COM and deallylation reactivity (Table 3). Aliquots of the reaction mixture were analyzed by ^{1}H NMR over time and compared with the respective reference reactions (entry 0). First, an experiment with 1.5 equivalents of tetrabutylammonium bromide (TBAB) was performed (entry 1). TBAB is a strong binding ammonium guest, which can effectively prevent cationic reactions inside capsule **I**.[23, 33-35] Reactivity observed under these conditions likely stems from a background reaction outside of the capsule. All substrates investigated did not show any formation of the COM product. In the case of the tosyl- and mesyl-protected derivates, some deallylation was observed, indicating that deallylation also takes place outside of the capsule. In entry 2, the capsule was efficiently disassembled by the addition of an excess of methanol. No reactivity was observed under these conditions. Next, the catalyst components (**I** and HCl) were tested separately (entries 3-4). No product formation was observed, which indicates that the COM only takes place inside **I** in the presence of HCl. Some deallylation product was observable for **2^{Ts}** and **2^{Ms}** in both cases. However, the low yield after extended reaction time (7d) is much lower than under regular conditions (entry 0). The following conclusions can be drawn from these control experiments. (1) The deallylation seems not to depend on either **I** or HCl, but is accelerated in the presence of the catalyst combination. (2) On the other hand, COM product formation is

only observed when both catalyst components (**I** and HCl) are present.

Table 3 Control Experiments



entry	I	HCl	2^{Ts}		2^{FTs}		2^{Ms}	
			A[a]	B[a]	A[a]	B[a]	A[a]	B[a]
			30°C, 1d		50°C, 14d		50°C, 2d	
0	10%	20%	74%	25%	9%	22%	27%	43%
			30°C, 7d		50°C, 14d		50°C, 7d	
1	10%	20%	n.d.	14%	n.d.	n.d.	n.d.	3%
	1.5 equiv nBu_4NBr							
2	10%	20%	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
	60 equiv MeOH							
3	0%	20%	n.d.	15%	n.d.	n.d.	n.d.	3%
4	10%	0%	n.d.	13%	n.d.	n.d.	n.d.	2%

[a]analyzed by ^{1}H NMR with tetraethylsilane as internal standard; n.d. = not detectable via ^{1}H NMR

What causes the observed inverse trends for the tosyl- and mesyl-protected substrates (Table 2)? As the cavity of **I** only offers limited space, we suspect that the restricted rotation of the substrate might be the key factor. Substrates that carry a large protecting group (Ts or ^{F}Ts) and additionally a larger R-residue (ethyl, phenyl), might suffer from a decreased conformational freedom required for the COM reaction. In these cases, deallylation, which does not depend on large conformational changes outcompetes the COM reaction. The smaller mesyl-protecting group, on the other hand, facilitates the conversion of the substrates with the larger R-residues (ethyl, benzyl).

In summary, we demonstrated that several 3-aryl-2,5-dihydropyrroles can be synthesized efficiently with the catalyst combination **I**/HCl. Most interestingly, this catalyst combination is able to convert mesyl-protected substrates. To our knowledge, such substrates have not been converted in a COM reaction before, as they would suffer from catalyst inhibition due to the high Lewis basicity. As the mesyl group can be deprotected selectively in the presence of other sulphonamides, it provides an orthogonal reactivity as compared to the protecting groups utilized so far for the COM reaction. Furthermore, a strong size dependence of the conversion inside capsule **I** was observed. These results combined with the performed control experiments provide very strong evidence that the COM reaction takes place inside the capsule exclusively. The results further highlight the unique reactivity observed inside the closed cavity of capsule **I** as compared to reactions in solution.

Experimental Section

General Information

Reagents were purchased from commercial sources (Acros, Alfa Aesar, Fluorochem, Sigmar-Aldrich, VWR) and used without prior purification. ^{1}H NMR spectra were recorded at 298 K at 500 MHz or 600 MHz on a Bruker UltraShield 500 spectrometer or a 600 MHz Bruker Avance III NMR spectrometer equipped with a cryogenic QCI-F probe, respectively. ^{13}C NMR spectra were recorded at 126 MHz or 151 MHz on a Bruker UltraShield 500 spectrometer or a 600 MHz Bruker AvanceIII NMR spectrometer equipped with a cryogenic QCI-F probe, respectively. Chemical shifts of ^{1}H NMR and ^{13}C NMR spectra (measured at 298 K) are given in ppm by using residual solvent signals as references ($CDCl_3$: 7.26 ppm and 77.16 ppm)). Coupling constants (J) are reported in Hertz (Hz). Standard abbreviations indicating multiplicity were used as follows: s(singlet), d (doublet), t (triplet), q (quartet), p (pentet), s (sextet), h (septet), m (multiplet), b(broad). High-resolution mass spectra were obtained using the electrospray ionization-time of flight (ESI-TOF) technique on a Bruker maXis 4G mass spectrometer. Analytical thin-layer chromatography (TLC) was performed on Merck silica gel 60 F_{254} glass-baked plates, which were analyzed by fluorescence detection with UV-light (λ = 254 nm, [UV]) and after exposure to standard staining reagents and subsequent heat treatment. The following staining solution was used: acidic cerium ammoniummolybdate solution [CAM] (40 g ammonium heptamolybdate, 1.6 g cerium sulfate in 900 mL H_2O with 100 mL conc. H_2SO_4).

General Procedure for NMR-Experiments

A stock solution of resorcinarene (99.5 mM) was prepared by suspending resorcinarene in chloroform-d_1 (filtered over basic aluminum oxide) in a 4 mL screw-cap vial. The capped vial was heated gently in a 50 °C waterbath until the suspension turned clear. After cooling to room temperature, tetraethylsilane was added to the resorcinarene stock solution to obtain a tetraethylsilane concentration of 66.4 mM (6.64 µmol, 0.4 equiv in the final reaction mixture). An aliquot of the resorcinarene stock solution (100 µL, 9.95 µmol, 0.6 equiv) was added to a 1.5 mL screw cap vial, equipped with a stirring bar. HCl (0.2 equiv) was added as HCl-saturated chloroform solution (freshly titrated). Filtered chloroform was added to receive a total volume of 400 µL. The substrate was added as a stock solution (100 µL, 166 mM, 16.6 µmol, 1.0 equiv). The vial was transferred to an aluminum heating block. Aliquots of 50 µL were dissolved in 0.5 mL of chloroform-d_1 and analyzed by ^{1}H NMR.

Preparation of Starting Materials

Substrates $\mathbf{3}^{Ts}$, $\mathbf{5}^{Ts}$, $\mathbf{5}^{FTs}$ were prepared according to literature procedures.[8]

General Procedure A: Synthesis of 2^{Ms}, 2^{FTs}, 2^{allyl}, 2^{styr} via Protection and *N*-alkenylation of 2-Aminoacetophenone

2-Aminoacetophenone hydrochloride (1.0 equiv) was suspended in a mixture of THF:H_2O (1:2) to obtain a 0.3 M solution. The solution was cooled to 0 °C with an ice bath and the sulfonyl chloride (1.2 equiv) and triethylamine (3.0 equiv) were added. The solution was stirred for 4h at 0 °C. The reaction was quenched with HCl (1 M) and extracted three times with EtOAc. The organic phase was dried with Na_2SO_4 and the solvent was removed under reduced pressure. The obtained protected aminoacetophenones (**PAP**) were purified by flash chromatography.

PAP was dissolved in dry DMF to obtain a 0.1 M solution. The solution was cooled to 0 °C in an ice bath and NaH (60% dispersion in mineral oil, 1.2 equiv) was added and the reaction was stirred for 15 min at 0 °C. Alkenyl bromide (1.2 equiv) was added and the reaction was allowed to warm to room temperature overnight. The reaction was quenched by the addition of a saturated NH_4Cl solution and extracted with EtOAc. The combined organic phase was dried with Na_2SO_4 and the solvent was removed under reduced pressure. The final compound was purified by flash chromatography (SiO_2 EtOAc : cHex).

General Procedure B: Synthesis of 3^{Ms}, 4^{Ms}, 3^{FTs}, 4^{FTs} via *N*-Prenylation and Addition of Phenyl Lithium to Amino Acid Esters

The amino acid (1.0 equiv) was suspended in MeOH to obtain a 1 M suspension. The mixture was cooled to 0 °C in an ice bath and thionyl chloride (1.2 equiv) was added dropwise. The reaction was allowed to warm to room temperature and stirred for 2h. The solvent and remaining thionyl chloride were removed under reduced pressure to afford the crude amino acid methyl ester. The product was used without further purification.

The amino acid methyl ester (1.0 equiv) was suspended in DCM to obtain a 0.5 M suspension. The mixture was cooled to 0 °C in an ice bath and the sulfonyl chloride (1.2 equiv) was added. Triethylamine (2.2 equiv) was added dropwise and the mixture was stirred for 4h at 0 °C. The reaction was quenched by the addition of water and extracted with EtOAc. The combined organic phase was dried with Na_2SO_4 and the solvent was removed under reduced pressure. The crude product was used without further purification.

