


Vitamin B₁₂-Catalyzed Dicarbofunctionalization of Bromoalkenes Under Visible Light Irradiation

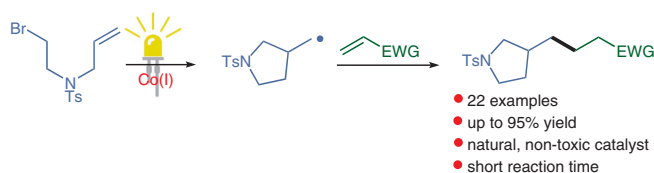
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Dedicated to Professor Grzegorz Młostoń on the occasion of his 70th birthday.



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Abstract Vitamin B₁₂ plays a crucial role in enzymatic transformations. This natural compound proved also useful as a catalyst in numerous organic reactions. Commercial availability and lower cost than precious metal complexes, make cobalamin an attractive candidate for a broader use as a benign Co-catalyst. Herein, the vitamin B₁₂-catalyzed dicarbofunctionalization of bromoalkenes with electrophilic olefins is reported leading to substituted pyrrolidines and piperidines in decent yields after only 15 minutes under light irradiation.

Key words cobalt, vitamin B12, radical cyclization, Giese addition

Vitamin B₁₂ [**1**, CN(Cbl), cyanocobalamin, Figure 1], as a cofactor is involved in enzymatic isomerization, methyl transfer, and dehalogenation reactions, consequently it plays a crucial role in proper functioning of living cells.¹ In organic synthesis, as a native compound, amphiphilic cobalaster **2**, or hydrophobic heptamethyl cobyrinate (**3**) has been utilized as a benign Co-catalyst in numerous reactions, including cyclopropanation,² reductive coupling of halides and non-activated alkyl tosylates,³ dehalogenation,⁴ deprotection of (allyloxy)arenes,⁵ or generation of radicals through strain release,⁶ etc.⁷ Catalytic properties of these compounds stem from the central Co(III) ion, which upon reduction generates either radical Co(II) **1a** or ‘supernucleophilic’ Co(I)-species **1b** (Scheme 1). As such, they react, respectively, with radicals and electrophiles furnishing alkyl cobalamins. Subsequent photolytic or thermal homolytic cleavage of the C–Co bond leads to C-centered radicals, which with suitable partners forge new C–C bonds.⁸

Pyrrolidines are important class of organic compounds with numerous applications in medicinal chemistry.⁹ Given their ubiquity in structures of natural products and synthetic compounds, a plethora of methods for their synthesis

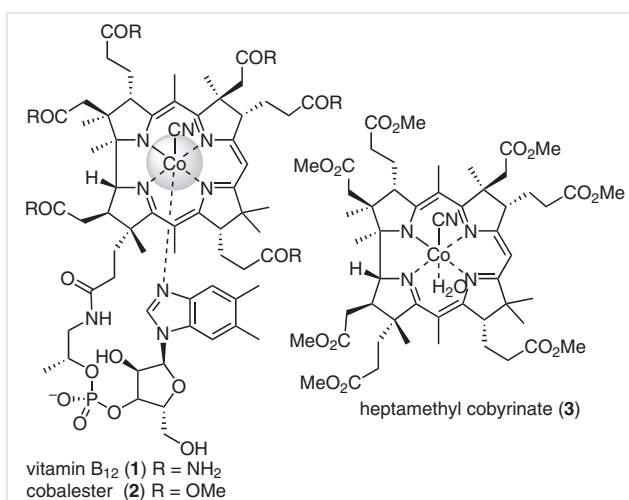
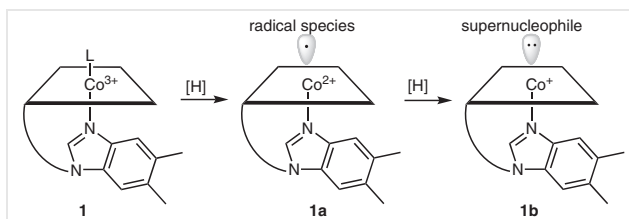


Figure 1 Vitamin B₁₂ and its derivatives



Scheme 1 Catalytically active cobalamin species

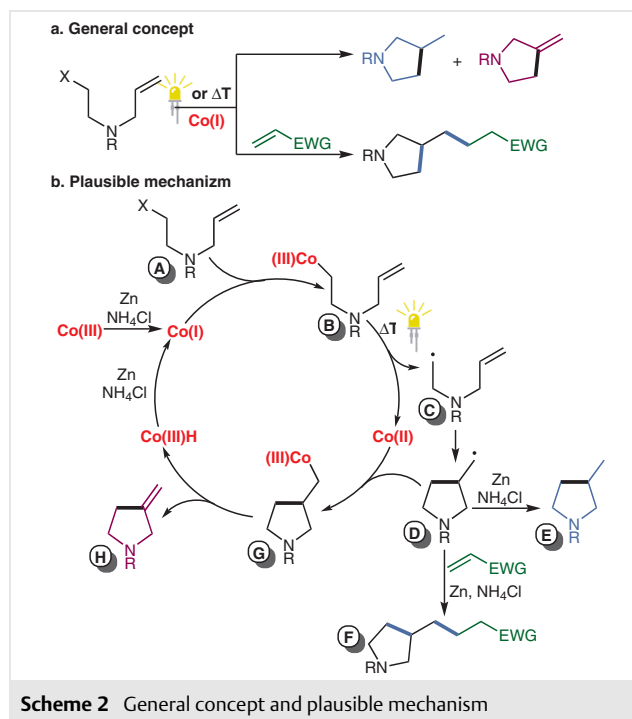
has been already developed¹⁰ among which cyclizations of specifically designed haloolefins occupy an important place.¹¹ In 1990, Hassner et al. reported the conventional intramolecular cyclization of (bromoalkyl)allyl amines to pyrrolidines induced by tributyltin hydride and AIBN as a radical initiator.¹² Later, transition-metal catalysis (Ru, Ti/Ni, Pd, Mn, Fe, etc.) was utilized for this purpose with cobalt

complexes also being efficient.¹³ Cobaloxime – considered as a model compound of vitamin B₁₂ – catalyzes Heck-type reactions.¹³ In particular, Carreira et al. developed intramolecular reaction of alkyl iodides to double bonds under blue light irradiation and applied it in the first total synthesis of daphmanidin alkaloids.¹⁴ More recently, cobalt-catalyzed directed arene C–H activation and 1,5-radical cyclization were merged into a single catalytic cycle to achieve dicarbofunctionalization of bromoalkenes.¹⁵ As a greener alternative for the synthesis of 3-methylpyrrolidine, the Stephenson group proposed photocatalytic hydrodebromination of unactivated alkyl and aryl halides.¹⁶ Despite recent advancement in the realm of the pyrrolidine ring formation, greener, selective, and high-yielding methods are still in high demand.

Recently, we have found that heptamethyl cobyrinate (**3**) catalyzes atom-transfer radical addition of organic halides to olefins.¹⁷ Based on the proposed mechanism for this transformation, we envisaged that vitamin B₁₂ (**1**) might be a suitable catalyst for constructing the pyrrolidine ring (Scheme 2a). Herein, we report vitamin B₁₂-catalyzed cyclization of bromoalkenes and tandem radical cyclization/Giese addition to electrophilic olefins furnishing substituted pyrrolidines and piperidines eliminating the need for toxic or expensive precious metal-based catalysts.

We presumed that the ‘supernucleophilic’ Co(I) form of vitamin B₁₂ would react with specifically designed bromoalkenes **A** forming alkylcobalamin **B** that upon light irradiation or heating would generate radical **C** and subsequently intermediate **D** (Scheme 2b). Radical **D** might follow different pathways, either could: 1) undergo reduction to give 3-methylpyrrolidine **E**, 2) recombine with Co(II) species to give **G** and after dehydrocobaltation generate 3-methylenepyrrolidine **H**, or 3) react with an electron-deficient olefin, if present, furnishing substituted pyrrolidine **F**. This concept holds a multitude of challenges with the selectivity being the major one.

Based on this mechanistic hypothesis, in the initial exploratory experiment, we tested vitamin B₁₂ in the cyclization of model bromoalkene *N*-(2-bromoethyl)-*N*-(prop-2-yn-1-yl)-*p*-toluenesulfonamide (**4**) (Table 1). Background experiments revealed that the cyclization only occurred if all reagents – vitamin B₁₂, zinc, and ammonium chloride – were present (see SI). With no external stimuli (light, heat) the reaction gave traces of 3-methylpyrrolidine **5a** (Table 1, entry 2), while heating the reaction mixture in dark at 50 °C for 18 hours selectively afforded this compound in 42% yield. In contrast, under light irradiation, the selectivity depended on the power of light (entries 6, 7) and color (entries 3–5) as alkyl cobalamins (an intermediate detected by MS, see SI, section 3: Mass spectrometric studies) absorb in the region 250–560 nm. With 3 W blue LED, the reaction selectively furnished product **5a** while with stronger, penetrating deeper, 10 W LED a mixture of compounds **5a/5b** were formed with pyrrolidine **5b** being the major product



(entry 7). Notably, the external stimuli changes the reaction pathway. This enabled us to optimize cyclizations leading either to product **5a** under irradiation with white light (LED tape) or to pyrrolidine **5b** when exposed to blue light (single LED, 10 W) (for details see SI).

