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ZINC-ACETIC ACID PROMOTED REDUCTIVE CARBON-NITROGEN BOND CLEAVAGE REACTION OF α-AMINOKETONES

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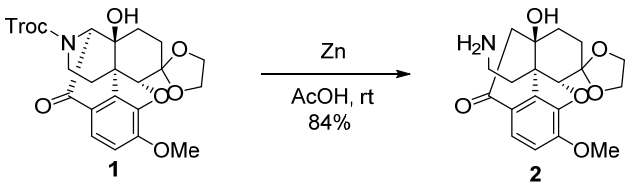
Abstract – Scope and limitation of the reductive cleavage reaction of α-aminoketone systems with zinc-acetic acid are described. The carbon-nitrogen bond cleavage reaction was applicable to a wide range of α-aminoalkyl aryl ketones possessing various substituents on the aromatic ring. In contrast, α-aminoalkyl alkyl ketones with protons at the α'-position or α-aminoesters were sluggish to the carbon-nitrogen cleavage reaction.

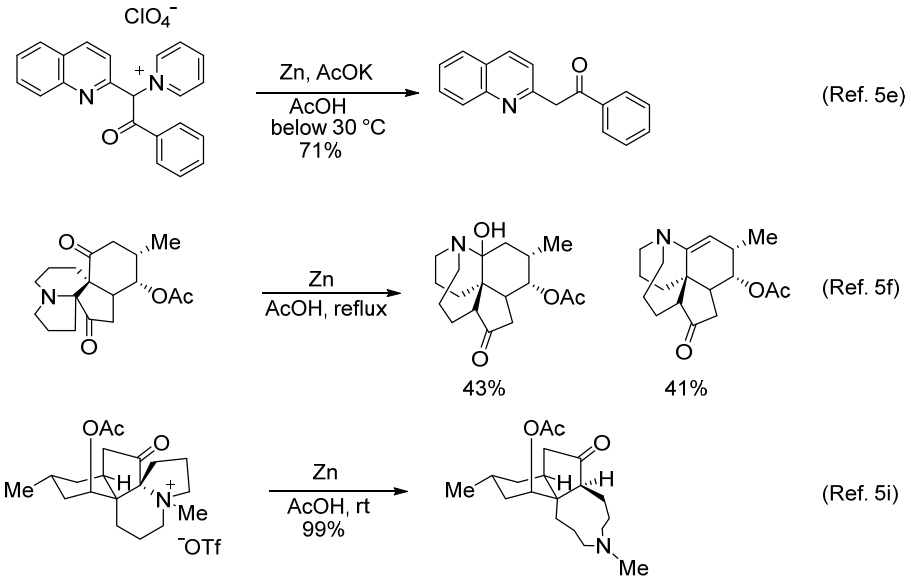
INTRODUCTION

We have developed ligands selective for the opioid receptor types with a 4,5-epoxymorphinan structure[1] and have reported many novel reactions using 4,5-epoxymorphinan derivatives.[2] In the course of our investigations, we found that attempts to remove the Troc (2,2,2-trichloroethoxycarbonyl) protecting group in the presence of zinc and acetic acid led to cleavage of the carbon-nitrogen bond of **1** (Scheme 1). Although carbon-nitrogen cleavage reactions of α-aminoketones have been reported previously,[3-6] many reactions included a ring-opening reaction of an aziridine ring.[3] Therefore, the scope of such reactions appeared to be limited. Among the reported methods, deamination reactions of α-aminoketones by samarium diiodide have been intensively investigated and utilized in a wide range of compounds.[3k,l,o,4] Although carbon-nitrogen cleavage reactions using zinc as a reducing agent have also been reported,[5] in almost all such reports the substrates possessed quaternary ammonium[5i] or pyridinium[5a-e] moieties or strained polycyclic system (Scheme 2).[5f,i] Therefore, we attempted to clarify the scope and limitation of

the reductive cleavage reaction of α-aminoketones with zinc-acetic acid. Herein, we report the scope and limitation of the reaction.