The protected amino acid was dissolved in dry DMF to obtain a 0.1 M solution. The solution was cooled to 0 °C in an ice bath and NaH (60% dispersion in mineral oil, 1.2 equiv) was added and the reaction was stirred for 15min at 0 °C. Prenyl bromide (1.2 equiv) was added and the reaction was allowed to warm to room temperature overnight. The reaction was quenched by the addition of a saturated NH_4Cl solution and extracted with EtOAc. The combined organic phase was dried with Na_2SO_4 and the solvent was removed under reduced pressure. Purification by flash chromatography (SiO_2 EtOAc : cHex) afforded the desired prenylated ester (**EST**)

Iodobenzene (1.1 equiv) was dissolved in THF to obtain a 0.1 M solution. The solution was cooled to -78 °C in a dry ice/acetone cooling bath. nBuLi (2.5 M, 1.1 equiv) was added and the mixture was stirred for 10min. **EST** (1.0 equiv) was added and the reaction was stirred for 1h at -78 °C. Higher temperature or longer reaction times lead to lower yields. The reaction was quenched by the addition of a saturated NH_4Cl solution and extracted with EtOAc. The combined organic phase was dried with Na_2SO_4 and the solvent was removed under reduced pressure. The final compound was purified by flash chromatography (SiO_2 EtOAc : cHex).

General Procedure C: Synthesis of 4^{Ts} and 5^{Ms} via *N*-protection, Weinreb-amidation, Grignard Addition, and *N*-Prenylation

The respective amino acid (1.0 equiv) was suspended in a mixture of THF:H_2O (1:2) to obtain a 0.3 M solution. The solution was cooled to 0 °C in an ice bath and the sulfonyl chloride (1.2 equiv) and triethylamine (3.0 equiv) were added. The solution was stirred for 4h at 0 °C. The reaction was quenched with HCl (1 M) and extracted three times with EtOAc. The organic phase was dried with Na_2SO_4 and the solvent was removed under reduced pressure. The obtained product was used without further purification.

The protected amino acid (1.0 equiv), N,O-dimethylhydroxylamine hydrochloride (1.1 equiv), and morpholine (1.1 equiv) were dissolved in DCM to obtain a 0.45 M solution. The mixture was cooled to 0 °C in an ice bath and DCC (1.1 equiv) was added in one portion. The reaction was allowed to warm up to room temperature overnight. The reaction was quenched by the addition of HCl (1 M) and the mixture was extracted with DCM. The organic phase was washed with sat. $NaHCO_3$ solution and brine. The organic phase was dried with Na_2SO_4 and filtered through a celite® pad. The solvent was removed under reduced pressure and the residue was purified by column chromatography to obtain the Weinreb amide (**WA**).

The aryl magnesium bromide (2.0 equiv) was dissolved in dry THF to obtain a 0.2 M solution. The solution was cooled to 0 °C in an ice bath and **WA** (1.0 equiv) was added as 2.5 M solution in dry THF. The reaction was allowed to warm to room temperature and stirred for 4h or until judged complete by TLC analysis. The reaction was quenched by the addition of a saturated NH_4Cl solution and extracted with EtOAc. The combined organic phase was dried with Na_2SO_4 and the solvent was removed under reduced pressure. Purification by flash chromatography (SiO_2 EtOAc : cHex) afforded the aryl ketone (**AK**).

AK was dissolved in dry DMF to obtain a 0.1 M solution. The solution was cooled to 0 °C in an ice bath, NaH (60% dispersion in mineral oil, 1.2 equiv) was added, and the reaction was stirred for 15 min at 0 °C. Prenyl bromide (1.2 equiv) was added and the reaction was allowed to warm to room temperature overnight. The reaction was quenched by the addition of a saturated NH_4Cl solution and extracted with EtOAc. The combined organic phase

was dried with Na_2SO_4 and the solvent was removed under reduced pressure. The final compound was purified by flash chromatography (SiO_2 EtOAc : cHex).

General Procedure D: Carbonyl-Olefin Metathesis

Preparation and Titration of HCl-concentrated Chloroform Solution

The HCl-concentrated chloroform solution was prepared by passing HCl-gas (prepared by dropwise addition of concentrated H_2SO_4 to dry NaCl) through chloroform for ca. 30min. The concentration of HCl in chloroform was determined as follows: to a solution of phenol red in EtOH (0.002wt%, 2.5 mL) was added HCl-saturated chloroform (100 µL) via a microman M1 pipette equipped with plastic tips. Upon addition, the solution turned from yellow (neutral) to pink (acidic). The resulting solution was then titrated with 0.1 M ethanolic solution of triethylamine (NEt_3). At the equivalence point, the solution turned from pink to yellow.

Resorcinarene (0.6 equiv) was weighed into a pressure vial and chloroform (filtered through basic aluminum oxide) was added to reach a concentration of 25.0 mM regarding resorcinarene. The capped vial was heated gently in a 50 °C water bath until the suspension turned clear. After cooling to room temperature, HCl (0.2 equiv) was added in the form of HCl-saturated chloroform. The substrate was added (1.0 equiv) and filtered chloroform was added to receive a total concentration of 33.1 mM regarding the substrate. The vial was equipped with a stirring bar and transferred to an oil bath set to 50 °C or 30 °C. The reaction mixture was transferred directly to the column (SiO_2 100% pentane) and was rinsed with pentane. The eluent was gradually changed to the desired mixture.

Synthesis of 2^{Ts} and $2A^{Ts}$

4-methyl-*N*-(2-oxo-2-phenylethyl)benzenesulfonamide ($2PAP^{Ts}$)

2-aminoacetophenone hydrochloride (450 mg, 2.62 mmol) and tosyl chloride (599 mg, 3.14 mmol) were treated according to the general procedure A. Flash chromatography (SiO_2 20% EtOAc : 80% cHex) afforded $\mathbf{2PAP^{Ts}}$ (687 mg, 2.37 mmol, 90%) as white solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.87 – 7.83 (m, 2H), 7.78 (d, J = 8.0 Hz, 2H), 7.64 – 7.59 (m, 1H), 7.47 (t, J = 7.7 Hz, 2H), 7.29 (d, J = 8.0 Hz, 2H), 5.62 (t, J = 4.7 Hz, 1H), 4.46 (d, J = 4.5 Hz, 3H), 2.40 (s, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 192.6, 143.9, 136.1, 134.6, 133.8, 129.9, 129.1, 128.0, 127.3, 48.8, 21.6.

The spectroscopic data matched those reported in the literature[36]

4-methyl-*N*-(3-methylbut-2-en-1-yl)-*N*-(2-oxo-2-phenylethyl)benzenesulfonamide (2^{Ts})

$\mathbf{2PAP^{Ts}}$ (300 mg, 1.05 mmol) and prenyl bromide (144 µL, 1.25 mmol) were treated according to the general procedure A. Flash chromatography (SiO_2 10% EtOAc : 90% cHex) afforded $\mathbf{2^{Ts}}$ (272 mg, 761 µmol, 72%) as colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.92 (dd, J = 8.4, 1.3 Hz, 2H), 7.75 (d, J = 8.3 Hz, 2H), 7.61 – 7.55 (m, 1H), 7.47 (t, J = 7.8 Hz, 2H), 7.32 – 7.29 (m, 2H), 5.04 – 4.97 (m, 1H), 4.64 (s, 2H), 3.89 (d, J = 7.5 Hz, 2H), 2.44 (s, 3H), 1.59 (d, J = 1.4 Hz, 3H), 1.45 (d, J = 1.4 Hz, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 194.6, 143.3, 139.2, 136.8, 135.1, 133.6, 129.6, 128.7, 128.0, 127.5, 118.3, 52.1, 45.5, 25.7, 21.6, 17.6.

The spectroscopic data matched those reported in the literature[16]

3-phenyl-1-tosyl-2,5-dihydro-1*H*-pyrrole ($2A^{Ts}$)

$\mathbf{2^{Ts}}$ (61.1 mg, 171 µmol) was treated according to the general procedure D. The reaction was carried out at 30 °C for 24h. Flash chromatography (SiO_2 10% EtOAc : 90% Pentane) afforded $\mathbf{2A^{Ts}}$ (31.8 mg, 106 µmol, 62 %) as colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (d, J = 8.1 Hz, 2H), 7.36 – 7.27 (m, 7H), 6.04 – 5.97 (m, 1H), 4.52 – 4.43 (m, 2H), 4.34 – 4.26 (m, 2H), 2.41 (s, 3H).^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 143.7, 137.5, 134.2, 132.6, 130.0, 128.8, 128.6, 127.6, 125.5, 119.0, 55.8, 55.0, 21.7.

The spectroscopic data matched those reported in the literature[7]

N-allyl-4-methyl-*N*-(2-oxo-2-phenylethyl)benzenesulfonamide (2^{allyl})

$\mathbf{2PAP^{Ts}}$ (201 mg, 693 µmol) and allyl bromide (72 µL, 832 µmol) were treated according to the general procedure A. Flash chromatography (SiO_2 10% EtOAc : 90% cHex) afforded $\mathbf{2^{allyl}}$ (186 mg, 0.565 mmol, 81%) as colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90 (dd, J = 8.4, 1.3 Hz, 2H), 7.76 (d, J = 8.3 Hz, 2H), 7.62 – 7.56 (m, 1H), 7.47 (dd, J = 8.1, 7.4 Hz, 2H), 7.32 – 7.29 (m, 2H), 5.70 (ddt, J = 16.8, 10.3, 6.6 Hz, 1H), 5.18 – 5.09 (m, 2H), 4.74 (s, 2H), 3.93 (d, J = 6.6 Hz, 2H), 2.44 (s, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 194.0, 143.5, 137.0, 135.0, 133.8, 132.5, 129.7, 128.9, 128.0, 127.6, 120.0, 51.8, 50.8, 21.7.