Table 1 Optimization: Influence of Light^a

| Entry | Light | Time (h) | Conditions | Yield (%) ^b |
|----------------|-------------------|----------|------------|---------------------------------------|
| 1 ^c | White (LED tape) | 18 | A | 50 (5a) |
| 2 | None | 18 | A | 5 (5a) |
| 3 ^c | Green (LED tape) | 18 | A | 39 (5a) |
| 4 ^c | Purple (LED tape) | 18 | A | 44 (5a) |
| 5 ^c | Blue (LED tape) | 18 | A | 35 (5a) |
| 6 | Blue (3 W) | 18 | A | 43 (5a) |
| 7 | Blue (10 W) | 0.25 | A | 59 (5a:5b 1:1.5) ^d |
| 8 | Blue (10 W) | 0.33 | B | 69 (5a:5b 1:7) ^d |

^a Reaction conditions; A: alkyl bromide **4** (0.25 mmol, 1.0 equiv), vitamin B₁₂ (**1**, 1.5 μmol, 6.0 mol%), NH₄Cl (0.875 mmol, 3.5 equiv), Zn (1.5 mmol, 6.0 equiv), MeOH (c = 0.1 M), rt; B: alkyl bromide **4** (0.25 mmol, 1.0 equiv), vitamin B₁₂ (**1**, 3 μmol, 12.0 mol%), NH₄Cl (0.25 mmol, 1 equiv), Zn (1.5 mmol, 6.0 equiv), MeOH (c = 0.1 M), rt.

^b GC yield.

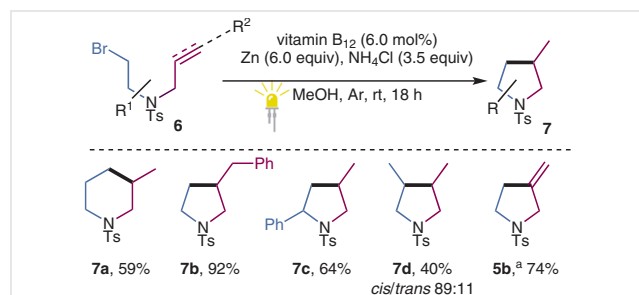
^c LED tape (for more details see SI), 18 h.

^d HPLC yield.

In the presence of vitamin B₁₂, the desired product **5a** was formed in 50% yield under white light irradiation for 18 h. The optimized conditions for the synthesis of pyrrolidine **5a** are as follows: Conditions A: vitamin B₁₂ (6.0 mol%), NH₄Cl (3.5 equiv), Zn (6.0 equiv), MeOH (*c* = 0.1 M of **4**), white LED tape, room temperature, 18 hours.

Optimization of the reaction exposed to strong blue light (single LED, 10 W) to selectively form pyrrolidine **5b** with the exocyclic double bond was more challenging. To this end, our effort was directed towards achieving both higher selectivity and yield of the reaction. Variation of the solvent, addition of acids, bases, or water had negligible effect on the reaction course (for details, see SI). Decreasing the amount of NH₄Cl to 1.0 equivalent increased the **5a/5b** ratio to 1:2. The strongest influence had the amount of cobalamin (**1**) used, with 12.0 mol% of vitamin B₁₂ the yield increased to 69% and the ratio **5a/5b** to 1:7. Conditions B: vitamin B₁₂ (12.0 mol%), NH₄Cl (1.0 equiv), Zn (6.0 equiv), MeOH (*c* = 0.1 M of **4**), blue LED (10 W), 20 minutes.

Under optimized conditions A, we tested structurally diverse haloolefins **6** (Scheme 3). Reactions irradiated with white LEDs enabled the synthesis of both pyrrolidine and piperidine derivatives **7** in good to excellent yields. Notably, substitution at the terminal position of the double bond as well as at the α -position to the bromide had beneficial influence on the reaction yield. In contrast, the use of secondary bromides, expectedly, led to product **7d** in diminished yield (40%).^{17,18}



Conditions B have several limitations and reactions often resulted in complex mixtures of products. Instead, using conditions A the same product – pyrrolidine **5b** – with the exocyclic double bond could be obtained from *N*-(2-bromoethyl)-*N*-(prop-2-yn-1-yl)-*p*-toluenesulfonamide (**4**) in high yield.

In the next step, we wondered if the presence of electron-deficient olefin would allow for a selective tandem reaction – the radical cyclization followed by the Giese addi-

tion – enabling difunctionalization of alkenyl halides (Scheme 2). Similar synthesis of pyrrolidines was reported by Kang and co-workers who utilized the Fe(CO)₅-phenanthroline system as a catalyst.¹⁹ Two-component reductive dicarbofunctionalization of alkenes via radical cyclization is also possible with Ni catalysis.²⁰ In this line, we have also shown that vitamin B₁₂ catalysis enables dicarbofunctionalization of electron-deficient alkenes.¹⁷ The cyclization proposed herein followed by the Giese addition would be the first example of dicarbofunctionalization of non-activated alkenes catalyzed by vitamin B₁₂. The reaction of substrate **4** with methyl acrylate under conventional heating (MeOH, 50 °C, 18 h) or in a microwave reactor (MeOH, 66 °C, 30 min) afforded product **8** in decent yield, 53% and 44%, respectively (Table 2, entries 1, 2). Irradiation of the reaction mixture for 18 hours with white light (LED tape) gave a similar result while the yield increased to 70% when stronger blue LED (10 W) was used (entries 3, 4). The undeniable advantage of using this light source is the short time of the reaction, just after 15 minutes, the yield reached maximum. Several polar solvents were tested with the aim to increase the yield, however, none was more efficient than MeOH presumably because of the solubility of vitamin B₁₂ in the reaction media (see SI).

Table 2 Optimization of the Reaction Conditions^a

| Entry | Conditions | Time | Yield (%) ^b of 8 |
|----------------|------------------|--------|------------------------------------|
| 1 ^c | 50 °C | 18 h | 53 |
| 2 ^c | microwave, 66 °C | 30 min | 44 |
| 3 ^c | white LED | 18 h | 53 |
| 4 ^d | blue LED | 15 min | 70 |

^a Reaction conditions: alkyl bromide **4** (0.25 mmol, 1.0 equiv), methyl acrylate (0.75 mmol, 3.0 equiv), vitamin B₁₂ (6.0 mol%), NH₄Cl (3.5 equiv), Zn (6.0 equiv), MeOH (*c* = 0.1 M), rt.

^b GC yield.

^c LED tape (for more details see SI), 18 h.

^d Single LED (10 W), 15 min.

Furthermore, we established 6.0 mol% of vitamin B₁₂ as the optimal catalyst loading. The ratio of zinc to NH₄Cl had negligible effect on the reaction outcome while the ratio of substrates influenced the selectivity most (Table 3). Even with 10 equivalents of methyl acrylate, pyrrolidines **5a** and **5b** were formed as the main by-products (Table 3, entry 2). In contrast, using an excess of alkyl bromide **4** improved the yield of product **8** up to 78% (entries 4–6).

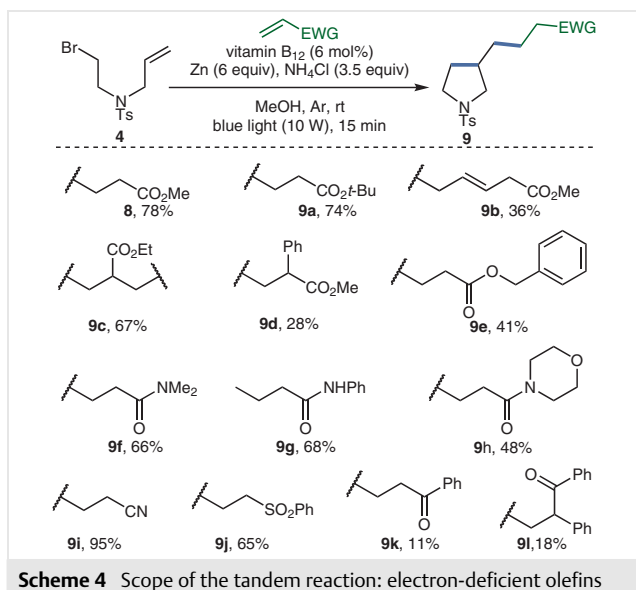
Table 3 Optimization the Ratio of Substrate **4** to Methyl Acrylate^a

| Entry | 4 (mmol) | Methyl acrylate (mmol) | Yield (%) ^b of 8 |
|----------|-----------------|------------------------|------------------------------------|
| 1 | 0.25 | 0.75 | 70 |
| 2 | 0.25 | 2.50 | 49 |
| 3 | 0.25 | 0.25 | 50 |
| 4 | 0.375 | 0.25 | 69 |
| 5 | 0.50 | 0.25 | 78 |
| 6 | 0.75 | 0.25 | 72 |

^a Reaction conditions: vitamin B₁₂ (1.6 μmol, 6.0 mol%), NH₄Cl (0.87 mmol, 3.5 equiv), Zn (1.5 mmol, 6.0 equiv), MeOH (c = 0.1 M of non-excess substrate), rt, single blue LED (10 W), 15 min.

