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Convenient approach to 2-substituted (thio)morpholin-3-ones from α-diazoacetates *via* X-H carbene insertion – lactamization sequence

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ABSTRACT

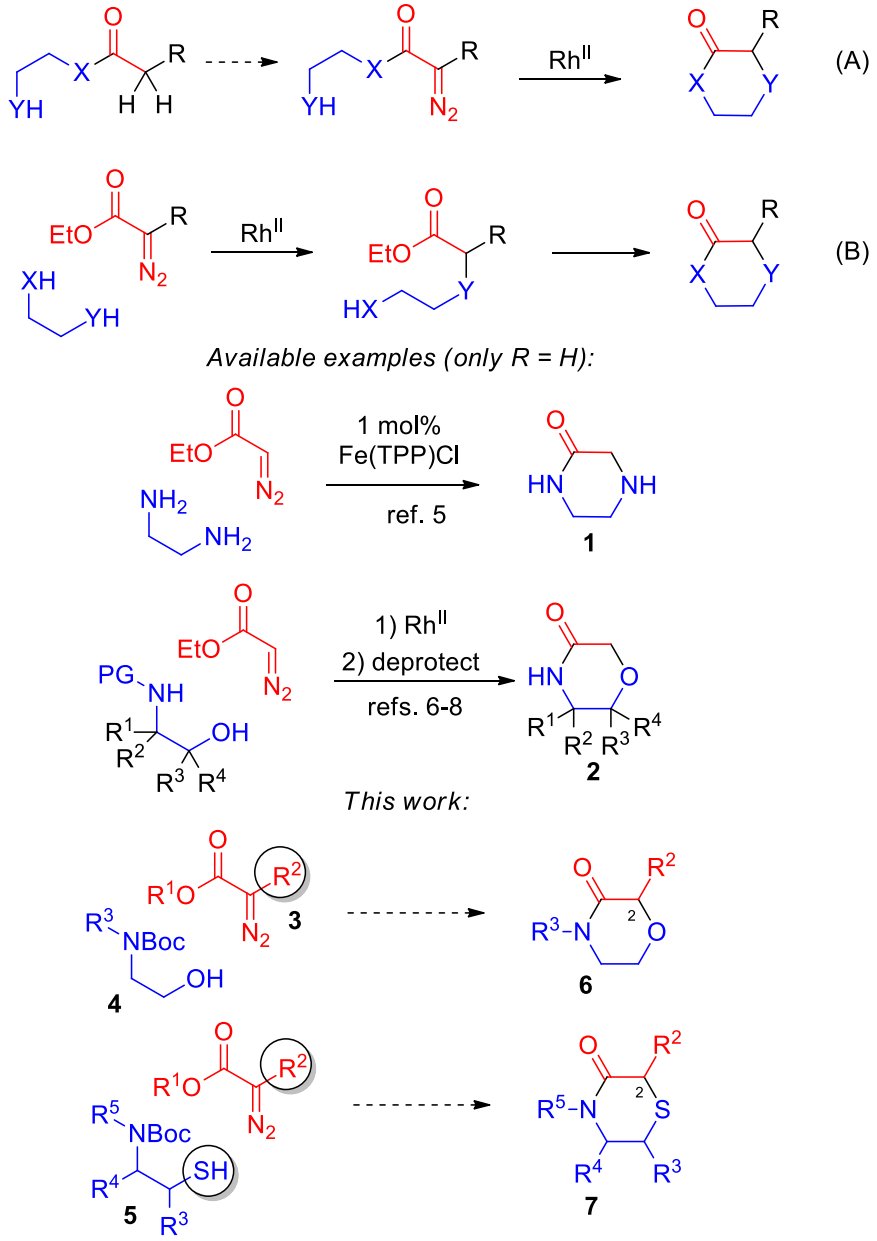
Stepwise coupling of *N*-Boc-protected β-aminoethanols or β-mercaptoethylamines with various α-diazoacetates provides a new, unified approach to constructing (thio)morpholin-3-ones. The process involves a $Rh_2(esp)_2$-catalyzed X-H insertion reaction, Boc group removal and ambient-temperature lactamization and is conveniently conducted in one-pot format.

Introduction

Esters of α-diazoacetic acids represent a common type of diazocarbonyl compounds (>190 000 hits in SciFinder, including diazomalonates[1]) and a densely functionalized template for ring-forming transformations which might take advantage of both the diazo and the ester functionalities. One common strategy (Figure 1A) involves attaching appropriately functionalized side chains at the carboxy group (*via* an ester or amide linkage) followed by intramolecular reactions (e. g., X-H insertion,[2] cycloaddition[3] or ylide formation[4]) with the carbenoid generated from the diazo group by metal-catalyzed decomposition. Newly formed heteroatom-containing six-membered rings represent the usual outcome of this approach. One obvious drawback of the latter is the need to pre-functionalize the acyclic template prior to the introduction of the diazo function instead of conveniently relying on an arsenal of common α-diazoacetate building blocks. An alternative approach (Figure 1B) would be to start from an appropriately substituted α-diazoacetate and couple it with a bifunctional building block engaging diazo group chemistry first followed by cyclization onto the nearby ester group. Surprisingly, such an apparently more convenient, modular approach can be only sporadically encountered in the literature. The isolated examples include two-step preparation of piperazin-2-one (**1**) from ethyl diazoacetate and ethylene diamine[5] and a similar 'couple-deprotect-cyclize' sequence realized with ethyl diazoacetate and protected β-aminoethanols toward morpholine-3-

ones **2** required for the design of mGluR5 modulators,[6] BACE inhibitors[7] and DPPIV inhibitors.[8]

Figure 1. Ring-forming approaches based on substituted α-diazoacetates (red) and bifunctional building blocks (blue).