The spectroscopic data matched those reported in the literature[37]

N-cinnamyl-4-methyl-*N*-(2-oxo-2-phenylethyl)benzenesulfonamide (2^{styr})

$\mathbf{2PAP^{Ts}}$ (300 mg, 1.04 mmol) and cinnamyl bromide (185 µL, 1.25 mmol) were treated according to the general procedure A. Flash chromatography (SiO_2 10% EtOAc : 90% cHex) afforded $\mathbf{2^{styr}}$ (258 mg, 0.636 mmol, 61%) as white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.91 – 7.86 (m, 2H), 7.81 – 7.77 (m, 2H), 7.60 – 7.55 (m, 1H), 7.46 – 7.41 (m, 2H), 7.34 – 7.30 (m, 2H), 7.29 – 7.19 (m, 5H), 6.43 – 6.35 (m, 1H), 6.03 (dt, J = 15.9, 6.9 Hz, 1H), 4.76 (s, 2H), 4.08 (dd, J = 6.9, 1.3 Hz, 2H), 2.44 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 194.3, 143.6, 137.1, 136.1, 135.1, 135.0, 133.8, 129.8, 128.9, 128.7, 128.2, 128.2, 127.7, 126.7, 123.6, 52.1, 50.5, 21.7. HRMS calcd. for $C_{24}H_{23}NO_3SNa$ $[(M+Na)]^+$: 428.1291 found: 428.1294

(*S*)-2-methyl-3-phenyl-1-tosyl-2,5-dihydro-1*H*-pyrrole ($3A^{Ts}$)

$\mathbf{3^{Ts}}$ (63.5 mg, 171 µmol) was treated according to the general procedure D. The reaction was carried out at 30 °C

for 24h Flash chromatography (SiO_2 10% EtOAc : 90% Pentane) afforded **3A^{Ts}** (42.4 mg, 135 µmol, 79%) as white solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.76 (d, J = 8.3 Hz, 2H), 7.38 – 7.23 (m, 7H), 5.82 (q, J = 2.0 Hz, 1H), 5.05 – 4.95 (m, 1H), 4.34 – 4.21 (m, 2H), 2.40 (s, 3H), 1.47 (d, J = 6.4 Hz, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 143.6, 143.5, 135.1, 133.1, 129.9, 128.8, 128.3, 127.4, 126.4, 118.9, 63.0, 54.9, 22.2, 21.6.

The spectroscopic data matched those reported in the literature[8]

Synthesis of 4^{Ts} and 4A^{Ts}

(*S*)-*N*-methoxy-*N*-methyl-2-((4-methylphenyl)sulfonamido)butanamide (4WA^{Ts})

L-2-aminobutyric acid (425 mg, 4.12 mmol, 1.0 equiv) was treated according to the general procedure C. Purification by flash chromatography (SiO_2 30% EtOAc : 70% cHex) yielded product **4WA^{Ts}** (895 mg, 2.98 mmol, 72%). as a white solid ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73 – 7.69 (m, 2H), 7.27 (d, J = 7.9 Hz, 2H), 5.44 (d, J = 9.9 Hz, 1H), 4.17 (td, J = 9.5, 9.0, 4.4 Hz, 1H), 3.53 (s, 3H), 2.96 (s, 3H), 2.40 (s, 3H), 1.69 (dtd, J = 14.7, 7.3, 4.5 Hz, 1H), 1.53 (dt, J = 13.8, 7.5 Hz, 1H), 0.99 – 0.89 (m, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 143.5, 137.1, 129.6, 127.5, 61.4, 54.3, 32.2, 26.9, 21.6, 9.8. HRMS calcd.for $C_{13}H_{20}N_2O_4SNa$ [(M+Na)]$^+$: 323.1036 found 323.1038

(*S*)-4-methyl-*N*-(1-oxo-1-phenylbutan-2-yl)benzenesulfonamide (4AK^{Ts})

4WA^{Ts} (1.00 g, 3.33 mmol, 1.0 equiv) was treated according to the general procedure C. Purification by flash chromatography (SiO_2 20% EtOAc : 80% cHex) yielded product **4AK^{Ts}** (426 mg, 1.34 mmol, 40%) as white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 (d, J = 8.4 Hz, 2H), 7.66 (d, J = 8.5 Hz, 2H), 7.61 – 7.55 (m, 1H), 7.47 – 7.40 (m, 2H), 7.13 (d, J = 7.6 Hz, 2H), 5.70 (d, J = 8.5 Hz, 1H), 4.84 – 4.77 (m, 1H), 2.29 (s, 3H), 1.93 – 1.82 (m, 1H), 1.65 – 1.55 (m, 1H), 0.94 – 0.87 (m, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 198.1, 143.6, 137.0, 134.13, 134.0, 129.7, 128.9, 128.4, 127.2, 58.7, 27.6, 21.5, 9.3.

The spectroscopic data matched those reported in the literature[38]

(*S*)-4-methyl-*N*-(3-methylbut-2-en-1-yl)-*N*-(1-oxo-1-phenylbutan-2-yl)benzenesulfonamide (4^{Ts})

4AK^{Ts} (549 mg, 1.73 mmol, 1.0 equiv) was treated according to the general procedure C. Purification by flash chromatography (SiO_2 10% EtOAc : 90% cHex) yielded product **4^{Ts}** as white solid (551 mg, 1.43mmol, 83%) ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.00 (dd, J = 8.4, 1.3 Hz, 2H), 7.57 (dd, J = 8.0, 6.5 Hz, 3H), 7.47 (dd, J = 8.4, 7.1 Hz, 2H), 7.18 (d, J = 8.0 Hz, 2H), 5.35 (dd, J = 7.8, 6.2 Hz, 1H), 4.92 (ddt, J = 6.9, 5.4, 1.4 Hz, 1H), 3.94 (ddt, J = 16.1, 6.9, 1.2 Hz, 1H), 3.77 – 3.69 (m, 1H), 2.37 (s, 3H), 2.08 – 1.95 (m, 1H), 1.53 (d, J = 1.3 Hz, 6H), 1.44 (tt, J = 13.5, 7.4 Hz, 1H), 0.95 (t, J = 7.3 Hz, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 197.9, 143.4, 137.6, 136.4, 135.4, 133.3, 129.6, 128.8, 128.7, 127.6, 121.3, 61.5, 43.1, 25.7, 22.0, 21.6, 17.8, 11.5. HRMS calcd for $C_{22}H_{27}NO_3SNa$ [(M+Na)]$^+$: 408.1604 found 408.1609

(*S*)-2-ethyl-3-phenyl-1-tosyl-2,5-dihydro-1*H*-pyrrole (4A^{Ts})

4^{Ts} (140 mg, 364 µmol) was treated according to the general procedure D. The reaction was carried out at 30 °C for 24h. Flash chromatography (SiO_2 10% EtOAc : 90% Pentane) afforded **4A^{Ts}** (41.0 mg, 125 µmol, 34%) as white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 – 7.73 (m, 2H), 7.36 – 7.24 (m, 7H), 5.85 (q, J = 2.0 Hz, 1H), 5.09 (dtt, J = 5.5, 3.7, 1.7 Hz, 1H), 4.32 – 4.18 (m, 2H), 2.39 (s, 3H), 2.04 (dqd, J = 14.7, 7.4, 4.0 Hz, 1H), 1.70 (dqd, J = 14.5, 7.3, 3.6 Hz, 1H), 0.78 (t, J = 7.4 Hz, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 143.5, 141.4, 135.2, 133.4, 129.9, 128.8, 128.3, 127.4, 126.5, 120.2, 67.7, 55.9, 26.5, 21.6, 7.4. HRMS calcd for $C_{19}H_{21}NO_2SNa$ [(M+Na)]$^+$: 350.1185 found 350.1188

(*S*)-2-benzyl-3-phenyl-1-tosyl-2,5-dihydro-1*H*-pyrrole (5A^{Ts})

5^{Ts} (38.8 mg, 86.6 µmol) was treated according to the general procedure D. The reaction was carried out at 30 °C for 24h Flash chromatography (SiO_2 10% EtOAc : 90% Pentane) afforded **5A^{Ts}** (5,80 mg, 14.9 µmol, 17%) as white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 – 7.74 (m, 2H), 7.36 (dd, *J* = 8.3, 6.6 Hz, 2H), 7.33 – 7.27 (m, 3H), 7.26 – 7.23 (m, 2H), 7.15 (dd, *J* = 4.8, 1.9 Hz, 3H), 7.03 – 6.98 (m, 2H), 5.62 (dt, *J* = 2.9, 1.6 Hz, 1H), 5.30 (dtd, *J* = 4.9, 2.9, 1.3 Hz, 1H), 4.04 (ddd, *J* = 15.7, 2.6, 1.5 Hz, 1H), 3.55 (ddd, *J* = 15.7, 5.2, 1.9 Hz, 1H), 3.36 (dd, *J* = 13.7, 4.8 Hz, 1H), 3.01 (dd, *J* = 13.7, 2.7 Hz, 1H), 2.39 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 143.6, 140.7, 136.3, 135.2, 133.4, 130.8, 129.9, 129.0, 128.4, 127.7, 127.3, 126.6, 126.4, 121.3, 67.4, 55.67, 39.8, 21.6.