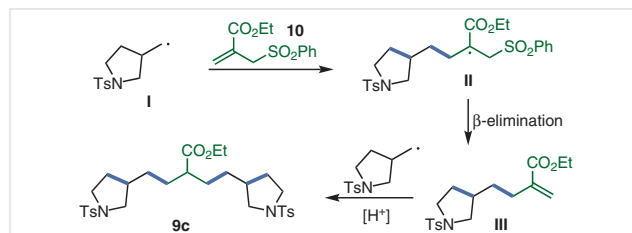
^b GC yield.

The use of iodide instead of bromide led to the loss of selectivity giving product **8** in 19% yield accompanied by a mixture of saturated and unsaturated pyrrolidine **5a** and **5b** (49%). Chloro and tosyl derivatives were almost unreactive under developed conditions. The substrate scope, with respect to the coupling partner, was then investigated (Scheme 4).

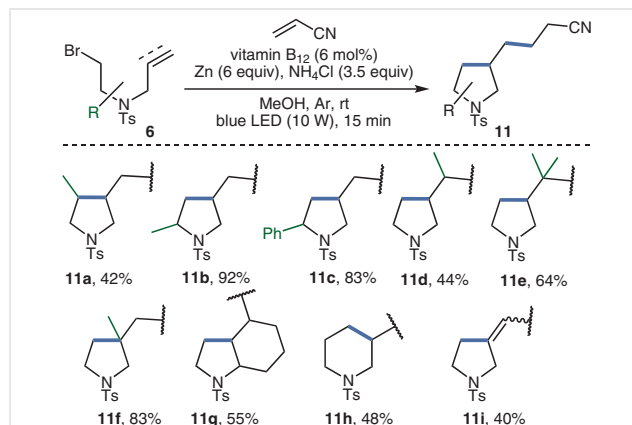


For the formation of esters **8**, **9a**, amides **9f–h**, nitrile **9i**, and sulfone **9j**, the reaction is highly efficient (48–95%) while keto products caused problems, mostly due to reduction of the carbonyl group. In the case of methyl 2,4-pentadienoate, only 1,6-addition is observed (→ **9b**, 36%). α,β -Substituted electrophilic olefins gave a mixture of products, only for α -phenyl-substituted substrate product **9d** was formed in 28% yield. For 4-iodobenzyl acrylate the desired product was not observed instead compound **9e** was isolated (41%) because of subsequent deiodination taking place. Reactions with ketones gave products **9k** and **9l** in low

yields (11–18%). The best result was obtained in the reaction with acrylonitrile, the desired product **9i** was formed in 95% yield. For ethyl 2-[(phenylsulfonyl)methyl]acrylate (**10**) the formation of disubstituted product **9c** was observed. A plausible mechanism involves addition of radical **I** to allyl sulfone **10** giving radical **II**, which after β -elimination generates intermediate **III** still being an electrophilic olefin (Scheme 5). This olefin reacts further with an excess of radical **I** to give product **9c** in 67% yield.

**Scheme 5** Formation of product **9c**: the proposed mechanism

Next, we tested if other bromoalkenes could be used in this transformation (Scheme 6). Secondary bromide and alkyl- and aryl-substituted bromoalkenes furnished products **11a** (42%) and **11b–f** (44–92%), respectively, in good to excellent yields. Moreover, the developed method is also suitable for the synthesis of bicyclic product **11g** (55%) and piperidine derivative **11h** (48%). *N*-(2-Bromoethyl)-*N*-propargyl-*p*-toluenesulfonamide enabled the synthesis of pyrrolidine **11i** with the exocyclic double bond.



The reaction proved to be easily scalable and on a bigger scale (1 mmol), only extension time was required (to 2 h) to achieve product **8** in 57% of yield.

In summary, vitamin B₁₂ catalyses intramolecular cyclization of bromoalkenes leading to substituted pyrrolidines and piperidines, while in the presence of an electrophilic olefin dicarbofunctionalization occurs. This demonstrate the versatility of vitamin B₁₂ catalysis, just by fine tuning of the reaction conditions different products from

the same substrate form with high selectivity. The presented methodology eliminates the need for toxic, expensive metals, thus it is potentially attractive for pharmaceutical industry.

All reagents and solvents used were supplied by commercial sources without further purification, unless otherwise specified. Bromoalkenes (see SI) **4**,²¹ **S1**,²² **S2**,²² **S4**,²³ **S5**,²⁴ **S6**,²⁴ **S7**,²⁵ **S8**,¹² and **S9**²⁶ were prepared according to the literature procedures. For the synthesis of **S3**, see the Supporting Information.

NMR spectra were recorded on Bruker 400 MHz, Bruker 500 MHz, and Varian 500 MHz spectrometers. Chemical shifts are reported in parts per million (δ) relative to the internal standard TMS (0 ppm) for CDCl_3 . The coupling constants, J , are reported in hertz (Hz). High-resolution mass spectra (HRMS) were recorded on a Waters SYNAPT G2-S HDMS instrument using electrospray ionization (ESI). Elemental analysis (C, H, N) were performed using a PerkinElmer 240 Elemental Analyzer. Melting points were recorded on a Marienfeld MPM-H2 melting point apparatus and are uncorrected (an average of three measurements). GC-MS analyses were performed using Shimadzu GCMS-QP2010 SE gas chromatograph with FID detector and Zebtron ZB 5MSi column. HPLC analyses were performed on reverse-phase (RP) Knauer HPLC with columns: Kromasil Eternity-5-C18, 250 mm V4.6 mm with a precolumn or Kromasil 100 C185 mm, 250 mm V4.6 mm; detection, UV/Vis. For column chromatography silica gel (200–300 mesh) was used.

Pyrrolidine Derivatives; General Procedure A

A glass reaction tube (inner diameter = 18 mm) equipped with a magnetic bar was charged with NH_4Cl (47 mg, 0.87 mmol, 3.5 equiv), vitamin B_{12} (21 mg, 0.016 mmol, 6.0 mol%), and activated Zn (98 mg, 1.5 mmol, 6.0 equiv), then MeOH (2.5 mL, HPLC grade) was added. The tube was sealed with a septum and the resulting mixture was degassed by purging the solution with argon for 20 min with simultaneous sonication in ultrasonic bath (the solution turned from red to dark green or brown). Subsequently, a bromoalkene (0.25 mmol) was added and the reaction vessel was placed in a photoreactor and irradiated with white LED (9.6 W/m) for 18 h. The reaction mixture was quenched with EtOAc, filtered through a cotton pad, and concentrated in vacuo. The crude product was purified using column chromatography (SiO_2 , gradient from 0 to 10% EtOAc in hexane).

Pyrrolidine Derivatives; General Procedure B

A glass reaction tube (inner diameter = 18 mm) equipped with a magnetic bar was charged with NH_4Cl (47 mg, 0.87 mmol, 3.5 equiv), vitamin B_{12} (21 mg, 0.016 mmol, 6.0 mol%), and activated Zn (98 mg, 1.5 mmol, 6.0 equiv), then MeOH (2.5 mL, HPLC grade) was added. The tube was sealed with a septum and the resulting mixture was degassed by purging the solution with argon for 20 min with simultaneous sonication in ultrasonic bath (the solution turned from red to dark green or brown). Subsequently, an electron-deficient olefin (0.25 mmol, 1.0 equiv) and bromoalkene (0.5 mmol, 2.0 equiv) were added and the reaction vessel was placed in a photoreactor and irradiated with blue LED (10 W) for 15–20 min. The reaction mixture was quenched with EtOAc, filtered through a cotton pad, and concentrated in vacuo. The crude product was purified using column chromatography (SiO_2 , gradient from 0 to 30% EtOAc in hexane).

3-Methyl-1-tosylpyrrolidine (**5a**)²⁷

Product was obtained according to General Procedure A from **4** as a rigid colorless oil; yield: 39 mg (64%).

^1H NMR (500 MHz, CDCl_3): δ = 7.64 (d, J = 8.3 Hz, 2 H), 7.25 (d, J = 7.4 Hz, 2 H), 3.35 (dd, J = 9.7, 7.1 Hz, 1 H), 3.27 (m, 1 H), 3.15 (m, 1 H), 2.68 (dd, J = 9.7, 7.8 Hz, 1 H), 2.36 (s, 3 H), 2.05 (m, 1 H), 1.78–1.87 (m, 1 H), 1.28 (m, 1 H), 0.84 (d, J = 6.7 Hz, 3 H).

^{13}C NMR (126 MHz, CDCl_3): δ = 143.1, 104.3, 129.5, 127.4, 55.0, 53.9, 40.5, 36.2, 21.5, 15.6, 12.8.

NMR spectra are consistent with the reported data.

3-Methylidene-1-tosylpyrrolidine (**5b**)²⁷

Product was obtained according to General Procedure A from **S5** as a rigid colorless oil; yield: 44 mg (74%).