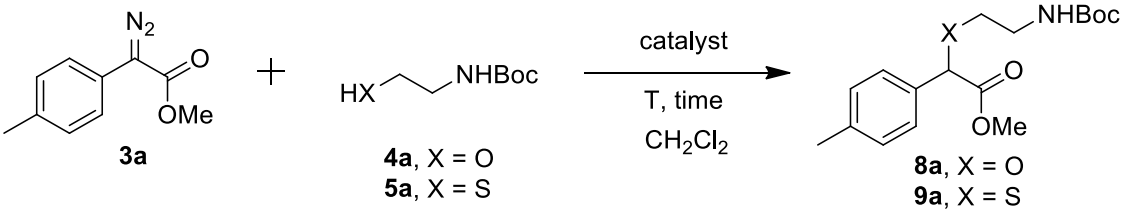
We thought it worthwhile to investigate this potentially universal strategy of constructing morpholin-3-ones beyond unsubstituted ethyl diazoacetate (so as to include reagents **3**) and to establish applicability of the same strategy not only to protected β-aminoalcohols **4** but also to protected β-aminomercaptanes **5** which have not been employed in these reactions. Achieving these aims will, on one hand, provide a far more streamlined entry into 2-substituted morpholin-3-ones **6** compared to the currently available multistep routes.[9] On the other hand, expanding the scope of this transformation to β-aminomercaptanes will offer a new approach to 2-

substituted thiomorpholin-3-ones **7**. The latter have a substantial track record as building blocks for medicinal chemistry[10] and are encountered in the natural products realm.[11] Herein, we present the results obtained in the course of working towards these goals.

Results and discussion

In order to test the viability of the proposed approach and to identify the optimal conditions for the transformation, we screened the reaction between known[12] diazo compound **3a** (prepared as detailed below) and *N*-Boc-protected β-aminoethanol (**4a**) and β-mercaptoethylamine (**5a**) with various catalysts capable of decomposing diazo compounds and generating the respective metal carbene. The results are summarized in Table 1. The formation of the respective X-H insertion product **8(9)a** was very rapid with 0.3 mol. % $Rh_2(esp)_2$ and virtually independent of the temperature. The highest yields (99% and 74% by ^{1}H NMR analysis, respectively; Entries 6 and 13) were achieved when using 0.3 mol% $Rh_2(esp)_2$ at room temperature. Thus, these conditions were subsequently employed throughout this study.

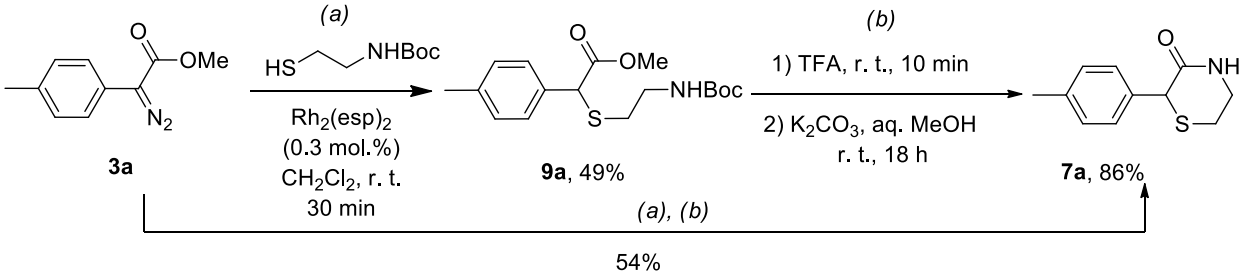
Table 1. Condition screening for the X-H insertion investigated in this work.



Entry	X	Temperature	Catalyst	Mol.%	Time (min)	^{1}H NMR yield (%)
1	O	RT	none	-	No reaction	0
2	O	RT	$Rh_2(OAc)_4$	1.0	<20	68
3	O	RT	$Rh_2(OPiv)_4$	1.0	<20	78
4	O	RT	$Rh_2(CF_3CO_2)_4$	1.0	<20	73
5	O	RT	$Rh_2(esp)_2$	1.0	<20	84
6	O	RT	$Cu(acac)_2$	5.0	No reaction	0
7	O	RT	$Rh_2(esp)_2$	0.3	<20	89
8	O	0 °C	$Rh_2(esp)_2$	0.3	<20	88
9	S	RT	none	-	No reaction	0
10	S	RT	$Rh_2(OAc)_4$	1.0	<20	61
11	S	RT	$Rh_2(OPiv)_4$	1.0	<20	65
12	S	RT	$Rh_2(CF_3CO_2)_4$	1.0	<20	60
13	S	RT	$Rh_2(esp)_2$	1.0	<20	74
14	S	RT	$Cu(acac)_2$	5.0	No reaction	0
15	S	RT	$Rh_2(esp)_2$	0.3	<20	74
16	S	0 °C	$Rh_2(esp)_2$	0.3	<20	76

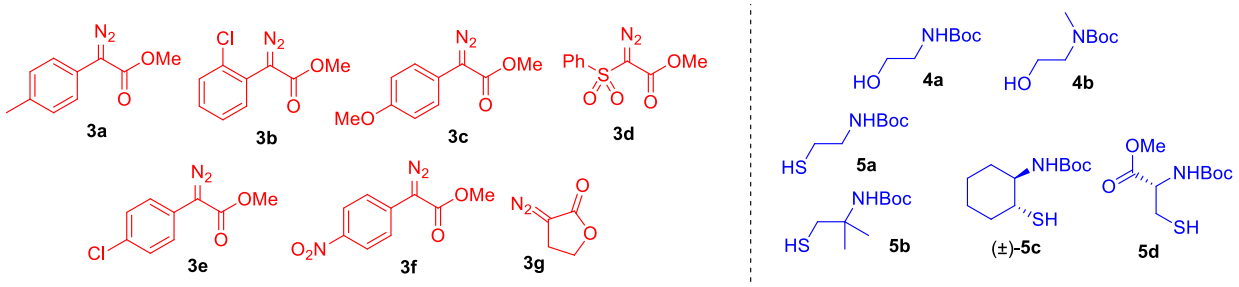
The 74% ^{1}H NMR yield of compound **9a** observed under the best conditions (Table 1, Entry 13) translated into 49% isolated yield after chromatography. With isolated compound **9a** at hand we proceeded to identify the workable conditions to convert it to the desired thiomorpholin-3-one **7a**. The Boc group was first removed with neat TFA (10 min at r. t.) followed by evaporation of the volatiles to dryness. Notably, using TFA solution in DCM at various concentrations and time and temperature regimens was not effective to achieve a complete Boc group removal. Attempts to basify the free amine obtained at this point and cyclize it to **7a** were ineffective with triethylamine in various solvents (DCM, MeOH, and toluene) and at various temperatures (r. t. to reflux). However, using potassium carbonate in aqueous methanol proved effective and furnished 86% yield of the target compound **7a** in 18 h at room temperature. Applying the same conditions to crude **9a** (i. e. in one-pot fashion, following the $Rh_2(esp)_2$-catalyzed S-H insertion step) resulted in 54% yield of compound **7a**, which constituted a noticeable improvement compared to the combined yield (42%) over two steps intermitted with chromatographic isolation of **9a** (Scheme 1).