The spectroscopic data matched those reported in the literature[8]

Synthesis of 2^{FTs} and 2A^{FTs}

N-(2-oxo-2-phenylethyl)-4-(trifluoromethyl)benzenesulfonamide (2PAP^{FTs})

2-aminoacetophenone hydrochloride (1.00 g, 5.83 mmol) and 4-trifluoromethylbenzene sulfonyl chloride (1.71 g, 6.98 mmol) were treated according to the general procedure A. Flash chromatography (SiO_2 20% EtOAc : 80% cHex) afforded **2PAP^{FTs}** (1.76 g, 5.14 mmol, 88%) as white solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.04 (d, J = 8.1 Hz, 2H), 7.85 (dd, J = 8.5, 1.3 Hz, 2H), 7.77 (d, J = 8.2 Hz, 2H), 7.63 (t, J = 7.5 Hz, 1H), 7.52 – 7.45 (m, 2H), 5.77 (s, 1H), 4.51 (s, 2H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 192.2, 143.0, 134.8, 134.8 (q, J = 33.1), 133.6, 129.2, 128.0, 127.8, 126.5 (q, J = 3.8 Hz), 123.3 (q, J = 273.1 Hz), 48.7.

The spectroscopic data matched those reported in the literature[39]

N-(3-methylbut-2-en-1-yl)-*N*-(2-oxo-2-phenylethyl)-4-(trifluoromethyl)benzenesulfonamide (2^{FTs})

2PAP^{FTs} (700 mg, 2.04 mmol) and prenyl bromide (283 µL, 2.45 mmol) were treated according to the general procedure A. Flash chromatography (SiO_2 10% EtOAc : 90% cHex) afforded **2^{FTs}** (603 mg, 1.47 mmol, 72%) as pale

yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.01 (d, J = 8.0 Hz, 2H), 7.88 (dd, J = 8.4, 1.3 Hz, 2H), 7.78 (d, J = 8.3 Hz, 2H), 7.63 – 7.57 (m, 1H), 7.48 (dd, J = 8.2, 7.4 Hz, 2H), 5.07 (dddd, J = 7.5, 6.1, 2.8, 1.5 Hz, 1H), 4.76 (s, 2H), 3.95 (d, J = 7.5 Hz, 2H), 1.64 (d, J = 1.4 Hz, 3H), 1.46 (d, J = 1.3 Hz, 3H).^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 194.1, 143.89, 143.88, 143.87, 143.86, 139.83, 134.87, 134.19 (q. J = 32.9 Hz), 134.00, 128.99, 128.09, 127.97, 126.10 (q, J = 3.7 Hz), 123.46 (q, J = 272.9 Hz), 117.98, 51.67, 45.56, 25.84, 17.70.

The spectroscopic data matched those reported in the literature[8]

3-phenyl-1-((4-(trifluoromethyl)phenyl)sulfonyl)-2,5-dihydro-1*H*-pyrrole (2A^{FTs})

2F^{Ts} (70.0 mg, 170 μmol) was treated according to the general procedure D. The reaction was carried out at 50 °C for 14d with 0.4 equiv of HCl. Flash chromatography (SiO_2 10% EtOAc : 90% Pentane) afforded **2A^{FTs}** (3.40 mg, 9.62 μmol, 6%) as colorless oil. Yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.05 – 7.98 (m, 2H), 7.81 (dt, J = 8.2, 0.7 Hz, 2H), 7.35 – 7.27 (m, 5H), 6.03 (p, J = 2.1 Hz, 1H), 4.55 – 4.50 (m, 2H), 4.34 (td, J = 4.4, 2.3 Hz, 2H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 141.0, 137.5, 134.6 (q, J = 33.1 Hz), 132.3, 128.9, 128.8, 128.0, 126.6 (q, J = 3.7 Hz), 125.5, 124.4 (m), 118.7, 55.7, 55.1.

The spectroscopic data matched those reported in the literature[8]

Synthesis of 3^{FTs} and 3A^{FTs}

methyl *N*-(3-methylbut-2-en-1-yl)-*N*-((4-(trifluoromethyl)phenyl)sulfonyl)-*L*-alaninate (3EST^{FTs})

L-alanine (286 g, 3.21 mmol) was treated according to the general procedure B. Flash chromatography (SiO_2 10% EtOAc : 90% cHex) afforded **3EST^{FTs}** (934 mg, 2.46 mmol, 77%) colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98 – 7.93 (m, 2H), 7.79 – 7.72 (m, 2H), 5.04 (tdd, *J* = 5.5, 2.9, 1.4 Hz, 1H), 4.69 (q, *J* = 7.3 Hz, 1H), 3.95 – 3.88 (m, 1H), 3.86 – 3.78 (m, 1H), 3.58 (s, 3H), 1.63 (dd, *J* = 10.5, 1.3 Hz, 6H), 1.44 (d, *J* = 7.3 Hz, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 171.8, 144.4 8 (m), 136.4, 134.2 (q. J = 33.0 Hz), 128.0, 126.0(q, J = 3.7 Hz),123.4 (q, J = 272.8 Hz), 120.2, 55.1, 52.3, 43.7, 25.8, 17.7, 16.6. $C_{16}H_{20}F_3NO_4SNa$ [(M+Na)]$^+$: 402.0957 found 402.0964

(*S*)-*N*-(3-methylbut-2-en-1-yl)-*N*-(1-oxo-1-phenylpropan-2-yl)-4-(trifluoromethyl)benzenesulfonamide (3^{FTs})

3EST^{FTs} (934 mg, 2.46 mmol) was treated according to the general procedure B. Flash chromatography (SiO_2 5% EtOAc : 95% Pentane) afforded **3^{FTs}** (108 mg, 254 μmol, 10%) as white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 – 7.97 (m, 2H), 7.89 – 7.85 (m, 2H), 7.72 – 7.68 (m, 2H), 7.60 – 7.55 (m, 1H), 7.50 – 7.44 (m, 2H), 5.59 (q, J = 7.0 Hz, 1H), 4.84 (tdd, J = 6.5, 2.8, 1.4 Hz, 1H), 3.91 (dd, J = 15.7, 6.4 Hz, 1H), 3.79 – 3.70 (m, 1H), 1.52 – 1.50 (m, 6H), 1.32 (d, J = 7.0 Hz, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 197.9, 143.9, 137.0, 135.6, 134.4 (q, J = 33.2 Hz), 133.5, 128.8, 128.8, 128.1, 126.2 (q, J = 3.6 Hz), 124.2 (q, J = 272.9 Hz), 120.4, 56.3, 43.2, 25.7, 17.8, 14.3. HRMS calcd for $C_{21}H_{22}F_3NO_3SNa$ [(M+Na)]$^+$: 448.1165 found 448.1172

(*S*)-2-methyl-3-phenyl-1-((4-(trifluoromethyl)phenyl)sulfonyl)-2,5-dihydro-1*H*-pyrrole (3A^{FTs})

3^{FTs} (71.2 mg, 167 μmol) was treated according to the general procedure D. The reaction was carried out at 50 °C for 14d with 0.4 equiv of HCl. Flash chromatography (SiO_2 10% EtOAc : 90% Pentane) afforded **3A^{FTs}** (31.0 mg, 84.4 μmol, 50%) as white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03 – 7.99 (m, 2H), 7.80 – 7.75 (m, 2H), 7.37 – 7.26 (m, 5H), 5.86 (q, J = 2.0 Hz, 1H), 5.12 – 5.00 (m, 1H), 4.39 – 4.24 (m, 2H), 1.49 (d, J = 6.3 Hz, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 143.6, 142.1 (q, J = 1.3 Hz), 134.5 (q, J = 33.0 Hz), 132.7, 128.9, 128.6, 127.8, 126.5 (m, 2C), 123.4 (q, J = 272.9), 118.6, 63.3, 54.9, 22.0. HRMS calcd. for $C_{18}H_{16}F_3NO_2SNa$ [(M+Na)]$^+$: 390.0746 found 390.0742

(*S*)-*N*-(1-oxo-1-phenylpropan-2-yl)-4-(trifluoromethyl)benzenesulfonamide (3B^{FTs})

Isolated as a white solid (28.0 mg, 78.3 μmol, 47%) ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 – 7.92 (m, 2H), 7.78 – 7.74 (m, 2H), 7.68 – 7.57 (m, 3H), 7.50 – 7.43 (m, 2H), 5.87 (d, J = 8.1 Hz, 1H), 4.98 (dq, J = 8.2, 7.2 Hz, 1H), 1.44 (d, J = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 197.7, 143.8, 134.6, 134.5 (q, J = 33.1 Hz), 133.2, 129.2, 128.6, 127.7, 126.4 (q, J = 3.7 Hz), 123.21 (q, J = 273.0 Hz), 53.6, 21.3. HRMS calcd. for $C_{16}H_{14}F_3NO_3SNa$ [(M+Na)]$^+$: 380.0539 found 380.0540

Synthesis of 4^{FTs} and 4A^{FTs}

Methyl-(*S*)-2-((*N*-(3-methylbut-2-en-1-yl)-4-(trifluoromethyl)phenyl)sulfonamido)butanoate (4EST^{FTs})