^1H NMR (500 MHz, CDCl_3): δ = 7.82 (d, J = 8.3 Hz, 2 H), 7.44 (d, J = 8.0 Hz, 2 H), 5.02 (m, 2 H), 3.89 (s, 2 H), 3.40 (t, J = 7.1 Hz, 2 H), 2.58 (m, 2 H), 2.54 (s, 3 H).

^{13}C NMR (126 MHz, CDCl_3): δ = 144.1, 143.6, 102.9, 129.6, 127.8, 107.4, 51.9, 48.07, 31.7.

NMR spectra are consistent with the reported data.

3-Methyl-1-tosylpiperidine (**7a**)²⁸

Product was obtained according to General Procedure A from **S8** as white crystals; yield: 39 mg (59%).

^1H NMR (400 MHz, CDCl_3): δ = 7.66 (d, J = 8.3 Hz, 2 H), 7.34 (d, J = 8.0 Hz, 2 H), 3.65 (m, 2 H), 2.45 (s, 3 H), 2.24 (td, J = 11.4, 2.9 Hz, 1 H), 1.91 (t, J = 10.7 Hz, 1 H), 1.84–1.49 (m, 4 H), 0.89 (d, J = 6.5 Hz, 3 H), 0.88–0.79 (m, 1 H).

NMR spectra are consistent with the reported data.

3-Benzyl-1-tosylpyrrolidine (**7b**)¹⁹

Product was obtained according to General Procedure A from **S10** as a colorless oil; yield: 22 mg (92%).

^1H NMR (500 MHz, CDCl_3): δ = 7.70 (d, J = 8.2 Hz, 2 H), 7.31 (d, J = 7.9 Hz, 2 H), 7.25 (d, J = 8.2 Hz, 2 H), 7.19 (t, J = 7.3 Hz, 1 H), 7.05 (d, J = 7.0 Hz, 2 H), 3.44–3.31 (m, 2 H), 3.19 (dt, J = 9.8, 7.9 Hz, 1 H), 2.92 (dd, J = 9.8, 7.5 Hz, 1 H), 2.58–2.51 (m, 2 H), 2.44 (s, 3 H), 2.34 (dq, J = 15.1, 7.5 Hz, 1 H), 1.87 (ddd, J = 19.1, 7.1, 4.4 Hz, 1 H), 1.52–1.44 (m, 1 H).

^{13}C NMR (126 MHz, CDCl_3): δ = 143.3, 109.7, 104.1, 129.6, 128.6, 128.5, 127.5, 126.3, 52.8, 47.4, 40.4, 39.1, 31.1, 21.5.

NMR spectra are consistent with the reported data.

4-Methyl-2-phenyl-1-tosylpyrrolidine (**7c**)²⁹

Product was obtained according to General Procedure A from **S3** as white crystals; yield: 50 mg (64%); dr = 1:3 (I/II).

^1H NMR (500 MHz, CDCl_3): δ = 7.67 (d, J = 8.2 Hz, 0.5 H, 2 H_I), 7.60 (d, J = 8.2 Hz, 1.5 H, 2 H_{II}), 7.33–7.18 (m, 7 H, 7 H_I + 7 H_{II}), 4.86–4.84 (m, 0.25 H, 1 H_I), 4.66–4.63 (m, 0.75 H, 1 H_{II}), 3.84 (dd, J = 11.1, 7.3 Hz, 0.75 H, 1 H_I), 3.73 (dd, J = 9.3, 7.0 Hz, 0.25 H, 1 H_I), 3.08 (t, J = 10.8 Hz, 0.75 H, 1 H_{II}), 2.88 (t, J = 9.2 Hz, 0.25 H, 1 H_I), 2.42 (s, 0.75 H, 3 H_I), 2.40 (s, 2.25 H, 3 H_{II}), 2.41–2.31 (m, 1 H_I , 1 H_I + 1 H_{II}), 1.91–1.79 (m, 1 H_I , 1 H_I + 1 H_{II}), 1.63–1.57 (m, 0.25 H, 1 H_I), 1.53–1.43 (m, 0.75 H, 1 H_{II}), 0.95 (d, J = 6.5 Hz, 2.25 H, 3 H_{II}), 0.88 (d, J = 6.6 Hz, 0.75 H, 3 H_I).

^{13}C NMR (126 MHz, CDCl_3): δ (isomer I) = 16.8, 21.5, 33.4, 43.6, 56.7, 64.6, 126.1, 126.3, 126.9, 127.1, 127.4, 127.5, 128.2, 128.3, 129.5, 105.7, 143.1, 143.3; δ (isomer II) = 16.4, 21.5, 31.3, 43.5, 55.8, 63.1,

126.1, 126.3, 126.9, 127.1, 127.4, 127.5, 128.2, 128.3, 129.46, 105.0, 143.0, 143.2.

NMR spectra are consistent with the reported data.

cis/trans-3,4-Dimethyl-1-tosylpyrrolidine (7d)¹⁹

Product was obtained according to General Procedure A from **S1** as a rigid colorless oil; yield: 25 mg (40%).

¹H NMR (500 MHz, CDCl₃): δ (cis/trans = 9:1) = 7.71 (d, *J* = 8.2 Hz, 2 H, 2 H_I + 2 H_{II}), 7.31 (d, *J* = 8.0 Hz, 2 H, 2 H_I + 2 H_{II}), 3.51 (dd, *J* = 9.8, 6.9 Hz, 0.20 H, 2 H_I), 3.38 (dd, *J* = 9.6, 6.6 Hz, 1.80 H, 2 H_{II}), 2.95 (dd, *J* = 9.7, 5.6 Hz, 1.80 H, 2 H_{II}), 2.79 (t, *J* = 9.4 Hz, 0.20 H, 2 H_I), 2.43 (s, 3.0 H, 3 H_I + 3 H_{II}), 2.12 (dd, *J* = 12.7, 6.4 Hz, 2 H, 2 H_I + 2 H_{II}), 0.91 (d, *J* = 6.1 Hz, 0.6 H, 6 H_I), 0.76 (d, *J* = 6.6 Hz, 5.4 H, 6 H_{II}).

¹³C NMR (126 MHz, CDCl₃): δ (cis/trans = 9:1) = 143.1, 104.3, 129.5, 127.4, 55.0, 53.9, 40.5, 36.2, 21.5, 15.6, 12.8.

NMR spectra are consistent with the reported data.

Methyl 4-(1-Tosylpyrrolidin-3-yl)butanoate (8)³⁰

Product was obtained according to General Procedure B as a white solid; yield: 64 mg (78%).

¹H NMR (400 MHz, CDCl₃): δ = 7.70 (d, *J* = 8.2 Hz, 2 H), 7.31 (d, *J* = 8.0 Hz, 2 H), 3.65 (s, 3 H), 3.42 (dd, *J* = 9.7, 7.4 Hz, 1 H), 3.36–3.30 (m, 1 H), 3.22–3.15 (m, 1 H), 2.77 (dd, *J* = 9.7, 8.0 Hz, 1 H), 2.43 (s, 3 H), 2.24 (t, *J* = 7.4 Hz, 2 H), 2.03–1.89 (m, 2 H), 1.59–1.48 (m, 2 H), 1.37 (dd, *J* = 12.0, 8.5 Hz, 1 H), 1.25 (dd, *J* = 15.4, 7.7 Hz, 2 H).

¹³C NMR (100 MHz, CDCl₃): δ = 173.8, 143.4, 134.1, 129.74, 127.66, 53.3, 51.7, 47.6, 38.7, 34.0, 32.7, 31.5, 23.5, 21.6.

NMR spectra are consistent with the reported data.

tert-Butyl 4-(1-Tosylpyrrolidin-3-yl)butanoate (9a)

Product was obtained according to General Procedure B as a yellowish oil; yield: 67 mg (74%).

¹H NMR (400 MHz, CDCl₃): δ = 7.70 (d, *J* = 8.2 Hz, 2 H), 7.31 (d, *J* = 8.0 Hz, 2 H), 3.42 (dd, *J* = 9.7, 7.3 Hz, 1 H), 3.36–3.29 (m, 1 H), 3.22–3.14 (m, 1 H), 2.77 (dd, *J* = 9.7, 8.0 Hz, 1 H), 2.42 (s, 3 H), 2.13 (t, *J* = 7.4 Hz, 2 H), 2.02–1.88 (m, 2 H), 1.54–1.44 (m, 2 H), 1.42 (s, 9 H), 1.39–1.33 (m, 1 H), 1.29–1.20 (m, 2 H).

¹³C NMR (100 MHz, CDCl₃): δ = 172.8, 143.4, 134.1, 129.7, 127.6, 80.4, 53.3, 47.7, 38.8, 35.5, 32.6, 31.5, 28.2, 23.7, 21.6.

HRMS (ESI): *m/z* [M + Na]⁺ calcd for C₁₉H₂₉NO₄SNa: 390.1714; found: 390.1715.

Anal. Calcd for C₁₉H₂₉NO₄S: C, 62.10; H, 7.95; N, 3.81. Found: C, 62.26; H, 7.98; N, 3.65.

(E)-Methyl 6-(1-Tosylpyrrolidin-3-yl)hex-3-enoate (9b)

Product was obtained according to General Procedure B as a colorless oil; yield: 32 mg (36%).