Scheme 1. Investigated syntheses of compound **7a**.



Thus, the same one-pot protocol was applied to various combinations of diazo compounds **3a-g** with *N*-Boc-protected β-aminoethanols (**4a-b**) and/or β-mercaptoethylamines (**5a-d**) (Figure 2). It should be noted that diazo compounds **3a-g** were conveniently prepared using the recently developed 'sulfonyl-azide-free' (SAFE) diazo transfer protocol[13] from the respective CH_2-acidic precursors (except for compound **3g** which was prepared from commercially available α-acetyl-γ-burtyrolactone[14]) directly (**3d,f**) or *via in situ* α-formylation (**3a-c**, **3e**).[15]

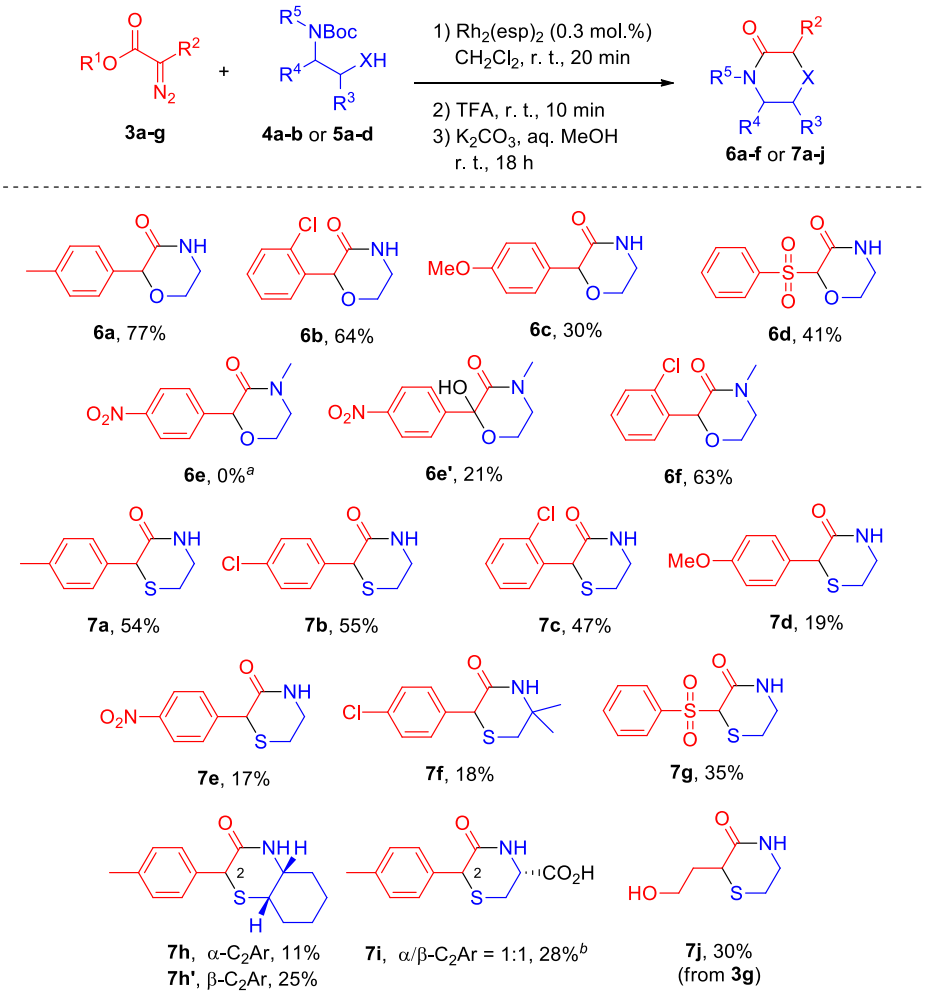
Figure 2. Selection of α-diazoacetates and Boc-protected partners for the X-H insertion – lactamization investigated herein.



As it follows from the results presented in Scheme 2, the general X-H insertion – lactamization sequence was found applicable to the preparation of a range of (thio)morpholin-3-ones **6**(**7**). The moderate yields obtained in some cases can be attributed to the low yield in the first step while the lactamization step was rather efficient, even for sterically hindered amines. For example, the low yield of compound **7f** is clearly due to the limitations of the S-H insertion step (which alone gave a disappointing 17% isolated yield) and not the lactamization which gave 70% yield when performed on the isolated S-H insertion product.

An interesting result was obtained with diazo compound **3f** (R^2 = 4-$NO_2C_6H_4$) for which no product **6e** was observed. In this case, a by-product which we believe could be product **6e′** based on NMR, HRMS and IR analysis was formed, most likely in the course of O-H insertion reaction.[16] The unwanted hydroxylation is probably facilitated by the nitro group in the phenyl ring as the analogous coupling with diazo compound **3e** (R^2 = 4-ClC_6H_4) gave only the desired product (**6f**). Interestingly, no unwanted hydroxylation was observed in the reaction of **3f** and **5a**; in this case, only the desired thiomorpholinone **7e** was obtained in low (17%) yield. *p*-Methoxy-substituted **3c** generally gave moderate yields of **6c** and **7d**, in contrast to **3a** or **3b** (R^2 = 4-$CH_3C_6H_4$ and 2-ClC_6H_4, respectively) which gave good yields of both **6** and **7**.