L-2-aminobutyric acid (316 mg, 3.07 mmol) was treated according to the general procedure B. Flash chromatography (SiO_2 10% EtOAc : 90% cHex) afforded **4EST^{FTs}** (857 g, 2.18 mmol, 71%) as colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98 – 7.93 (m, 2H), 7.77 – 7.71 (m, 2H), 5.06 (dddd, J = 8.4, 5.6, 2.8, 1.4 Hz, 1H), 4.48 (dd, J = 9.6, 5.8 Hz, 1H), 3.87 (dt, J = 7.0, 1.1 Hz, 2H), 3.51 (s, 3H), 1.97 (dqd, J = 14.8, 7.4, 5.9 Hz, 1H), 1.70 (ddq, J = 14.6, 9.6, 7.3 Hz, 1H), 1.63 (s, 6H), 0.99 (t, J = 7.4 Hz, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 171.4, 144.4 (d, J=1.4 Hz), 136.0, 134.2 (q, J = 32.9 Hz), 128.1, 125.9 (q, J = 3.7 Hz), 123.5 (q, J = 272.9 Hz), 61.3, 52.1, 43.6, 25.8, 23.3, 17.8, 11.0. HRMS calcd. for $C_{17}H_{22}F_3NO_4SNa$ [(M+Na)]$^+$: 416.1114 found: 416.1117

(*S*)-*N*-(3-methylbut-2-en-1-yl)-*N*-(1-oxo-1-phenylbutan-2-yl)-4-(trifluoromethyl)benzenesulfonamide (4^{FTs})

4EST^{FTs} (857 mg, 2.18 mmol) was treated according to the general procedure B. Flash chromatography (SiO_2 5% EtOAc : 95% Pentane) afforded **4^{FTs}** (98.0 mg, 223 μmol, 10%) as white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.93 (dd, J = 8.4, 1.3 Hz, 2H), 7.79 – 7.75 (m, 2H), 7.62 – 7.56 (m, 3H), 7.47 (dd, J = 8.3, 7.3 Hz, 2H), 5.41 (t, J = 7.1 Hz, 1H), 4.96 (dddd, J = 7.7, 6.0, 2.9, 1.4 Hz, 1H), 4.03 (ddt, J = 16.2, 7.4, 1.0 Hz, 1H), 3.86 (ddt, J = 16.1, 6.3, 1.2 Hz, 1H), 2.04 (dt, J = 14.2, 7.2 Hz, 1H), 1.60 – 1.54 (m, 7H), 1.01 (t, J = 7.3 Hz, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ

197.8, 144.2, 136.1, 135.8, 134.2 (q, J = 33.1 Hz) 133.7, 128.9, 128.6, 128.0, 126.0 (q, J = 3.7 Hz), 123.3 (q, J = 272.9 Hz), 120.6, 61.7, 43.4, 25.7, 22.7, 17.9, 11.5. HRMS calcd for $C_{22}H_{24}F_3NO_3SNa$ $[(M+Na)]^+$: 462.1321 found 462.1326

(*S*)-2-ethyl-3-phenyl-1-((4-(trifluoromethyl)phenyl)sulfonyl)-2,5-dihydro-1*H*-pyrrole (4A^{FTs})

4^{FTs} (59.6 mg, 136 µmol) was treated according to the general procedure D The reaction was carried out at 50 °C for 14d with 0.4 equiv of HCl. Flash chromatography (SiO_2 10% EtOAc : 90% Pentane) afforded **4A^{FTs}** (9.0 mg, 23.6 µmol, 17%) as white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.00 (d, J = 8.2 Hz, 2H), 7.77 (d, J = 8.3 Hz, 2H), 7.36 – 7.24 (m, 5H), 5.89 (q, J = 2.0 Hz, 1H), 5.13 (tq, J = 4.1, 1.9 Hz, 1H), 4.44 – 4.16 (m, 2H), 2.05 (dtd, J = 14.7, 7.4, 4.2 Hz, 1H), 1.79 – 1.66 (m, 1H), 0.77 (t, J = 7.3 Hz, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 141.9, 141.3, 134.6 (q, J = 33.1 Hz), 132.9, 128.9, 128.59, 127.8, 126.4 (m), 123.3 (q, J = 272.9 Hz), 119.9, 67.9, 56.0, 26.4, 7.3. HRMS calcd. for $C_{19}H_{18}F_3NO_2SNa$ $[(M+Na)]^+$: 404.0903 found 404.0900

(*S*)-*N*-(1-oxo-1-phenylbutan-2-yl)-4-(trifluoromethyl)benzenesulfonamide (4B^{FTs})

Isolated as a white solid (26.0 mg, 70.0 µmol, 51%) ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.93 – 7.88 (m, 2H), 7.74 – 7.70 (m, 2H), 7.62 – 7.57 (m, 3H), 7.45 (dd, J = 8.3, 7.4 Hz, 2H), 5.80 (d, J = 8.6 Hz, 1H), 4.86 (ddd, J = 8.7, 7.2, 4.4 Hz, 1H), 1.92 (dqd, J = 14.8, 7.4, 4.4 Hz, 1H), 1.63 (dp, J = 14.6, 7.3 Hz, 1H), 0.93 (t, J = 7.4 Hz, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 197.6, 143.6, 134.5, 134.5 (q, J = 33.0 Hz), 134.2, 133.7, 129.1, 128.4, 127.7, 126.3 (q, J = 3.8 Hz), 123.2 (q, J = 273.0 Hz) 58.8, 27.6, 9.3. HRMS calcd. for $C_{17}H_{16}F_3NO_3SNa$ $[(M+Na)]^+$: 394.0695 found 394.0695

1(*S*)-2-benzyl-3-phenyl-1-((4-(trifluoromethyl)phenyl)sulfonyl)-2,5-dihydro-1*H*-pyrrole (5A^{FTs})

5^{FTs} (51.6 mg, 103 µmol) was treated according to the general procedure D. The reaction was carried out at 50 °C for 14d with 0.4 equiv of HCl. Flash chromatography (SiO_2 10% EtOAc : 90% Pentane) afforded **5A^{FTs}** (16.0 mg, 36.1 µmol, 35%) as white solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.01 – 7.97 (m, 2H), 7.80 – 7.75 (m, 2H), 7.40 – 7.33 (m, 3H), 7.28 – 7.25 (m, 2H), 7.17 (dd, J = 5.0, 1.9 Hz, 3H), 7.01 – 6.98 (m, 2H), 5.67 (dt, J = 2.9, 1.6 Hz, 1H), 5.32 (tdt, J = 5.1, 2.7, 1.3 Hz, 1H), 4.04 (ddd, J = 15.6, 2.6, 1.4 Hz, 1H), 3.58 (ddd, J = 15.7, 5.1, 1.9 Hz, 1H), 3.36 (dd, J = 13.8, 4.8 Hz, 1H), 3.03 (dd, J = 13.8, 2.7 Hz, 1H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 141.8, 140.7, 135.9, 134.5 (q, J = 33.0 Hz), 132.9, 130.7, 129.1, 128.6, 126.5 (m), 123.3 (q, J = 273.0 Hz), 121.0, 67.6, 55.7, 39.7.

The spectroscopic data matched those reported in the literature[8]

Synthesis of 2^{Ms} and 2A^{Ms}

***N*-(2-oxo-2-phenylethyl)methanesulfonamide (2PAP^{Ms})**

2-aminoacetophenone hydrochloride (1.00 g, 5.83 mmol)and mesyl chloride (540 µL, 6.98 mmol) were treated according to the general procedure A. Flash chromatography (SiO_2 30% EtOAc : 70% cHex) afforded **2PAP^{Ms}** (800 mg, 3.75 mmol, 64%) as white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.00 – 7.91 (m, 2H), 7.68 – 7.63 (m, 1H), 7.55 – 7.49 (m, 2H), 5.34 (s, 1H), 4.68 (d, J = 4.8 Hz, 2H), 3.01 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 193.4, 134.7, 133.9, 129.2, 128.1, 49.3, 41.0.

The spectroscopic data matched those reported in the literature[40]

***N*-(3-methylbut-2-en-1-yl)-*N*-(2-oxo-2-phenylethyl)methanesulfonamide (2^{Ms})**

2PAP^{Ms} (400 mg, 1.88 mmol) and prenyl bromide (260 µL, 2.25 mmol) were was treated according to the general procedure A. Flash chromatography (SiO_2 20% EtOAc : 80% cHex) afforded **2^{Ms}** (296 mg, 1.05 mmol, 56%) as pale yellow solid. 1H NMR (500 MHz, $CDCl_3$) δ 7.93 – 7.89 (m, 2H), 7.64 – 7.59 (m, 1H), 7.52 – 7.47 (m, 2H), 5.20 (tdt, J = 7.5, 2.9, 1.4 Hz, 1H), 4.76 (s, 2H), 4.02 – 3.96 (m, 2H), 3.09 (s, 3H), 1.70 (q, J = 1.1 Hz, 3H), 1.53 (d, J = 1.4 Hz, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 195.6, 139.2, 134.9, 134.1, 129.1, 128.0, 118.8, 51.9, 45.1, 40.3, 25.9, 17.8. HRMS calcd. For $C_{14}H_{19}NO_3SNa$ $[(M+Na)]^+$: 304.0978 found 304.0979

1-(methylsulfonyl)-3-phenyl-2,5-dihydro-1*H*-pyrrole (2A^{Ms})

2^{Ms} (45.5 mg, 162 µmol) was treated according to the general procedure D. The reaction was carried out at 50 °C for 48h. Flash chromatography (SiO_2 10% EtOAc : 90% Pentane) afforded **2A^{Ms}** (9.00 mg, 40.3 µmol, 25%) as colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 – 7.29 (m, 5H), 6.14 (p, J = 2.1 Hz, 1H), 4.56 (ddd, J = 4.6, 4.0, 2.0 Hz, 2H), 4.39 – 4.34 (m, 2H), 2.89 (s, 3H).^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 137.8, 132.5, 128.9, 128.8, 125.6, 119.1, 55.9, 55.2, 34.8.