¹H NMR (400 MHz, CDCl₃): δ = 7.70 (d, *J* = 8.2 Hz, 2 H), 7.31 (d, *J* = 8.1 Hz, 2 H), 5.54–5.40 (m, 2 H), 3.67 (s, *J* = 3.1 Hz, 3 H), 3.42 (dd, *J* = 9.6, 7.4 Hz, 1 H), 3.35–3.29 (m, 1 H), 3.21–3.14 (m, 1 H), 3.05–2.98 (m, 2 H), 2.80–2.73 (m, 1 H), 2.43 (s, 3 H), 2.03–1.88 (m, 4 H), 1.38–1.28 (m, 3 H).

¹³C NMR (100 MHz, CDCl₃): δ = 172.5, 143.5, 134.2, 133.8, 129.8, 127.7, 122.5, 53.3, 52.0, 47.7, 38.5, 38.0, 32.7, 31.6, 31.1, 21.7.

HRMS (ESI): *m/z* [M + Na]⁺ calcd for C₁₈H₂₅NO₄SNa: 374.1402; found: 374.1392.

Anal. Calcd for C₁₈H₂₅NO₄S: C, 61.51; H, 7.17; N, 3.99. Found: C, 61.35; H, 7.01; N, 3.83.

Ethyl 4-(1-Tosylpyrrolidin-3-yl)-2-[2-(1-tosylpyrrolidin-3-yl)-ethyl]butanoate (9c)

Product was obtained according to General Procedure B as a yellowish oil; yield: 50 mg (67%).

¹H NMR (400 MHz, CDCl₃): δ = 7.69 (d, *J* = 8.2 Hz, 4 H), 7.31 (d, *J* = 8.1 Hz, 4 H), 4.12–4.04 (m, 2 H), 3.42–3.29 (m, 4 H), 3.19–3.12 (m, 2 H), 2.78–2.68 (m, 2 H), 2.42 (s, 6 H), 2.19–2.09 (m, 1 H), 2.00–1.85 (m, 4 H), 1.56–1.43 (m, 2 H), 1.39–1.24 (m, 5 H), 1.23–1.15 (m, 6 H).

¹³C NMR (100 MHz, CDCl₃): δ = 143.6, 134.2, 129.9, 127.8, 60.6, 53.3, 47.8, 39.0, 31.7, 31.6, 31.0, 21.8, 14.6.

HRMS (ESI): *m/z* [M + Na]⁺ calcd for C₃₀H₄₂N₂O₆S₂Na: 613.2382; found: 613.2399.

Anal. Calcd for C₃₀H₄₂N₂O₆S₂: C, 60.99; H, 7.17; N, 4.74. Found: C, 60.90; H, 7.19; N, 4.77.

Methyl 2-Phenyl-4-(1-tosylpyrrolidin-3-yl)butanoate (9d)

Product was obtained according to General Procedure B as a colorless oil; yield: 32 mg (28%).

¹H NMR (500 MHz, CDCl₃): δ = 7.67 (dd, *J* = 8.2, 3.0 Hz, 2 H), 7.32–7.27 (m, 4 H), 7.25–7.20 (m, 3 H), 3.62 (d, *J* = 2.3 Hz, 3 H), 3.43–3.36 (m, 2 H), 3.33–3.26 (m, 1 H), 3.17–3.11 (m, 1 H), 2.72 (ddd, *J* = 16.0, 9.7, 8.2 Hz, 1 H), 2.42 (s, 3 H), 2.00–1.86 (m, 3 H), 1.73–1.62 (m, 1 H), 1.37–1.28 (m, 1 H), 1.24–1.11 (m, 2 H).

¹³C NMR (126 MHz, CDCl₃): δ = 174.2, 143.4, 138.8, 138.7, 134.1, 129.7, 129.7, 128.9, 128.8, 127.9, 127.9, 127.6, 127.5, 53.2, 53.2, 52.1, 52.1, 51.6, 47.6, 47.6, 38.8, 32.1, 32.0, 31.4, 31.4, 31.2, 31.0, 21.6.

HRMS (ESI): *m/z* [M + H]⁺ calcd for C₂₂H₂₈NO₄SNa: 402.1739; found: 402.1738.

Anal. Calcd for C₂₂H₂₇NO₄S: C, 65.80; H, 6.80; N, 3.50. Found: C, 65.63; H, 6.61; N, 3.36.

Benzyl 4-(1-Tosylpyrrolidin-3-yl)butanoate (9e)

Product was obtained according to General Procedure B as a yellowish oil; yield: 40 mg (41%).

¹H NMR (400 MHz, CDCl₃): δ = 7.70 (d, *J* = 8.2 Hz, 2 H), 7.37–7.29 (m, 7 H), 5.09 (s, 2 H), 3.41 (dd, *J* = 9.7, 7.3 Hz, 1 H), 3.35–3.29 (m, 1 H), 3.21–3.14 (m, 1 H), 2.76 (dd, *J* = 9.7, 8.0 Hz, 1 H), 2.42 (s, 3 H), 2.29 (t, *J* = 7.4 Hz, 2 H), 2.02–1.87 (m, 2 H), 1.61–1.51 (m, 2 H), 1.38–1.30 (m, 1 H), 1.27–1.21 (m, 2 H).

¹³C NMR (100 MHz, CDCl₃): δ = 173.1, 143.4, 136.1, 134.1, 129.7, 128.7, 128.4, 128.3, 127.6, 66.3, 53.2, 47.6, 38.7, 34.2, 32.6, 31.4, 23.5, 21.6.

HRMS (ESI): *m/z* [M + Na]⁺ calcd for C₂₂H₂₇NO₄SNa: 424.1558; found: 424.1547.

Anal. Calcd for C₂₂H₂₇NO₄S: C, 65.81; H, 6.78; N, 3.49. Found: C, 65.73; H, 6.67; N, 3.63.

N,N-Dimethyl-4-(1-tosylpyrrolidin-3-yl)butanamide (9f)

Product was obtained according to General Procedure B as a colorless oil; yield: 58 mg (66%).

^1H NMR (500 MHz, CDCl_3): δ = 7.68 (d, J = 8.2 Hz, 2 H), 7.30 (d, J = 8.0 Hz, 2 H), 3.41 (dd, J = 9.6, 7.4 Hz, 1 H), 3.35–3.29 (m, 1 H), 3.19–3.13 (m, 1 H), 2.93 (s, 6 H), 2.78–2.74 (m, 1 H), 2.41 (s, 3 H), 2.23 (t, J = 7.4 Hz, 2 H), 2.01–1.97 (m, 1 H), 1.95–1.89 (m, 1 H), 1.61–1.48 (m, 2 H), 1.40–1.33 (m, 1 H), 1.30–1.24 (m, 2 H).

^{13}C NMR (126 MHz, CDCl_3): δ = 172.6, 143.4, 134.1, 129.7, 127.6, 53.3, 47.7, 38.9, 33.1, 33.0, 31.5, 23.6, 21.6.

HRMS (ESI): m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{17}\text{H}_{27}\text{N}_2\text{O}_3\text{S}$: 339.1742; found: 339.1743.

Anal. Calcd for $\text{C}_{17}\text{H}_{26}\text{N}_2\text{O}_3\text{S} + 0.2\text{H}_2\text{O}$: C, 59.69; H, 7.78; N, 8.19. Found: C, 59.75; H, 7.73; N, 8.12.

N-Phenyl-4-(1-tosylpyrrolidin-3-yl)butanamide (9g)

Product was obtained according to General Procedure B as a white solid; yield: 66 mg (68%); mp 96 °C.

^1H NMR (400 MHz, CDCl_3): δ = 7.69 (d, J = 8.2 Hz, 2 H), 7.50 (d, J = 7.9 Hz, 2 H), 7.42 (s, 1 H), 7.32–7.27 (m, 4 H), 7.08 (t, J = 7.3 Hz, 1 H), 3.44–3.39 (m, 1 H), 3.35–3.30 (m, 1 H), 3.20–3.13 (m, 1 H), 2.78 (d, J = 1.2 Hz, 1 H), 2.42 (s, 3 H), 2.29 (t, J = 7.3 Hz, 2 H), 2.05–1.88 (m, 2 H), 1.71–1.57 (m, 2 H), 1.40–1.28 (m, 3 H).

^{13}C NMR (100 MHz, CDCl_3): δ = 171.0, 143.6, 138.1, 133.9, 129.8, 129.1, 127.6, 124.3, 119.9, 53.3, 47.7, 38.8, 37.4, 32.7, 31.4, 24.1, 21.6.

HRMS (ESI): m/z $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{21}\text{H}_{26}\text{N}_2\text{O}_3\text{SNa}$: 409.1562; found: 409.1552.

Anal. Calcd for $\text{C}_{21}\text{H}_{26}\text{N}_2\text{O}_3\text{S}$: C, 65.26; H, 6.78; N, 7.25. Found: C, 65.09; H, 6.66; N, 7.19.

1-Morpholino-4-(1-tosylpyrrolidin-3-yl)butan-1-one (9h)

Product was obtained according to General Procedure B as a yellowish solid; yield: 52 mg (48%); mp 84 °C.