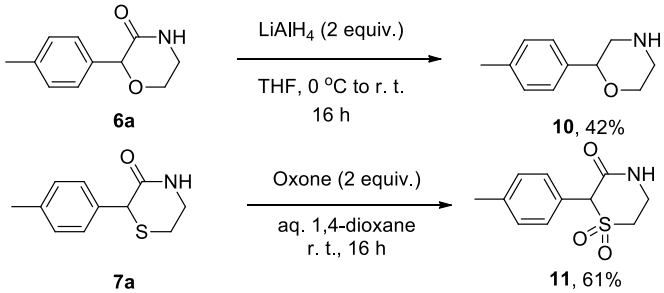
Scheme 2. Preparation of morpholin-3-ones **6a-f** and thiomorpholin-3-ones **7a-j**.



[a] Product of hydroxylation at C_2 (**6e'**) was isolated instead.
[b] The ester group was completely hydrolyzed under the cyclization conditions.

In order to further demonstrate the utility of the synthetic approach presented herein and of the resulting (thio)morpholin-3-ones **6**(**7**), we exemplified two rather straightforward possibilities for the downstream processing of the latter. Reduction of the carbonyl group in **6a** with $LiAlH_4$ resulted in morpholine **10** which is related to the recently reported agonists of trace amine-associated receptors.[17] Oxidation of the sulfur atom in **7a** with oxone gave sulfone **11** which is related to compounds endowed with sedative properties[18] (Scheme 3).

Scheme 3. Examples of the downstream processing of (thio)morpholin-3-ones **6**(**7**).



Conclusion

We developed a stepwise coupling of *N*-Boc-protected β-aminoethanols or β-mercaptoethylamines with various α-diazoacetates. The process involves a $Rh_2(esp)_2$-catalyzed X-H insertion reaction, Boc group removal and ambient-temperature lactamization and is conveniently conducted in one-pot format. While there are a handful of examples describing a similar assembly of morpholin-3-ones from ethyl diazoacetate in the literature, the approach has not been explored neither for substituted α-diazoacetates nor for β-aminoethanols. These results represent a new, unified approach to constructing (thio)morpholin-3-ones which are medicinally important on their own or as building blocks for bioactive compound design.

Experimental section

General considerations. *N*-Boc protected 2-aminoethanol[S1], 2-(methylamino)ethanol[S2], 2-aminoethanethiol[S3], (*S*)-methyl 2-amino-3-mercaptopropanoate[S4], methyl 2-diazo-2-(4-nitrophenyl)acetate and methyl 2-diazo-2-(phenylsulfonyl)acetate[S5], 3-diazodihydrofuran-2(3*H*)-one[S6] were prepared according literature methods, other reagents were obtained from commercial sources and used without additional purification. Tetrahydrofuran and dichloromethane were distilled over suitable drying agents. Mass spectra were recorded with a Bruker Maxis HRMS-ESI-qTOF spectrometer (electrospray ionization mode). NMR spectroscopic data were recorded with Bruker Avance 400 spectrometer (400.13 MHz for ^{1}H and 100.61 MHz for ^{13}C) and were referenced to residual solvent proton peaks and solvent carbon peaks. Melting points were determined with a Stuart SMP50 instrument in open capillary tubes.

Preparation of *tert*-butyl (2-mercaptocyclohexyl)carbamate (5c)

2-Aminocyclohexanol (1.0 g, 8.7 mmol) in carbon tetrachloride (50 mL) was cooled in an ice bath. Chlorosulfonic acid (1.0 g, 8.7 mmol) was slowly added to the solution under stirring. The reaction mixture was stirred overnight and carbon tetrachloride was removed *in vacuo* to give 1.3 g of crude 2-aminocyclohexyl hydrogen sulfate. 2-Aminocyclohexyl hydrogen sulfate (1.3 g, 6.8 mmol) was dissolved in 50 mL of aqueous ethanol (50%) and cooled in an ice bath. To the resulting solution CS_2 (1.6 g, 20.6 mmol) and KOH (1.0 g, 17.2 mmol) in 10 mL of aqueous ethanol (50%) were slowly added and the mixture was refluxed over 3 h and evaporated to dryness. The resulting solid was refluxed in water for 1 h, cooled, collected by filtration and dried *in vacuo* to give 650 mg of hexahydrobenzo[*d*]thiazole-2(3*H*)-thione. Hexahydrobenzo[*d*]thiazole-2(3*H*)-thione (650 mg, 3.7 mmol) was refluxed for 3 days in 10 mL of 48% aq. HBr under argon and evaporated to dryness. Residue was triturated with Et_2O (10 mL) to give 480 mg of 2-aminocyclohexanethiol hydrobromide. The obtained crude

hydrobromide (480 mg, 2.2 mmol) was dissolved in 50 mL of dichloromethane and Et_3N (250 mg, 2.5 mmol) at room temperature, di-*t*-butyl dicarbonate (494 mg, 2.2 mmol) was dissolved in 10 mL of dichloromethane and added gradually to the reaction mixture. The reaction was stirred overnight and the resulting solution was washed with saturated solution of sodium bicarbonate (2 × 50 mL) and water (2 × 50 mL), dried over $MgSO_4$ and evaporated. *tert*-Butyl (2-mercaptocyclohexyl)carbamate was purified using column chromatography on silica gel. Eluent ethyl acetate – *n*-hexane 1:10. Yield 392 mg, 20%. Colorless oil. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 4.88 (s, 1H), 3.94 – 3.68 (m, 1H), 3.53 – 3.20 (m, 1H), 1.95 – 1.82 (m, 2H), 1.71 – 1.24 (m, 15H).

Preparation of *tert*-butyl (1-mercapto-2-methylpropan-2-yl)carbamate (5b)

Prepared according to the procedure described for *tert*-butyl (2-mercaptocyclohexyl)carbamate from 2-amino-2-methylpropan-1-ol. Yield 375 mg, 21%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 3.23 (s, 1H), 2.88 (s, 2H), 1.46 (s, 9H), 1.33 (s, 6H).

General procedure for the synthesis of diazocarbonyl compounds (3a-c,e)

Preparation of the 'SAFE cocktail'. To a stirred solution of sodium azide (1.96 g, 30 mmol) and potassium carbonate (5.52 g, 40.0 mmol) in water (80 mL) was added 3-(chlorosulfonyl)benzoic acid (5.88 g, 26.8 mmol) and the mixture was stirred at ambient temperature for 10 minutes to give clear solution. The resulting aqueous solution was used for diazo transfer reactions.