The spectroscopic data matched those reported in the literature[7]

Synthesis of 3^{Ms} and 3A^{Ms}

methyl *N*-(3-methylbut-2-en-1-yl)-*N*-(methylsulfonyl)-*L*-alaninate (3EST^{Ms})

L-alanine (1.33 g, 14.9 mmol) was treated according to the general procedure B. Flash chromatography (SiO_2 20% EtOAc : 80% cHex) afforded **3EST^{Ms}** (2.55 g, 10.2 mmol, 68%) colorless oil ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.24 – 5.17 (m, 1H), 4.61 (q, J = 7.3 Hz, 1H), 3.93 – 3.81 (m, 2H), 3.74 (s, 3H), 2.95 (s, 3H), 1.71 (q, J = 1.3 Hz, 3H), 1.66 (d, J = 1.4 Hz, 3H), 1.47 (d, J = 7.3 Hz, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 172.6, 136.0, 120.9, 55.4, 52.5, 43.5, 40.5, 25.9, 17.9, 16.9. HRMS calcd. For $C_{10}H_{19}NO_4SNa$ $[(M+Na)]^+$: 272.0927 found 272.0929

(*S*)-*N*-(3-methylbut-2-en-1-yl)-*N*-(1-oxo-1-phenylpropan-2-yl)methanesulfonamide (3^{Ms})

$3EST^{Ms}$ (1.00 g, 4.01 mmol) was treated according to the general procedure B. Flash chromatography (SiO_2 5% EtOAc : 95% Pentane) afforded **3^{Ms}** (172 mg, 582 μmol, 14%) as colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 – 7.97 (m, 2H), 7.60 – 7.55 (m, 1H), 7.51 – 7.44 (m, 2H), 5.55 (q, J = 7.1 Hz, 1H), 5.03 (ddq, J = 8.3, 5.6, 1.4 Hz, 1H), 3.94 – 3.78 (m, 2H), 2.84 (s, 3H), 1.63 – 1.57 (m, 6H), 1.49 (d, J = 7.1 Hz, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 198.8, 136.4, 135.6, 133.5, 128.8, 128.8, 121.1, 56.6, 43.0, 40.6, 25.8, 17.7, 15.4. HRMS calcd. for $C_{15}H_{21}NO_3SNa$ [(M+Na)]$^+$: 318.1134 found 318.1139

(*S*)-2-methyl-1-(methylsulfonyl)-3-phenyl-2,5-dihydro-1*H*-pyrrole ($3A^{Ms}$)

3^{Ms} (50.0 mg, 169 μmol) was treated according to the general procedure D. The reaction was carried out at 50 °C for 48h. Flash chromatography (SiO_2 10% EtOAc : 90% Pentane) afforded **$3A^{Ms}$** (22.0 mg, 92.7 μmol, 55%) as colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 – 7.28 (m, 5H), 6.05 – 5.98 (m, 1H), 5.08 – 5.00 (m, 1H), 4.39 – 4.25 (m, 2H), 2.86 (s, 3H), 1.45 (d, J = 6.4 Hz, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 143.9, 132.9, 129.0, 128.6, 126.5, 118.9, 62.9, 54.7, 35.6, 21.7. HRMS calcd for $C_{12}H_{15}NO_2SNa$ [(M+Na)]$^+$: 260.0717 found 260.0716

(*S*)-*N*-(1-oxo-1-phenylpropan-2-yl)methanesulfonamide ($3B^{Ms}$)

Isolated as a white solid (9.00 mg, 39.6 μmol, 23%) ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.99 – 7.95 (m, 2H), 7.65 (ddt, J = 7.8, 7.0, 1.3 Hz, 1H), 7.53 (ddd, J = 7.7, 6.9, 1.1 Hz, 2H), 5.45 (d, J = 8.1 Hz, 1H), 5.15 (dq, J = 8.2, 7.2 Hz, 1H), 2.92 (s, 3H), 1.51 (d, J = 7.2 Hz, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 198.6, 134.6, 133.5, 129.3, 128.9, 54.0, 41.9, 21.5. HRMS calcd. for $C_{10}H_{13}NO_3SNa^+$: 250.0508 found 250.0513

Synthesis of 4^{Ms} and $4A^{Ms}$

methyl (*S*)-2-(*N*-(3-methylbut-2-en-1-yl)methylsulfonamido)butanoate ($4EST^{Ms}$)

L-2-aminobutyric acid (533 mg, 5.17 mmol) was treated according to the general procedure B. Flash chromatography (SiO_2 20% EtOAc : 80% cHex) afforded **$4EST^{Ms}$** (879 mg, 3.34 mmol, 65%) colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.23 (ddp, J = 9.3, 6.4, 1.5 Hz, 1H), 4.39 (dd, J = 10.1, 5.5 Hz, 1H), 3.94 – 3.79 (m, 2H), 3.74 (s, 3H), 2.96 (s, 3H), 1.99 (dqd, J = 14.7, 7.4, 5.5 Hz, 1H), 1.78 – 1.69 (m, 4H), 1.66 (d, J = 1.3 Hz, 3H), 1.01 (t, J = 7.4 Hz, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 172.2, 136.1, 120.5, 61.4, 52.4, 43.3, 40.5, 25.9, 23.0, 17.9, 11.0. HRMS calcd. for $C_{11}H_{21}NO_4SNa$ [(M+Na)]$^+$: 286.1083 found 286.1085

(*S*)-*N*-(3-methylbut-2-en-1-yl)-*N*-(1-oxo-1-phenylbutan-2-yl)methanesulfonamide (4^{Ms})

$4EST^{Ms}$ (879 mg, 3.34 mmol) was treated according to the general procedure B. Flash chromatography (SiO_2 5% EtOAc : 95% Pentane) afforded **4^{Ms}** (81.0 mg, 262 μmol, 8%) as colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.00 – 7.96 (m, 2H), 7.62 – 7.57 (m, 1H), 7.52 – 7.46 (m, 2H), 5.35 (dd, J = 8.4, 6.2 Hz, 1H), 5.11 (ddp, J = 7.6, 6.0, 1.4 Hz, 1H), 3.99 (ddt, J = 16.3, 7.8, 0.9 Hz, 1H), 3.87 – 3.78 (m, 1H), 2.76 (s, 3H), 2.02 (dtd, J = 14.6, 7.3, 6.2 Hz, 1H), 1.75 (ddq, J = 14.5, 8.4, 7.3 Hz, 1H), 1.67 – 1.62 (m, 6H), 1.05 (t, J = 7.3 Hz, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 198.7, 136.2, 135.9, 133.7, 129.0, 128.7, 121.15, 61.9, 42.7, 41.0, 25.8, 22.7, 17.9, 11.2. HRMS calcd. for $C_{16}H_{23}NO_3SNa$ [(M+Na)]$^+$: 332.1291 found 332.1294

(*S*)-2-ethyl-1-(methylsulfonyl)-3-phenyl-2,5-dihydro-1*H*-pyrrole ($4A^{Ms}$)

4^{Ms} (81.0 mg, 262 μmol) was treated according to the general procedure D. The reaction was carried out at 50 °C for 48h. Flash chromatography (SiO_2 10% EtOAc : 90% Pentane) afforded **$4A^{Ms}$** (27.0 mg, 107 μmol, 41%) as colorless oil. Yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 – 7.29 (m, 5H), 6.07 (dd, J = 2.5, 1.5 Hz, 1H), 5.10 – 5.06 (m, 1H), 4.36 (ddd, J = 16.0, 2.6, 1.7 Hz, 1H), 4.25 (ddd, J = 16.0, 5.1, 1.9 Hz, 1H), 2.83 (s, 3H), 1.97 (dqd, J = 14.8, 7.4, 4.1 Hz, 1H), 1.72 (dqd, J = 14.6, 7.3, 4.0 Hz, 1H), 0.83 (t, J = 7.4 Hz, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 141.7, 132.9, 128.8, 128.5, 126.4, 120.1, 67.4, 55.7, 34.8, 26.3, 7.4. HRMS calcd for $C_{13}H_{17}NO_2SNa$ [(M+Na)]$^+$: 274.0872 found 274.0873

(*S*)-*N*-(1-oxo-1-phenylbutan-2-yl)methanesulfonamide ($4B^{Ms}$)

Isolated as a white solid (16.0 mg, 66.3 μmol, 25%) ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98 – 7.94 (m, 2H), 7.68 – 7.63 (m, 1H), 7.56 – 7.51 (m, 2H), 5.41 (d, J = 8.6 Hz, 1H), 5.02 (ddd, J = 8.6, 7.4, 4.2 Hz, 1H), 2.88 (s, 3H), 1.99 (ddd, J = 14.4, 7.3, 4.2 Hz, 1H), 1.66 (dt, J = 14.5, 7.3 Hz, 1H), 0.99 (t, J = 7.4 Hz, 3H).$^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 198.5, 134.5, 134.0, 129.3, 128.8, 59.4, 41.5, 27.7, 9.5. HRMS calcd. for $C_{11}H_{15}NO_3SNa$ [(M+Na)]$^+$: 264.0665 found 264.0669