^1H NMR (400 MHz, CDCl_3): δ = 7.69 (d, J = 8.2 Hz, 2 H), 7.31 (d, J = 8.0 Hz, 2 H), 3.66–3.63 (m, 4 H), 3.60–3.57 (m, 2 H), 3.44–3.39 (m, 3 H), 3.34 (ddd, J = 9.7, 8.4, 3.5 Hz, 1 H), 3.20–3.13 (m, 1 H), 2.78 (dd, J = 9.7, 8.1 Hz, 1 H), 2.43 (s, 3 H), 2.24 (t, J = 7.4 Hz, 2 H), 2.06–1.89 (m, 2 H), 1.62–1.50 (m, 2 H), 1.43–1.35 (m, 1 H), 1.33–1.26 (m, 2 H).

^{13}C NMR (100 MHz, CDCl_3): δ = 171.2, 143.4, 134.1, 129.7, 127.7, 67.0, 66.7, 53.3, 47.7, 46.0, 42.0, 38.9, 33.0, 32.9, 31.5, 23.6, 21.6.

HRMS (ESI): m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{19}\text{H}_{29}\text{N}_2\text{O}_4\text{S}$: 381.1848; found: 381.1848.

Anal. Calcd for $\text{C}_{19}\text{H}_{28}\text{N}_2\text{O}_4\text{S}$: C, 59.98; H, 7.42; N, 7.36. Found: C, 60.01; H, 7.24; N, 7.28.

4-(1-Tosylpyrrolidin-3-yl)butanenitrile (9i)

Product was obtained according to General Procedure B as a yellowish oil; yield: 69 mg (95%); mp 67 °C.

^1H NMR (500 MHz, CDCl_3): δ = 7.64 (d, J = 8.2 Hz, 2 H), 7.26 (d, J = 8.0 Hz, 2 H), 3.37 (dd, J = 9.7, 7.3 Hz, 1 H), 3.28 (ddd, J = 9.8, 8.4, 3.7 Hz, 1 H), 3.14 (ddd, J = 9.8, 8.5, 7.3 Hz, 1 H), 2.72 (dd, J = 9.7, 8.0 Hz, 1 H), 2.37 (s, 3 H), 2.27–2.18 (m, 2 H), 1.99–1.92 (m, J = 15.6 Hz, 1 H), 1.92–1.85 (m, 1 H), 1.57–1.48 (m, 2 H), 1.38–1.28 (m, 3 H).

^{13}C NMR (100 MHz, CDCl_3): δ = 143.5, 103.7, 129.7, 127.5, 119.1, 52.9, 47.3, 38.1, 32.0, 31.2, 23.9, 21.5, 17.2.

HRMS (ESI): m/z $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{15}\text{H}_{20}\text{N}_2\text{O}_2\text{SNa}$: 315.1143; found: 315.1134.

Anal. Calcd for $\text{C}_{15}\text{H}_{20}\text{N}_2\text{O}_2\text{S}$: C, 61.62; H, 6.89; N, 9.58. Found: C, 61.63; H, 6.78; N, 9.33.

3-[3-(Phenylsulfonyl)propyl]-1-tosylpyrrolidine (9j)

Product was obtained according to General Procedure B as a yellowish oil; yield: 66 mg (65%).

^1H NMR (500 MHz, CDCl_3): δ = 7.81 (d, J = 7.2 Hz, 2 H), 7.64–7.58 (m, 3 H), 7.54–7.47 (m, 2 H), 7.25 (d, J = 7.9 Hz, 2 H), 3.33–3.28 (m, 1 H), 3.27–3.22 (m, 1 H), 3.13–3.07 (m, 1 H), 2.93 (t, J = 7.8 Hz, 2 H), 2.70–2.65 (m, 1 H), 2.36 (s, 3 H), 1.93–1.80 (m, 2 H), 1.65–1.55 (m, 2 H), 1.32–1.21 (m, 3 H).

^{13}C NMR (126 MHz, CDCl_3): δ = 143.6, 139.2, 134.0, 129.8, 129.5, 128.1, 127.6, 56.2, 53.0, 47.5, 38.5, 31.8, 31.3, 21.7, 21.4.

HRMS (ESI): m/z $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{20}\text{H}_{25}\text{NO}_4\text{S}_2\text{Na}$: 430.1123; found: 430.1117.

Anal. Calcd for $\text{C}_{20}\text{H}_{25}\text{NO}_4\text{S}_2 + 0.5\text{H}_2\text{O}$: C, 57.30; H, 5.95; N, 3.30. Found: C, 57.28; H, 5.95; N, 3.25.

1-Phenyl-4-(1-tosylpyrrolidin-3-yl)butan-1-one (9k)¹⁹

Product was obtained according to General Procedure B as a white solid; yield: 10 mg (11%); mp 80 °C.

^1H NMR (400 MHz, CDCl_3): δ = 7.85 (d, J = 7.2 Hz, 2 H), 7.64 (d, J = 8.2 Hz, 2 H), 7.52–7.46 (m, 1 H), 7.41–7.36 (m, 2 H), 7.24 (d, J = 8.0 Hz, 2 H), 3.41–3.35 (m, 1 H), 3.31–3.25 (m, 1 H), 3.16–3.09 (m, 1 H), 2.84 (t, J = 7.1 Hz, 2 H), 2.77–2.71 (m, 1 H), 2.35 (s, 3 H), 2.03–1.93 (m, 1 H), 1.92–1.84 (m, 1 H), 1.67–1.53 (m, 2 H), 1.38–1.30 (m, 1 H), 1.29–1.20 (m, 2 H).

^{13}C NMR (100 MHz, CDCl_3): δ = 199.9, 143.4, 137.1, 134.2, 133.2, 129.8, 128.7, 128.1, 127.7, 53.3, 47.7, 39.0, 38.4, 32.9, 31.5, 22.7, 21.7.

NMR spectra are consistent with the reported data.

1,2-Diphenyl-4-(1-tosylpyrrolidin-3-yl)butan-1-one (9l)

Product was obtained according to General Procedure B as a white solid; yield: 22 mg (18%); mp 129 °C.

^1H NMR (400 MHz, CDCl_3): δ = 7.83 (d, J = 8.2 Hz, 2 H), 7.61 (dd, J = 8.2, 5.2 Hz, 2 H), 7.42–7.37 (m, 1 H), 7.35–7.25 (m, 2 H), 7.24–7.12 (m, 7 H), 4.35 (td, J = 7.3, 2.0 Hz, 1 H), 3.37–3.19 (m, 2 H), 3.12–3.04 (m, 1 H), 2.72–2.63 (m, 1 H), 2.34 (s, 3 H), 2.10–1.77 (m, 3 H), 1.74–1.57 (m, 1 H), 1.34–1.05 (m, 3 H).

^{13}C NMR (100 MHz, CDCl_3): δ = 199.6, 143.4, 139.4, 136.8, 134.1, 133.1, 129.7, 129.2, 129.1, 128.8, 128.7, 128.2, 128.2, 127.7, 127.3, 53.9, 53.8, 53.3, 47.7, 39.0, 32.7, 32.5, 31.4, 31.2, 21.6.

HRMS (ESI): m/z $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{27}\text{H}_{29}\text{NO}_3\text{SNa}$: 470.1766; found: 470.1758.

Anal. Calcd for $\text{C}_{27}\text{H}_{29}\text{NO}_3\text{S} + 0.3\text{H}_2\text{O}$: C, 71.59; H, 6.59; N, 3.09. Found: C, 71.21; H, 6.76; N, 2.82.

4-(5-Methyl-1-tosylpyrrolidin-3-yl)butanenitrile (11a)

Product was obtained according to General Procedure B from **S1** as a colorless oil; yield: 43 mg (42%).

^1H NMR (500 MHz, CDCl_3): δ = 7.64 (d, J = 8.2 Hz, 2 H), 7.26 (d, J = 7.9 Hz, 2 H), 3.31 (td, J = 9.7, 6.8 Hz, 2 H), 2.97 (dd, J = 9.9, 3.6 Hz, 1 H), 2.90–2.82 (m, 1 H), 2.37 (s, 3 H), 2.27–2.19 (m, 2 H), 2.14–2.10 (m, 1 H), 1.95–1.91 (m, 1 H), 1.52–1.46 (m, 2 H), 1.40–1.32 (m, 1 H), 1.20–1.12 (m, 1 H), 0.65 (d, J = 7.1 Hz, 3 H).

^{13}C NMR (125 MHz, CDCl_3): δ = 143.4, 104.0, 129.6, 127.4, 119.2, 54.7, 50.7, 41.3, 35.1, 26.8, 23.9, 21.5, 17.3, 10.0.

HRMS (ESI): m/z $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{16}\text{H}_{22}\text{N}_2\text{O}_2\text{SNa}$: 329.1300; found: 329.1295.

Anal. Calcd for $C_{16}H_{22}N_2O_2S$: C, 62.72; H, 7.24; N, 9.19. Found: C, 62.56; H, 7.24; N, 9.40.

4-(5-Methyl-1-tosylpyrrolidin-3-yl)butanenitrile (11b)

Product was obtained according to General Procedure B from **S2** as a colorless oil; yield: 71 mg (92%). Mixture of diastereoisomers; *dr* = 1:3.3.