Preparation of diazocarbonyl compounds. To a cooled with ice bath stirred solution of phenylacetic acid ester (5.0 mmol) and methyl formate (1.20 g, 20.0 mmol) in dry THF (10 mL) was added *t*-BuOK (1.40 g, 12.5 mmol) in one portion. The mixture was stirred for 1 h, then the cooling bath was removed and stirring was continued for overnight at ambient temperature. The resulting mixture was cooled with ice bath followed by addition of a 20 mL of the 'SAFE cocktail' prepared as described above. After addition the ice bath was removed and the mixture was stirred for 1 h at ambient temperature. Upon completion of diazo transfer reaction, the product was extracted with chloroform (3×20 mL), organic phase was dried over calcium chloride and evaporated to dryness.

Methyl 2-diazo-2-(*p*-tolyl)acetate (3a). Yield 668 mg, 70%. Red oil. ^{1}H NMR (400 MHz, Chloroform-d) δ 7.44 – 7.35 (m, 2H), 7.26 – 7.15 (m, 2H), 3.88 (s, 3H), 2.37 (s, 3H).

Methyl 2-(2-chlorophenyl)-2-diazoacetate (3b). Yield 754 mg, 72%. Yellow solid, mp 37.0-38.0 ºC. ^{1}H NMR (400 MHz, Chloroform-d) δ 7.57 (dd, J = 7.6, 1.9 Hz, 1H), 7.45 (dd, J = 7.8, 1.7 Hz, 1H), 7.38 – 7.30 (m, 2H), 3.87 (s, 3H).

Methyl 2-diazo-2-(4-methoxyphenyl)acetate (3c). Yield 380 mg, 37%. Orange solid, mp 45-45.8 ºC. ^{1}H NMR (400 MHz, Chloroform-d) δ 7.45 – 7.37 (m, 2H), 7.00 – 6.94 (m, 2H), 3.88 (s, 3H), 3.84 (s, 3H).

Methyl 2-(4-chlorophenyl)-2-diazoacetate (3e). Yield 705 mg, 67%. Orange solid, mp 57.0-58.3 °C. ^{1}H NMR (400 MHz, Chloroform-d) δ 7.48 – 7.42 (m, 2H), 7.41 – 7.34 (m, 2H), 3.89 (s, 3H).

General procedure for morpholinone (6a-f)/thiomorpholinone (7a-j) synthesis

To a vigorously stirred solution of corresponding *N*-Boc aminoalcohol (*N*-Boc aminothiol) (0.6 mmol) and diazo compound (0.65 mmol) in dichloromethane (5 mL) was added $Rh_2(esp)_2$ (1.6 mg, 0.002 mmol, 0.3 mol %). After completion of nitrogen evolution (30 minutes) the reaction mixture was evaporated to dryness. To the resulting oil TFA (2 mL) was added. After 10 minutes the resulting mixture was evaporated to dryness, dissolved in methanol (5 mL), then K_2CO_3 (3 mmol) and water (1 mL) were added. The resulting suspension was stirred at room temperature overnight. On the next day water (4 mL) was added and the solution was extracted with EtOAc (3×5 mL). Extracts were combined, washed with water, dried ($MgSO_4$), evaporated and purified using column chromatography on silica gel if needed.

2-(*p*-Tolyl)morpholin-3-one (6a). Eluent ethyl acetate – *n*-hexane 1:2. Yield 89 mg, 77%. White solid, mp 119.0-120.8 °C. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.91 (s, 1H), 7.36 (d, *J* = 8.2 Hz, 2H), 7.21 (d, *J* = 7.9 Hz, 2H), 5.14 (s, 1H), 4.00 (dt, *J* = 11.8, 4.2 Hz, 1H), 3.88 – 3.78 (m, 1H), 3.63 – 3.50 (m, 1H), 3.44 – 3.34 (m, 1H), 2.37 (s, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 170.5, 138.3, 134.1, 129.2, 128.0, 79.5, 61.7, 42.0, 21.2. HRMS (ESI/Q-TOF) m/z: $[M+Na]^+$ Calcd for $C_{11}H_{13}NO_2$ 214.0838; Found 214.0844.

2-(2-Chlorophenyl)morpholin-3-one (6b). Yield 81 mg, 64%. Colorless oil. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.91 (s, 1H), 7.59 – 7.39 (m, 2H), 7.35 – 7.28 (m, 2H), 5.49 (s, 1H), 4.03 (dt, *J* = 11.9, 3.8 Hz, 1H), 3.95 – 3.82 (m, 1H), 3.75 – 3.55 (m, 1H), 3.41 – 3.25 (m, 1H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 169.8, 134.9, 134.6, 130.7, 130.1, 126.9, 77.6, 62.5, 41.9. HRMS (ESI/Q-TOF) m/z: $[M+Na]^+$ Calcd for $C_{10}H_{10}ClNO_2$ 234.0292; Found 234.0295.

2-(4-Methoxyphenyl)morpholin-3-one (6c). Eluent ethyl acetate–*n*-hexane 1:3. Yield 38 mg, 30%. White solid, mp 140.5-141.9 °C. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.39 (d, *J* = 8.8 Hz,

2H), 6.93 (d, *J* = 8.8 Hz, 2H), 5.14 (s, 1H), 4.11 – 3.98 (m, 1H), 3.82 (s, 4H), 3.67 – 3.59 (m, 1H), 3.49 – 3.38 (m, 1H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 170.2, 159.8, 129.4, 129.2, 114.0, 79.4, 61.6, 55.3, 42.2, 1.01. HRMS (ESI/Q-TOF) m/z: $[M+Na]^+$ Calcd for $C_{11}H_{13}NO_3$ 230.0788; Found 230.0797.