Synthesis of 5^{Ms} and $5A^{Ms}$

(*S*)-*N*-methoxy-*N*-methyl-2-(methylsulfonamido)-3-phenylpropanamide ($5WA^{Ms}$)

L-phenylalanine (2.03 g, 12.3 mmol, 1.0 equiv) was treated according to the general procedure C. Purification by flash chromatography (SiO_2 40% EtOAc : 60% cHex) yielded product **$5WA^{Ms}$** as colorless oil (1.40 g, 4.89 mmol, 40%) ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 – 7.21 (m, 5H), 5.25 (d, J = 9.6 Hz, 1H), 4.67 (td, J = 9.3, 4.7 Hz, 1H), 3.76 (s, 3H), 3.26 (s, 3H), 3.11 (dd, J = 13.5, 4.7 Hz, 1H), 2.79 (dd, J = 13.5, 9.1 Hz, 1H), 2.49 (s, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 171.7, 136.7, 129.8, 128.8, 128.8, 128.8, 127.4, 61.9, 55.4, 41.4, 39.6, 32.4. HRMS calcd. $C_{12}H_{18}N_2O_4SNa$ [(M+Na)]$^+$: 309.0879 found 309.0885

(*S*)-*N*-(1-oxo-1,3-diphenylpropan-2-yl)methanesulfonamide ($5AK^{Ms}$)

$5WA^{Ms}$ (1.40 g, 4.89 mmol, 1.0 equiv) was treated according to the general procedure C. Purification by flash chromatography (SiO_2 20% EtOAc : 80% cHex) yielded product **$5AK^{Ms}$** (700 mg, 2.31 mmol, 47%) as white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03 – 7.98 (m, 2H), 7.69 – 7.63 (m, 1H), 7.57 – 7.52 (m, 2H), 7.31 – 7.21 (m, 3H), 7.17 –

7.12 (m, 2H), 5.38 – 5.29 (m, 2H), 3.26 – 3.18 (m, 1H), 2.94 – 2.84 (m, 1H), 2.58 (s, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 197.7, 135.6, 134.5, 134.2, 129.8, 129.3, 128.9, 128.8, 127.6, 59.3, 41.6, 40.5. HRMS calcd. $C_{16}H_{17}NO_3SNa$ [(M+Na)]$^+$: 326.0821 found 326.0825

(*S*)-*N*-(3-methylbut-2-en-1-yl)-*N*-(1-oxo-1,3-diphenylpropan-2-yl)methanesulfonamide (5^{Ms})

$5AK^{Ms}$ (700 mg, 2.31 mmol, 1.0 equiv) was treated according to the general procedure C. Purification by flash chromatography (SiO_2 10% EtOAc : 90% cHex) yielded product **5^{Ms}** as white solid (453 mg, 1.22 mmol, 53%) ^1H NMR (500 MHz, $CDCl_3$) δ 8.03 – 7.97 (m, 2H), 7.58 – 7.51 (m, 1H), 7.47 – 7.41 (m, 2H), 7.34 – 7.27 (m, 4H), 7.20 (ddt, J = 8.6, 6.3, 1.7 Hz, 1H), 5.81 (t, J = 7.4 Hz, 1H), 4.96 (dddd, J = 8.5, 5.6, 2.8, 1.4 Hz, 1H), 3.87 (dt, J = 7.1, 1.1 Hz, 2H), 3.42 (dd, J = 14.2, 7.1 Hz, 1H), 3.06 (dd, J = 14.2, 7.7 Hz, 1H), 2.43 (s, 3H), 1.67 – 1.58 (m, 6H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 197.5, 137.4, 136.7, 135.9, 133.6, 129.7, 128.9, 128.8, 128.8, 127.0, 120.6, 61.4, 42.8, 41.0, 35.5, 25.8, 17.9. HRMS calcd for $C_{21}H_{25}NO_3SNa$ [(M+Na)]$^+$:394.1447 found 394.1455

(*S*)-2-benzyl-1-(methylsulfonyl)-3-phenyl-2,5-dihydro-1*H*-pyrrole ($5A^{Ms}$)

5^{Ms} (62.5 mg, 168 µmol) was treated according to the general procedure D. The reaction was carried out at 50 °C for 48h. Flash chromatography (SiO_2 10% EtOAc : 90% Pentane) afforded **$5A^{Ms}$** (33.0 mg, 105 µmol, 62%) as colorless oil. ^1H NMR (500 MHz, $CDCl_3$) δ 7.47 – 7.33 (m, 5H), 7.18 – 7.13 (m, 3H), 7.04 – 6.98 (m, 2H), 5.86 (q, J = 2.5, 2.0 Hz, 1H), 5.31 (dd, J = 4.8, 3.2 Hz, 1H), 4.10 (ddd, J = 16.0, 2.7, 1.3 Hz, 1H), 3.55 (ddd, J = 16.0, 5.1, 1.8 Hz, 1H), 3.26 (dd, J = 13.8, 4.8 Hz, 1H), 3.01 (dd, J = 13.7, 3.1 Hz, 1H), 2.81 (s, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 141.2, 136.1, 133.1, 130.8, 129.1, 128.6, 127.8, 126.6, 126.5, 121.4, 67.3, 55.5, 39.7, 34.8. HRMS calcd for $C_{18}H_{19}NO_2SNa$ [(M+Na)]$^+$: 336.1029 found 336.1033

Large scale synthesis of $3A^{Ts}$

Resorcinarene (1.78 g, 1.61 mmol, 0.6 equiv) was weighed into a pressure vial and chloroform (filtered through basic aluminum oxide) was added to reach a concentration of 25.0 mM regarding resorcinarene. The capped vial was heated gently with a heatgun until the suspension turned clear. After cooling to room temperature, HCl (3.85 mL, 0.14 M, 538 µmol, 0.2 equiv) was added in the form of HCl-saturated chloroform. The substrate **3^{Ts}** (1.00 g, 2.69 mmol, 1.0 equiv) and filtered chloroform was added to receive a total concentration of 33.1 mM regarding the substrate. The vial was equipped with a stirring bar and transferred to an oil bath set to 30 °C. After 24h, the reaction mixture was transferred directly to the column (SiO_2, 100% cHex) and was rinsed with cHex. The eluent was gradually changed to a mixture of 90% cHex and 10% EtOAc. **$3A^{Ts}$** (646 mg, 2.06 mmol, 77%) was obtained as a white solid.

ASSOCIATED CONTENT

Supporting Information. Experimental details and NMR spectra of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

Konrad Tiefenbacher − Department of Chemistry, University of Basel, CH-4058 Basel, Switzerland; Department of Biosystems Science and Engineering, ETH Zürich, CH-4058 Basel, orcid.org/0000-0002-3351-6121
Email: konrad.tiefenbacher@unibas.ch, tkonrad@ethz.ch
Author

Fabian Huck − Department of Chemistry, University of Basel, CH-4058 Basel, Switzerland

orcid.org/ 0000-0002-8764-4903

Lorenzo Catti − Laboratory for Chemistry and Life Science

Institute of Innovative Research Tokyo Institute of Technology, 4259-R1-28, Nagatsuta, Midori-ku, Yokohama 226-8503, Japan

orcid.org/0000-0003-0727-0620

Gian Lino Reber− Department of Chemistry, University of Basel, CH-4058 Basel, Switzerland

Author Contributions

K.T. conceived and supervised the project. K.T., L.C., and F.H. planned the project. F.H. carried out all the experiments besides the synthesis of substrates 4^{FTs} and 5^{FTs}, which were prepared by G.R. F.H. analyzed the data. K.T. and F.H. compiled a first version of the manuscript. All authors contributed to the final version of the manuscript.

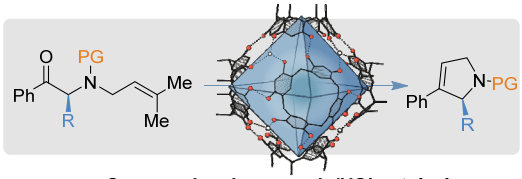
ACKNOWLEDGMENT

We thank Dr. Michael Pfeffer for the HR-MS analysis.

REFERENCES

1. Groso, E. J.; Schindler, C. S., Recent Advances in the Application of Ring-Closing Metathesis for the Synthesis of Unsaturated Nitrogen Heterocycles. *Synthesis* **2019,** *51* (05), 1100-1114.
2. Li, X.; Li, J., Recent Advances in the Development of MMPIs and APNIs Based on the Pyrrolidine Platforms. *Mini-Rev. Med. Chem.* **2010,** *10* (9), 794-805.
3. R. Liddell, J., Pyrrolizidine alkaloids. *Nat. Prod. Rep.* **1999,** *16* (4), 499-507.
4. O'Hagan, D., Pyrrole, pyrrolidine, pyridine, piperidine and tropane alkaloids. *Nat. Prod. Rep.* **2000,** *17* (5), 435-446.
5. Huang, P.-Q., Asymmetric Synthesis of Five-Membered Ring Heterocycles. In *Asymmetric Synthesis of Nitrogen Heterocycles*, 2009; pp 51-94.
6. Schultz, D. M.; Wolfe, J. P., Recent Developments in Palladium-Catalyzed Alkene Aminoarylation Reactions for the Synthesis of Nitrogen Heterocycles. *Synthesis* **2012,** *44* (03), 351-361.
7. Ma, L.; Li, W.; Xi, H.; Bai, X.; Ma, E.; Yan, X.; Li, Z., FeCl3-Catalyzed Ring-Closing Carbonyl–Olefin Metathesis. *Angew. Chem. Int. Ed.* **2016,** *55* (35), 10410-10413.
8. Groso, E. J.; Golonka, A. N.; Harding, R. A.; Alexander, B. W.; Sodano, T. M.; Schindler, C. S., 3-Aryl-2,5-Dihydropyrroles via Catalytic Carbonyl-Olefin Metathesis. *ACS Catal.* **2018**, 2006-2011.