1H NMR (400 MHz, $CDCl_3$): δ = 7.65 (d, *J* = 8.2 Hz, 2 H, 2 H_{II}), 7.26 (d, *J* = 8.0 Hz, 2 H, 2 H_I + 2 H_{II}), 3.72 (ddd, *J* = 8.5, 6.5, 2.3 Hz, 0.3 H, 1 H_I), 3.58–3.46 (m, 1.70 H, 1 H_I + 2 H_{II}), 2.89 (dd, *J* = 11.2, 9.8 Hz, 0.70 H, 1 H_{II}), 2.58 (t, *J* = 9.3 Hz, 0.3 H, 1 H_I), 2.38 (s, 3 H, 3 H_I + 3 H_{II}), 2.24–2.18 (m, 2 H, 2 H_I + 2 H_{II}), 2.08–2.02 (m, 0.70 H, 1 H_{II}), 1.59–1.07 (m, 9.30 H, 10 H_I + 9 H_{II}).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 143.3, 143.3, 105.2, 104.4, 129.6, 129.0, 127.4, 127.3, 119.1, 56.7, 55.6, 54.1, 53.9, 41.0, 39.2, 37.3, 36.2, 31.6, 31.5, 23.9, 23.9, 23.3, 22.6, 21.4, 17.2, 17.1.

HRMS (ESI): *m/z* [$M + Na$]⁺ calcd for $C_{16}H_{22}N_2O_2SNa$: 329.1300; found: 329.1290.

Anal. Calcd for $C_{16}H_{22}N_2O_2S$: C, 62.72; H, 7.24; N, 9.14. Found: C, 62.76; H, 7.09; N, 9.21.

4-(5-Phenyl-1-tosylpyrrolidin-3-yl)butanenitrile (11c)

Product was obtained according to General Procedure B from **S3** as a colorless oil; yield: 92 mg (83%). Mixture of diastereomers; *dr* = 1:2.3 (I:II).

1H NMR (500 MHz, $CDCl_3$): δ = 7.64 (d, *J* = 8.2 Hz, 0.5 H, 2 H_I), 7.55 (d, *J* = 8.2 Hz, 1.5 H, 2 H_{II}), 7.29–7.17 (m, 7 H, 7 H_I + 7 H_{II}), 4.83 (dd, *J* = 8.4, 2.1 Hz, 0.25 H, 1 H_I), 4.62 (dd, *J* = 9.4, 7.2 Hz, 0.75 H, 1 H_{II}), 3.84 (dd, *J* = 11.0, 7.3 Hz, 0.75 H, 1 H_{II}), 3.73 (dd, *J* = 9.4, 7.0 Hz, 0.25 H, 1 H_I), 3.09 (t, *J* = 10.7 Hz, 0.75 H, 1 H_{II}), 2.89 (t, *J* = 9.3 Hz, 0.25 H, 1 H_I), 2.40–2.35 (m, 4 H, 4 H_I + 4 H_{II}), 2.25–2.20 (m, 2 H, 2 H_I + 2 H_{II}), 1.88 (ddd, *J* = 12.2, 5.9, 2.1 Hz, 0.25 H, 1 H_I), 1.80–1.69 (m, 0.75 H, 1 H_{II}), 1.6–1.24 (m, 6 H, 6 H_I + 6 H_{II}).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 143.5, 143.3, 142.9, 142.5, 135.5, 134.7, 129.6, 129.5, 128.4, 128.3, 127.5, 127.4, 127.2, 127.1, 126.3, 125.9, 119.1, 64.2, 62.8, 60.3, 54.9, 54.0, 43.5, 41.4, 38.0, 36.2, 31.5, 31.3, 23.9, 21.5, 21.4, 17.2, 17.1.

HRMS (ESI): *m/z* [$M + Na$]⁺ calcd for $C_{21}H_{24}N_2O_2SNa$: 391.1456; found: 391.1443.

Anal. Calcd for $C_{21}H_{24}N_2O_2S$: C, 68.45; H, 6.57; N, 7.60; S, 8.70. Found: C, 68.22; H, 6.77; N, 7.54; S, 8.83.

4-(1-Tosylpyrrolidin-3-yl)pentanenitrile (11d)

Product was obtained according to General Procedure B from **S4** as a colorless oil; yield: 34 mg (44%).

1H NMR (500 MHz, $CDCl_3$): δ = 7.71–7.55 (m, 2 H), 7.34–7.22 (m, 2 H), 3.40 (dt, *J* = 9.2, 7.0 Hz, 1 H), 3.31 (tt, *J* = 11.3, 2.4 Hz, 1 H), 3.12 (qd, *J* = 9.9, 6.9 Hz, 1 H), 2.79–2.64 (m, 1 H), 2.37 (s, 3 H), 2.30 (dddd, *J* = 16.9, 7.5, 5.3, 0.9 Hz, 1 H), 2.26–2.16 (m, 1 H), 1.88 (tdd, *J* = 10.9, 7.0, 2.2 Hz, 1 H), 1.79 (dt, *J* = 12.8, 8.8 Hz, 1 H), 1.73–1.59 (m, 1 H), 1.41–1.26 (m, 3 H), 0.81 (dd, *J* = 6.5, 2.7 Hz, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 143.5, 103.71, 103.66, 129.7, 127.5, 119.32, 119.27, 118.6, 51.54, 51.52, 47.8, 47.7, 44.33, 44.27, 35.6, 35.4, 30.6, 30.3, 29.7, 29.3, 24.3, 21.5, 16.8, 16.6, 16.3, 14.8, 14.7.

HRMS (ESI): *m/z* [$M + H$]⁺ calcd for $C_{16}H_{23}N_2O_2S$: 307.1480; found: 307.1462.

Anal. Calcd for $C_{16}H_{23}N_2O_2S$: C, 62.72; H, 7.24; N, 9.14; S, 10.46. Found: C, 62.54; H, 7.20; N, 9.29; S, 10.43.

4-Methyl-4-(1-tosylpyrrolidin-3-yl)pentanenitrile (11e)

Product was obtained according to General Procedure B from **S5** as a colorless oil; yield: 52 mg (64%).

1H NMR (500 MHz, $CDCl_3$): δ = 7.64 (d, *J* = 8.2 Hz, 2 H), 7.27 (d, *J* = 8.0 Hz, 2 H), 3.41–3.29 (m, 1 H), 3.28–3.11 (m, 1 H), 3.03 (td, *J* = 9.9, 6.7 Hz, 1 H), 2.88 (t, *J* = 9.8 Hz, 1 H), 2.37 (s, 3 H), 2.20–2.10 (m, 2 H), 1.90–1.79 (m, 1 H), 1.74–1.65 (m, 1 H), 1.55–1.43 (m, 3 H), 0.75 (d, *J* = 2.4 Hz, 6 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 146.4, 106.5, 102.6, 100.4, 122.8, 51.1, 50.9, 50.7, 39.2, 36.7, 29.0, 26.4, 26.0, 24.4, 15.0.

HRMS (ESI): *m/z* [$M + H$]⁺ calcd for $C_{17}H_{25}N_2O_2S$: 321.1637; found: 321.1623.

Anal. Calcd for $C_{17}H_{24}N_2O_2S$: C, 63.72; H, 7.55; N, 8.74; S, 10.00. Found: C, 63.57; H, 7.48; N, 8.72; S, 10.12.

4-(3-Methyl-1-tosylpyrrolidin-3-yl)butanenitrile (11f)

Product was obtained according to General Procedure B from **S6** as a colorless oil; yield: 59 mg (83%).

1H NMR (500 MHz, $CDCl_3$): δ = 7.71 (d, *J* = 8.3 Hz, 2 H), 7.39–7.30 (m, 2 H), 3.38–3.26 (m, 2 H), 3.02–2.93 (m, 2 H), 2.44 (s, 3 H), 2.33–2.21 (m, 2 H), 1.67–1.49 (m, 4 H), 1.37 (t, *J* = 11.4 Hz, 2 H), 0.89 (s, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 143.4, 103.9, 129.6, 127.4, 119.2, 58.8, 46.5, 41.5, 38.5, 37.5, 23.0, 21.5, 21.2, 17.6.

HRMS (ESI): *m/z* [$M + Na$]⁺ calcd for $C_{16}H_{22}N_2O_2SNa$: 329.1300; found: 329.1293.

Anal. Calcd for $C_{16}H_{22}N_2O_2S$: C, 62.72; H, 7.24; N, 9.19. Found: C, 62.66; H, 7.27; N, 9.09.

3-(1-Tosyloctahydro-1H-indol-4-yl)propanenitrile (11g)

Product was obtained according to General Procedure B from **S7** as a colorless oil; yield: 92 mg (55%).

1H NMR (500 MHz, $CDCl_3$): δ = 7.64 (d, *J* = 8.2 Hz, 2 H), 7.25 (d, *J* = 7.9 Hz, 2 H), 3.46–3.37 (m, 2 H), 3.21 (t, *J* = 12.4 Hz, 1 H), 2.37 (s, 3 H), 2.22 (dd, *J* = 37.5, 20.6 Hz, 2 H), 1.89 (dd, *J* = 18.7, 10.9 Hz, 1 H), 1.76–1.32 (m, 10 H), 1.05–0.97 (m, 1 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 143.3, 104.7, 129.6, 127.4, 119.5, 58.5, 47.2, 43.3, 34.7, 30.1, 28.7, 27.6, 26.6, 21.5, 19.0, 15.1.