2-(Phenylsulfonyl)morpholin-3-one (6d). Eluent ethyl acetate. Yield 60 mg, 41%. White solid, mp 136.0-138.2 °C. ^{1}H NMR (400 MHz, Acetone-d_6) δ 8.00 – 7.83 (m, 2H), 7.80 – 7.74 (m, 1H), 7.70 – 7.63 (m, 2H), 7.62 (s, 1H), 5.26 (s, 1H), 4.51 – 4.35 (m, 1H), 4.04 – 3.87 (m, 1H), 3.62 – 3.51 (m, 1H), 3.48 – 3.33 (m, 1H). ^{13}C NMR (101 MHz, Acetone-d_6) δ 159.9, 138.8, 133.9, 129.3, 128.9, 90.2, 61.8, 40.6. HRMS (ESI/Q-TOF) m/z: $[M+Na]^+$ Calcd for $C_{10}H_{11}NO_4S$ 264.0301; Found 264.0289.

2-Hydroxy-4-methyl-2-(4-nitrophenyl)morpholin-3-one (6e′). Eluent ethyl acetate. Yield 30 mg, 21%. Yellow solid, mp 161.8-162.6 °C. ^{1}H NMR (400 MHz, Acetone-d_6) δ 8.35 – 8.15 (m, 2H), 8.07 – 7.89 (m, 2H), 6.36 (s, 1H), 4.51 (td, *J* = 11.6, 3.4 Hz, 1H), 4.08 – 3.81 (m, 2H), 3.51 – 3.30 (m, 1H), 2.93 (s, 3H). ^{13}C NMR (101 MHz, Acetone-d_6) δ 165.7, 149.1, 147.9, 128.4, 122.3, 96.2, 57.9, 48.8, 33.8. IR (KBr) ν 3303 (O-H), 1660, 1514, 1354, 1076, 845 cm^{-1}. HRMS (ESI/Q-TOF) m/z: $[M+Na]^+$ Calcd for $C_{11}H_{12}N_2O_5$ 275.0644; Found 275.0623.

2-(2-Chlorophenyl)-4-methylmorpholin-3-one (6f). Yield 85 mg, 63%. Colorless oil. ^{1}H NMR (400 MHz, Chloroform-d) δ 7.44 – 7.39 (m, 1H), 7.37 – 7.33 (m, 1H), 7.31 – 7.20 (m, 2H), 5.46 (s, 1H), 4.11 – 4.03 (m, 1H), 3.99 – 3.88 (m, 1H), 3.79 – 3.62 (m, 1H), 3.33 (dt, J = 12.2, 3.6 Hz, 1H), 3.06 (s, 3H). ^{13}C NMR (101 MHz, Chloroform-d) δ 167.19, 135.37, 134.46, 130.66, 130.08, 129.90, 126.77, 77.85, 62.35, 48.83, 34.48. HRMS (ESI/Q-TOF) m/z: $[M+Na]^+$ Calcd for $C_{11}H_{12}ClNO_2$ 226.0629; Found 226.0633.

Methyl 2-((2-((tert-butoxycarbonyl)amino)ethyl)thio)-2-(*p*-tolyl)acetate (9a). Purified using column chromatography on silica gel. Eluent ethyl acetate – *n*-hexane 1:5. Yield 80 mg, 49%. Colorless oil. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.34 (d, *J* = 8.2 Hz, 1H), 7.14 (d, *J* = 7.9 Hz, 2H), 4.98 (s, 1H), 4.62 (s, 1H), 3.72 (s, 3H), 3.38 – 3.14 (m, 2H), 2.75 – 2.55 (m, 2H), 2.33 (s, 3H), 1.44 (s, 9H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 171.38, 155.74, 138.12, 132.84, 129.45, 128.33, 79.34, 52.71, 51.56, 32.19, 28.37, 21.10. $[M+Na]^+$ Calcd for $C_{17}H_{25}NO_4S$ 362.1402; Found 362.1385.

2-(*p*-Tolyl)thiomorpholin-3-one (7a). Eluent ethyl acetate – *n*-hexane 1:1. Yield 63 mg, 54%. White solid, mp 168.0-170.0 °C. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.43 – 7.30 (m, 2H), 7.23 – 7.10 (m, 2H), 6.96 (s, 1H), 4.64 (s, 1H), 3.74 – 3.59 (m, 2H), 3.04 – 2.80 (m, 2H), 2.36 (s, 3H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 169.7, 137.6, 134.1, 129.3, 128.5, 46.3, 44.2, 25.4, 21.1. HRMS (ESI/Q-TOF) m/z: $[M+Na]^+$ Calcd for $C_{11}H_{13}NOS$ 230.0610; Found 230.0601.

2-(4-Chlorophenyl)thiomorpholin-3-one (7b). Eluent ethyl acetate–*n*-hexane 1:3. Yield 75 mg, 55%. White solid, mp 134.9-137.0 C. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.41 – 7.37 (m, 2H), 7.37 – 7.32 (m, 2H), 6.63 (s, 1H), 4.64 (s, 1H), 3.77 – 3.62 (m, 2H), 2.99 – 2.81 (m, 2H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 169.4, 135.6, 133.8, 130.1, 128.8, 45.8, 44.1, 25.6. HRMS (ESI/Q-TOF) m/z: $[M+Na]^+$ Calcd for $C_{10}H_{10}ClNOS$ 250.0064; Found 250.0066.

2-(2-Chlorophenyl)thiomorpholin-3-one (7c). Eluent ethyl acetate – *n*-hexane 1:3. Yield 64 mg, 47%. White solid, mp 162.2-163.6 °C. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.46 – 7.42 (m, 1H), 7.42 – 7.37 (m, 1H), 7.31 – 7.23 (m, 3H), 6.89 (s, 1H), 5.11 (s, 1H), 3.93 – 3.68 (m, 2H), 2.97 – 2.84 (m, 2H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 168.7, 135.5, 134.3, 130.1, 129.8, 129.1, 126.9, 44.9, 43.3, 24.6. HRMS (ESI/Q-TOF) m/z: $[M+Na]^+$ Calcd for $C_{10}H_{10}ClNOS$ 250.0064; Found 250.0067.