9. Becker, M. R.; Watson, R. B.; Schindler, C. S., Beyond olefins: new metathesis directions for synthesis. *Chem. Soc. Rev.* **2018,** *47* (21), 7867-7881.
10. Albright, H.; Davis, A. J.; Gomez-Lopez, J. L.; Vonesh, H. L.; Quach, P. K.; Lambert, T. H.; Schindler, C. S., Carbonyl–Olefin Metathesis. *Chem. Rev.* **2021,** *121* (15), 9359-9406.
11. Ludwig, J. R.; Zimmerman, P. M.; Gianino, J. B.; Schindler, C. S., Iron(III)-catalysed carbonyl–olefin metathesis. *Nature* **2016,** *533* (7603), 374-379.
12. Ludwig, J. R.; Phan, S.; McAtee, C. C.; Zimmerman, P. M.; Devery, J. J.; Schindler, C. S., Mechanistic Investigations of the Iron(III)-Catalyzed Carbonyl-Olefin Metathesis Reaction. *J. Am. Chem. Soc.* **2017,** *139* (31), 10832-10842.
13. Rykaczewski, K. A.; Groso, E. J.; Vonesh, H. L.; Gaviria, M. A.; Richardson, A. D.; Zehnder, T. E.; Schindler, C. S., Tetrahydropyridines via FeCl3-Catalyzed Carbonyl–Olefin Metathesis. *Org. Lett.* **2020,** *22* (7), 2844-2848.
14. Tran, U. P. N.; Oss, G.; Breugst, M.; Detmar, E.; Pace, D. P.; Liyanto, K.; Nguyen, T. V., Carbonyl–Olefin Metathesis Catalyzed by Molecular Iodine. *ACS Catal.* **2018**, 912-919.
15. Oss, G.; Nguyen, T. V., Iodonium-Catalyzed Carbonyl–Olefin Metathesis Reactions. *Synlett* **2019,** *30* (17), 1966-1970.
16. Wang, R.; Chen, Y.; Shu, M.; Zhao, W.; Tao, M.; Du, C.; Fu, X.; Li, A.; Lin, Z., AuCl3-Catalyzed Ring-Closing Carbonyl–Olefin Metathesis. *Chem. Eur. J.* **2020,** *26* (9), 1941-1946.
17. Zhang, Y.; Sim, J. H.; MacMillan, S. N.; Lambert, T. H., Synthesis of 1,2-Dihydroquinolines via Hydrazine-Catalyzed Ring-Closing Carbonyl-Olefin Metathesis. *Org. Lett.* **2020**.
18. Catti, L.; Tiefenbacher, K., Brønsted Acid-Catalyzed Carbonyl-Olefin Metathesis inside a Self-Assembled Supramolecular Host. *Angew. Chem. Int. Ed.* **2018,** *57* (44), 14589-14592.
19. MacGillivray, L. R.; Atwood, J. L., A chiral spherical molecular assembly held together by 60 hydrogen bonds. *Nature* **1997,** *389* (6650), 469-472.
20. Avram, L.; Cohen, Y., The Role of Water Molecules in a Resorcinarene Capsule As Probed by NMR Diffusion Measurements. *Org. Lett.* **2002,** *4* (24), 4365-4368.
21. Avram, L.; Cohen, Y., Spontaneous Formation of Hexameric Resorcinarene Capsule in Chloroform Solution as Detected by Diffusion NMR. *J. Am. Chem. Soc.* **2002,** *124* (51), 15148-15149.
22. Avram, L.; Cohen, Y.; Rebek Jr, J., Recent advances in hydrogen-bonded hexameric encapsulation complexes. *Chem. Commun.* **2011,** *47* (19), 5368-5375.
23. Cavarzan, A.; Scarso, A.; Sgarbossa, P.; Strukul, G.; Reek, J. N. H., Supramolecular Control on Chemo- and Regioselectivity via Encapsulation of (NHC)-Au Catalyst within a Hexameric Self-Assembled Host. *J. Am. Chem. Soc.* **2011,** *133* (9), 2848-2851.
24. Bianchini, G.; Sorella, G. L.; Canever, N.; Scarso, A.; Strukul, G., Efficient isonitrile hydration through encapsulation within a hexameric self-assembled capsule and selective inhibition by a photo-controllable competitive guest. *Chem. Commun.* **2013,** *49* (46), 5322-5324.
25. Giust, S.; La Sorella, G.; Sperni, L.; Fabris, F.; Strukul, G.; Scarso, A., Supramolecular Catalysis in the Synthesis of Substituted 1 H-Tetrazoles from Isonitriles by a Self-Assembled Hexameric Capsule. *Asian J. Org. Chem.* **2015,** *4* (3), 217-220.
26. Caneva, T.; Sperni, L.; Strukul, G.; Scarso, A., Efficient epoxide isomerization within a self-assembled hexameric organic capsule. *RSC Advances* **2016,** *6* (87), 83505-83509.
27. Zhang, Q.; Catti, L.; Tiefenbacher, K., Catalysis inside the Hexameric Resorcinarene Capsule. *Acc. Chem. Res.* **2018,** *51* (9), 2107-2114.
28. La Manna, P.; Talotta, C.; Floresta, G.; De Rosa, M.; Soriente, A.; Rescifina, A.; Gaeta, C.; Neri, P., Mild Friedel–Crafts Reactions inside a Hexameric Resorcinarene Capsule: C–Cl Bond Activation through Hydrogen Bonding to Bridging Water Molecules. *Angew. Chem. Int. Ed.* **2018,** *57* (19), 5423-5428.
29. Gaeta, C.; Talotta, C.; De Rosa, M.; La Manna, P.; Soriente, A.; Neri, P., The Hexameric Resorcinarene Capsule at Work: Supramolecular Catalysis in Confined Spaces. *Chem. Eur. J.* **2019,** *25* (19), 4899-4913.
30. Zhu, Y.; Rebek Jr, J.; Yu, Y., Cyclizations catalyzed inside a hexameric resorcinarene capsule. *Chem. Commun.* **2019,** *55* (25), 3573-3577.
31. Gaeta, C.; La Manna, P.; De Rosa, M.; Soriente, A.; Talotta, C.; Neri, P., Supramolecular Catalysis with Self-Assembled Capsules and Cages: What Happens in Confined Spaces. *ChemCatChem* **2021,** *13* (7), 1638-1658.
32. Naito, H.; Hata, T.; Urabe, H., Selective Deprotection of Methanesulfonamides to Amines. *Org. Lett.* **2010,** *12* (6), 1228-1230.
33. Shivanyuk, A.; Rebek, J., Reversible encapsulation by self-assembling resorcinarene subunits. *Proc. Natl. Acad. Sci. U.S.A.* **2001,** *98* (14), 7662-7665.
34. Zhang, Q.; Tiefenbacher, K., Hexameric Resorcinarene Capsule is a Brønsted Acid: Investigation and Application to Synthesis and Catalysis. *J. Am. Chem. Soc.* **2013,** *135* (43), 16213-16219.
35. La Sorella, G.; Sperni, L.; Strukul, G.; Scarso, A., Supramolecular Encapsulation of Neutral Diazoacetate Esters and Catalyzed 1,3-Dipolar Cycloaddition Reaction by a Self-Assembled Hexameric Capsule. *ChemCatChem* **2015,** *7* (2), 291-296.
36. Li, X.; Chen, M.; Xie, X.; Sun, N.; Li, S.; Liu, Y., Synthesis of Multiple-Substituted Pyrroles via Gold(I)-Catalyzed Hydroamination/Cyclization Cascade. *Org. Lett.* **2015,** *17* (12), 2984-2987.
37. Tarantino, K. T.; Liu, P.; Knowles, R. R., Catalytic Ketyl-Olefin Cyclizations Enabled by Proton-Coupled Electron Transfer. *J. Am. Chem. Soc.* **2013,** *135* (27), 10022-10025.
38. Rao, W.; Koh, M. J.; Kothandaraman, P.; Chan, P. W. H., Gold-Catalyzed Cycloisomerization of 1,7-Diyne Benzoates to Indeno[1,2-c]azepines and Azabicyclo[4.2.0]octa-1(8),5-dines. *J. Am. Chem. Soc.* **2012,** *134* (26), 10811-10814.
39. Zhang, X.; Li, S.-S.; Wang, L.; Xu, L.; Xiao, J.; Liu, Z.-J., 2-Methylquinoline promoted oxidative ring-opening of N-sulfonyl aziridines with DMSO: facile synthesis of α-amino aryl ketones. *Tetrahedron* **2016,** *72* (49), 8073-8077.
40. Miura, T.; Biyajima, T.; Fujii, T.; Murakami, M., Synthesis of α-Amino Ketones from Terminal Alkynes via Rhodium-Catalyzed Denitrogenative Hydration of N-Sulfonyl-1,2,3-triazoles. *J. Am. Chem. Soc.* **2012,** *134* (1), 194-196.



- **Supramolecular capsule/HCl catalysis**
- **Lewis basic PGs tolerated**
- **conservation of optical activity**