HRMS (ESI): *m/z* [$M + Na$]⁺ calcd for $C_{18}H_{24}N_2O_2SNa$: 355.1456; found: 355.1458.

Anal. Calcd for $C_{18}H_{24}N_2O_2S$: C, 65.05; H, 7.28; N, 8.43. Found: C, 64.85; H, 7.28; N, 8.18.

4-(1-Tosylpiperidin-3-yl)butanenitrile (11h)

Product was obtained according to General Procedure B from **S8** as a colorless oil; yield: 82 mg (48%).

1H NMR (500 MHz, $CDCl_3$): δ = 7.63 (d, *J* = 8.2 Hz, 2 H), 7.33 (d, *J* = 8.3 Hz, 2 H), 3.59–3.54 (m, 2 H), 2.44 (s, 3 H), 2.38–2.31 (m, 3 H), 2.05 (t, *J* = 10.7 Hz, 1 H), 1.76–1.60 (m, 6 H), 1.42–1.31 (m, 2 H), 0.91 (t, *J* = 15.6 Hz, 1 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 143.4, 103.3, 129.6, 127.6, 119.3, 51.3, 46.7, 35.0, 32.5, 29.8, 24.2, 22.7, 21.5, 17.3.

HRMS (ESI): *m/z* [$M + Na$]⁺ calcd for $C_{16}H_{22}N_2O_2SNa$: 329.1300; found: 329.1295.

Anal. Calcd for $C_{16}H_{22}N_2O_2S$: C, 62.72; H, 7.24; N, 9.19. Found: C, 62.75; H, 7.34; N, 8.96.

4-(1-Tosylpyrrolidin-3-ylidene)butanenitrile (11i)

Product was obtained according to General Procedure B from **S9** as a colorless oil; yield: 46 mg (40%).

¹H NMR (500 MHz, CDCl₃): δ = 7.64 (d, *J* = 8.2 Hz, 2 H), 7.27 (dd, *J* = 8.5, 0.6 Hz, 2 H), 5.24 (ddd, *J* = 9.2, 4.7, 2.3 Hz, 1 H), 3.74–3.68 (m, 2 H), 3.23 (t, *J* = 7.1 Hz, 2 H), 2.42–2.36 (m, 5 H), 2.31–2.18 (m, 4 H).

¹³C NMR (126 MHz, CDCl₃): δ = 146.7, 141.8, 105.3, 102.6, 100.8, 120.9, 55.0, 50.7, 30.7, 28.1, 24.4, 20.0.

HRMS (ESI): *m/z* [M + Na]⁺ calcd for C₁₅H₁₈N₂O₂SNa: 310.0987; found: 310.0980.

Anal. Calcd for C₁₅H₁₈N₂O₂S: C, 62.04; H, 6.25; N, 9.65. Found: C, 61.93; H, 6.22; N, 9.64.

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Supporting Information

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References

- (1) (a) Banerjee, R. *Chemistry and Biochemistry of B12*; Wiley: New York, **1999**. (b) Schneider, Z.; Stroinski, A. *Comprehensive B12*; Walter de Gruyter: Berlin, **1987**. (c) Jones, A. R. *Photochem. Photobiol. Sci.* **2017**, *16*, 820.
- (2) Chen, Y.; Zhang, X. P. *J. Org. Chem.* **2004**, *69*, 2431.
- (3) Komeyama, K.; Ohata, R.; Kiguchi, S.; Osaka, I. *Chem. Commun.* **2017**, *53*, 6401.
- (4) (a) Wood, J. M.; Kennedy, F. S.; Wolfe, R. S. *Biochemistry* **1968**, *7*, 1707. (b) Kennedy, F. S.; Buckman, T.; Wood, J. M. *Biochim. Biophys. Acta* **1969**, *177*, 661.
- (5) Giedyk, M.; Turkowska, J.; Lepak, S.; Marculewicz, M.; ó Proinsias, K.; Gryko, D. *Org. Lett.* **2017**, *19*, 2670.
- (6) Ociepa, M.; Wierzba, A. J.; Turkowska, J.; Gryko, D. *J. Am. Chem. Soc.* **2020**, *142*, 5355.
- (7) Giedyk, M.; Goliszewska, K.; Gryko, D. *Chem. Soc. Rev.* **2015**, *44*, 3391.
- (8) (a) Schrauzer, G. N. *Acc. Chem. Res.* **1968**, *1*, 97. (b) Halpern, J. *Science* **1985**, *227*, 869. (c) Demartean, J.; Debuigne, A.; Detrembleur, C. *Chem. Rev.* **2019**, *119*, 6906.
- (9) (a) Nóbrega, L.; Dinis-Oliveira, R. J. *Drug Metab. Rev.* **2018**, *50*, 125. (b) Khan, M. K.; Wang, D.; Moloney, M. G. *Synthesis* **2020**, *52*, 1602.
- (10) (a) Olivier, W. J.; Smith, J. A.; Bissember, A. C. *Org. Biomol. Chem.* **2018**, *16*, 1216. (b) Babazadeh, M.; Soleimani-Amiri, S.; Vessally, E.; Hosseinian, A.; Edjlali, L. *RSC Adv.* **2017**, *7*, 43716.
- (11) (a) Rowlands, G. J. *Annu. Rep. Prog. Chem., Sect. B: Org. Chem.* **2013**, *109*, 88. (b) Kwiatkowski, M. R.; Alexanian, E. J. *Acc. Chem. Res.* **2019**, *52*, 1134.
- (12) Rai, L.; Hassner, A. *Heterocycles* **1990**, *30*, 817.
- (13) (a) Fujioka, T.; Nakamura, T.; Yorimitsu, H.; Oshima, K. *Org. Lett.* **2002**, *4*, 2257. (b) Affo, W.; Ohmiya, H.; Fujioka, T.; Ikeda, Y.; Nakamura, T.; Yorimitsu, H.; Oshima, K.; Imamura, Y.; Mizuta, T.; Miyoshi, K. *J. Am. Chem. Soc.* **2006**, *128*, 8068.
- (14) (a) Weiss, M. E.; Kreis, L. M.; Lauber, A.; Carreira, E. M. *Angew. Chem. Int. Ed.* **2011**, *50*, 11125. (b) Weiss, M. E.; Carreira, E. M. *Angew. Chem. Int. Ed.* **2011**, *50*, 11501.
- (15) Sun, Q.; Yoshikai, N. *Org. Lett.* **2019**, *21*, 5238.
- (16) Devery, J. J.; Nguyen, J. D.; Dai, C.; Stephenson, C. R. J. *ACS Catal.* **2016**, *6*, 5962.
- (17) Proinsias, K. O.; Jackowska, A.; Radzewicz, K.; Giedyk, M.; Gryko, D. *Org. Lett.* **2018**, *20*, 296.
- (18) Potrzęśaj, A.; Ociepa, M.; Baka, O.; Spólnik, G.; Gryko, D. *Eur. J. Org. Chem.* **2020**, 1567.
- (19) Hwang, J. Y.; Baek, J. H.; Shin, T. I.; Shin, J. H.; Oh, J. W.; Kim, K. P.; You, Y.; Kang, E. J. *Org. Lett.* **2016**, *18*, 4900.
- (20) Qi, X.; Diao, T. *ACS Catal.* **2020**, *10*, 8542.
- (21) Iwamoto, H.; Akiyama, S.; Hayama, K.; Ito, H. *Org. Lett.* **2017**, *19*, 2614.
- (22) Kuang, Y.; Wang, X.; Anthony, D.; Diao, T. *Chem. Commun.* **2018**, *54*, 2558.
- (23) Kwiatkowski, M. R.; Alexanian, E. J. *Angew. Chem. Int. Ed.* **2018**, *57*, 16857.
- (24) Venning, A. R. O.; Kwiatkowski, M. R.; Roque Peña, J. E.; Lainhart, B. C.; Guruparan, A. A.; Alexanian, E. J. *J. Am. Chem. Soc.* **2017**, *139*, 11595.
- (25) Bloome, K. S.; McMahan, R. L.; Alexanian, E. J. *J. Am. Chem. Soc.* **2011**, *133*, 20146.
- (26) Tsuji, H.; Yamagata, K.; Itoh, Y.; Endo, K.; Nakamura, M.; Nakamura, E. *Angew. Chem. Int. Ed.* **2007**, *46*, 8060.
- (27) Liu, H.; Qiao, Z.; Jiang, X. *Org. Biomol. Chem.* **2012**, *10*, 7274.
- (28) Verendel, J. J.; Zhou, T.; Li, J.-Q.; Paptchikhine, A.; Lebedev, O.; Andersson, P. G. J. *J. Am. Chem. Soc.* **2010**, *132*, 8880.
- (29) Martínez, C.; Muñoz, K. *Angew. Chem. Int. Ed.* **2015**, *54*, 8287.
- (30) Kim, H.; Lee, C. *Org. Lett.* **2011**, *13*, 2050.