2-(4-Methoxyphenyl)thiomorpholin-3-one (7d). Eluent ethyl acetate – *n*-hexane 1:3. Yield 25 mg, 19%. White solid, mp 162.2-163.8 °C. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.39 – 7.32 (m, 2H), 7.04 (s, 1H), 6.95 – 6.86 (m, 2H), 4.64 (s, 1H), 3.82 (s, 3H), 3.73 – 3.60 (m, 2H), 2.99 – 2.82 (m, 2H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 169.9, 159.2, 129.8, 128.9, 114.0, 55.3, 45.9, 44.2, 25.6. HRMS (ESI/Q-TOF) m/z: $[M+Na]^+$ Calcd for $C_{11}H_{13}NO_2S$ 246.0559; Found 246.0548.

2-(4-Nitrophenyl)thiomorpholin-3-one (7e). Eluent ethyl acetate. Yield 24 mg, 17%. White solid, mp 167.8-170.1 °C. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.29 – 8.17 (m, 2H), 7.68 – 7.60 (m, 2H), 6.19 (s, 1H), 4.76 (s, 1H), 3.79 – 3.70 (m, 2H), 3.03 – 2.86 (m, 2H). ^{13}C NMR (101 MHz, Acetone-d_6) δ 167.3, 147.3, 145.8, 130.3, 123.2, 44.9, 43.4, 26.1. HRMS (ESI/Q-TOF) m/z: $[M+Na]^+$ Calcd for $C_{10}H_{10}N_2O_3S$ 261.0304; Found 261.0307.

2-(4-Chlorophenyl)-5,5-dimethylthiomorpholin-3-one (7f). Eluent ethyl acetate – *n*-hexane 1:3. Yield 28 mg, 18%. White solid, mp 160.0-161.7 °C. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.34 (s, 4H), 5.93 (s, 1H), 4.51 (s, 1H), 2.93 – 2.34 (m, 2H), 1.46 (s, 6H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 167.7, 136.2, 133.6, 129.8, 128.7, 56.1, 46.0, 35.7, 30.1, 29.7. HRMS (ESI/Q-TOF) m/z: $[M+Na]^+$ Calcd for $C_{12}H_{14}ClNOS$ 278.0377; Found 278.0367.

2-(Phenylsulfonyl)thiomorpholin-3-one (7g). Eluent ethyl acetate. Yield 56 mg, 35%. White solid, mp 175.0-177.0 °C. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.16 – 7.90 (m, 2H), 7.75 – 7.68 (m, 1H), 7.63 – 7.56 (m, 1H), 6.24 (s, 1H), 4.64 (s, 1H), 4.00 – 3.89 (m, 1H), 3.78 – 3.66 (m, 1H), 3.56 – 3.38 (m, 1H), 2.88 – 2.64 (m, 1H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 207.2,

159.9, 137.6, 134.4, 129.4, 129.0, 66.3, 44.1, 24.2. HRMS (ESI/Q-TOF) m/z: $[M+Na]^+$ Calcd for $C_{10}H_{11}NO_3S_2$ 280.0073; Found 280.0085.

(±) (2S,4aS,8aR)-2-(*p*-Tolyl)hexahydro-2*H*-benzo[*b*][1,4]thiazin-3(4*H*)-one (7h) and (±) (2R,4aS,8aR)-2-(*p*-Tolyl)hexahydro-2*H*-benzo[*b*][1,4]thiazin-3(4*H*)-one (7h')

Prior to chromatography the mixture of diastereomers was obtained. Individual diastereomers were isolated by column chromatography, eluent ethyl acetate–*n*-hexane 1:10.

(7h) Yield 16 mg, 11%. White solid, mp 197.0-198.2 °C. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.29 (d, *J* = 6.3 Hz, 2H), 7.18 (d, *J* = 8.0 Hz, 2H), 6.10 (s, 1H), 4.71 (s, 1H), 3.88 – 3.77 (m, 1H), 3.52 – 3.44 (m, 1H), 2.36 (s, 3H), 2.22 – 2.07 (m, 1H), 1.99 – 1.87 (m, 1H), 1.86 – 1.74 (m, 2H), 1.71 – 1.59 (m, 2H), 1.54 – 1.47 (m, 1H), 1.46 – 1.36 (m, 1H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 170.2, 137.9, 132.3, 129.6, 129.2, 53.2, 46.3, 43.6, 30.6, 30.2, 23.3, 21.6, 21.2. HRMS (ESI/Q-TOF) m/z: $[M+Na]^+$ Calcd for $C_{15}H_{19}NOS$ 284.1080; Found 284.1083.

(7h') Yield 40 mg, 25%. White solid, mp 163.4-164.4 °C. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.38 (d, *J* = 8.1 Hz, 2H), 7.16 (d, *J* = 8.0 Hz, 2H), 7.05 – 6.84 (m, 1H), 4.64 (s, 1H), 3.87 – 3.62 (m, 1H), 3.25 – 3.06 (m, 1H), 2.35 (s, 3H), 2.05 – 1.76 (m, 1H), 1.73 – 1.55 (m, 2H), 1.49 – 1.34 (m, 2H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 169.3, 137.2, 135.4, 129.3, 128.0, 54.1, 45.7, 39.0, 30.8, 29.4, 23.6, 21.3, 21.1. HRMS (ESI/Q-TOF) m/z: $[M+Na]^+$ Calcd for $C_{15}H_{19}NOS$ 284.1080; Found 284.1086.

5-Oxo-6-(*p*-tolyl)thiomorpholine-3-carboxylic acid (7i) Last step reaction conditions lead to hydrolysis of ester group to give mixture of *cis/trans* 1:1 product. Water (20 mL) was added to the resulting suspension and washed with EtOAc (2x10). The resulting aqueous layer was acidified with HCl and extracted with EtOAc (3x10). Combined organic layers were washed with brine (2x5), dried ($MgSO_4$) end evaporated to give pure product. Yield 42 mg, 28%. Yellow solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 14.28 (s, 2H), 9.44 (s, 1H), 9.32 (s, 1H), 7.37 (d, *J* = 7.8 Hz, 2H), 7.31 – 7.24 (m, 3H), 7.22 – 7.16 (m, 3H), 4.70 (s, 1H), 4.60 (s, 1H), 4.56 – 4.43 (m, 1H), 4.33 – 4.23 (m, 1H), 3.39 – 3.23 (m, 2H), 3.14 – 2.81 (m, 2H), 2.36 (s, 6H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 172.42, 172.28, 167.43, 167.03, 137.05, 136.87, 136.81, 135.79, 129.45, 129.28, 129.17, 128.59, 56.97, 56.76, 46.01, 45.27, 27.76, 25.39, 21.16, 21.11. HRMS (ESI/Q-TOF) m/z: $[M+Na]^+$ Calcd for $C_{12}H_{13}NO_3S$ 274.0508; Found 274.0512.

2-(2-Hydroxyethyl)thiomorpholin-3-one (7j)

On the first step *tert*-butyl (2-((2-oxotetrahydrofuran-3-yl)thio)ethyl)carbamate was purified by column chromatography to give 113 mg. Eluent ethyl acetate – *n*-hexane 1:3. To the resulting oil

2 mL of TFA were added. After 10 minutes the resulting mixture was evaporated to dryness, dissolved in methanol (5 mL) and K_2CO_3 (3 mmol) was added. The resulting suspension was stirred at room temperature overnight, evaporated and 10 ml of EtOAc were added. The resulting suspension was filtered and filtrate was evaporated to give pure product. Yield 29 mg, 30%. Colorless oil. ^{1}H NMR (400 MHz, Deuterium Oxide) δ 3.80 – 3.73 (m, 1H), 3.71 – 3.61 (m, 1H), 3.58 – 3.48 (m, 1H), 2.97 – 2.89 (m, 1H), 2.31 – 2.17 (m, 1H), 1.96 – 1.82 (m, 1H). ^{13}C NMR (101 MHz, Deuterium Oxide) δ 174.3, 59.1, 42.7, 37.5, 33.0, 24.8. HRMS (ESI/Q-TOF) m/z: $[M+Na]^+$ Calcd for $C_6H_{11}NO_2S$ 184.0403; Found 184.0410.

2-(*p*-Tolyl)morpholine (10)

LAH (68 mg, 1.8 mmol) in THF (5 mL) was cooled to 0 °C in an ice bath under argon. A solution of 2-(p-tolyl)morpholine (115 mg, 0.6 mmol) in THF (4 mL) was added dropwise, and the resulting solution was stirred at RT for 16 hrs. The reaction mixture was cooled to 0 °C and carefully quenched with water (0.5 mL), 2 N NaOH (0.5 mL) and water (1 mL). The resulting slurry was stirred at RT for 1 h and filtered through Celite. The filter cake was washed with ethyl acetate and discarded. The filtrate was dried (Na_2SO_4), separated, concentrated and purified using column chromatography on silica gel. Eluent ethyl acetate – methanol 10:1. Yield 45 mg, 42%. Yellow oil. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.28 – 7.24 (m, 2H), 7.19 – 7.14 (m, 2H), 4.51 (dd, *J* = 10.5, 2.5 Hz, 1H), 4.10 – 4.01 (m, 1H), 3.83 (td, *J* = 11.4, 3.0 Hz, 1H), 3.47 (s, 2H), 3.14 – 3.07 (m, 1H), 3.07 – 2.93 (m, 2H), 2.83 (dd, *J* = 12.5, 10.4 Hz, 1H), 2.35 (s, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 137.6, 137.1, 129.1, 126.0, 78.7, 67.8, 52.5, 45.2, 21.1. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{11}H_{15}N_1O$ 178.1226; Found 178.1227.

2-(*p*-Tolyl)thiomorpholin-3-one 1,1-dioxide (11)

Oxone (62 mg, 0.3 mmol) was added to the solution of 2-(*p*-tolyl)thiomorpholin-3-one (7a) (369 mg, 0.6 mmol) in 10 mL of dioxane/water 5:1. The resulting suspension was stirred at room temperature overnight. The resulting suspension was filtered and EtOAc (20 mL), water (20 mL) were added to the filtrate. Organic layer was separated and aqueous layer was washed with EtOAc (2x10 mL). Combined organic layers were washed with brine (2x10 mL), dried ($MgSO_4$) and evaporated to give pure product. Yield 44 mg, 61%. White solid, mp 201.8-202.5 °C ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.55 – 8.18 (m, 1H), 7.20 (s, 4H), 5.57 (s, 1H), 3.72 – 3.57 (m, 4H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 165.6, 138.6, 132.1, 129.1, 124.8, 70.3, 47.7, 36.8, 21.2. HRMS (ESI/Q-TOF) m/z: $[M+Na]^+$ Calcd for $C_{11}H_{13}N_1O_3S$ 262.0508; Found 262.0502.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures, analytical data and copies of the ^{1}H and ^{13}C NMR spectra.

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Notes

The authors declare no competing financial interest.

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KEYWORDS: α-diazoacetates; diazo transfer; $Rh(esp)_2$ catalysis; metal carbene insertion; lactamization.

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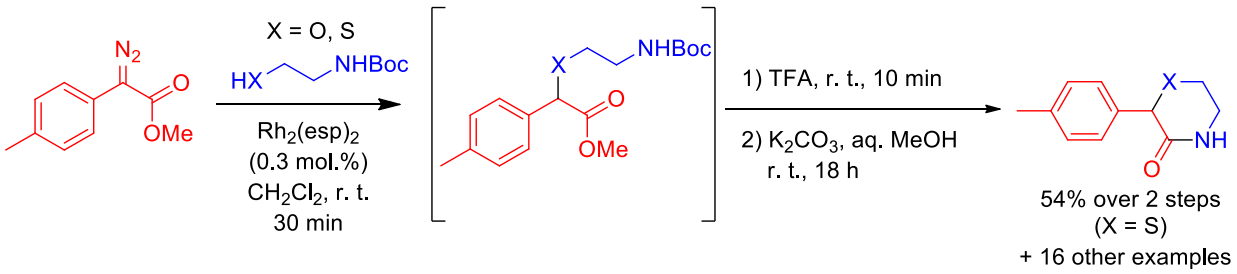
Graphical abstract



TOC text

Substituted α-diazo acetates are coupled with *N*-Boc-protected β-aminoethanols or β-mercaptoethylamines to give medicinally important (thio)morpholin-3-ones.

Key topic

Diazo compounds