Scheme 1. Cleavage reaction of a carbon-nitrogen bond of **1**

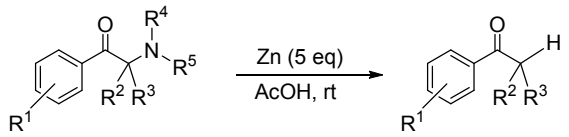


Scheme 2. Representative examples of reductive cleavage reactions of the carbon-nitrogen bond in the presence of zinc and acetic acid. Attempted ring-opening reaction of the corresponding tertiary cyclic amine furnished poor yield.[5i]

RESULTS AND DISCUSSION

We attempted the cleavage of carbon-nitrogen bonds of various α-aminoketones **3** in the presence of zinc and acetic acid (Table 1). The reactions of unsubstituted aryl ketones **3a** and **3b** and aryl ketones **3c** and **3d** with electron donating group smoothly proceeded to give the corresponding acetophenone derivatives **4a-d** in good to excellent yield (entries 1-4). The position of the substituent had little effect on the isolated yields (entries 4, 7, and 8). In contrast to the electron donating substituents, some electron withdrawing groups tended to decrease the isolated yields (entries 5 and 6) except for carbomethoxy group (entry 9). Although **3l** required reflux reaction conditions, the carbon-nitrogen cleavage reaction was tolerated by the substituents on the nitrogen (entries 10-15). In the reaction of **3n**, dibenzylamine was

Table 1. Reductive cleavage of the carbon-nitrogen bonds of various ketones **3**



3a-u **4a-u**

Entry	SM	R^1	R^2	R^3	R^4	R^5	Reaction Time (h)	Yield (%)
1	**3a**	H	H	H	H	H	1.0	80
2	**3b**	H	H	H	Me	Me	1.0	85
3	**3c**	*p*-Me	H	H	Me	Me	1.0	94
4	**3d**	*p*-OMe	H	H	Me	Me	1.5	78
5	**3e**	*p*-F	H	H	Me	Me	1.0	68
6	**3f**	*p*-CF_3	H	H	Me	Me	1.0	33
7	**3g**	*m*-OMe	H	H	Me	Me	1.0	71
8	**3h**	*o*-OMe	H	H	Me	Me	1.0	68
9	**3i**	*p*-CO_2Me	H	H	-(CH_2)-O-(CH_2)-		1.0	86
10	**3j**	*p*-OMe	H	H	H	H	1.0	86
11	**3k**	*p*-OMe	H	H	H	Me	3.0	69
12[a]	**3l**	*p*-OMe	H	H	H	Ph	1.0	75
13	**3m**	*p*-OMe	H	H	Me	Bn	2.0	75
14	**3n**	*p*-OMe	H	H	Bn	Bn	1.0	84
15	**3o**	*p*-OMe	H	H	-(CH_2)-O-(CH_2)-		1.0	92
16[a]	**3p**	*p*-OMe	H	H	H	Ac	24	NR[b]
17[a]	**3q**	*p*-OMe	H	H	H	Cbz	24	NR[b]
18	**3r**	*p*-OMe	H	H	H	Boc	24	NR[b]
19[a]	**3r**	*p*-OMe	H	H	H	Boc	1.0	65
20[c]	**3r**	*p*-OMe	H	H	H	Boc	1.0	67
21	**3s**	*p*-OMe	H	Me	Me	Me	1.0	77
22	**3t**	H	H	Ph	-(CH_2)-O-(CH_2)-		1.0	92
23[d]	**3u**	*p*-morpholino	Et	Bn	Me	Me	1.0	99
24[a]	**3u**	*p*-morpholino	Et	Bn	Me	Me	2.0	96

[a] A reaction was carried out at the reflux temperature of AcOH.
[b] NR: no reaction.
[c] Trifluoroacetic acid was used instead of acetic acid.
[d] A reaction was carried out using 20 eq. of zinc.[7]

isolated in 90% yield along with the acetophenone derivative **4n**. It is noteworthy that the reactions of ketones **3p-r** with the acetyl, Cbz, or Boc group as an *N*-substituent did not proceed (entries 16-18) and that the reaction of **3p** and **3q** did not proceed, furnishing only starting material even under the reflux reaction conditions (entries 16 and 17). On the other hand, the elevation of the reaction temperature to the boiling point and the use of trifluoroacetic acid instead of acetic acid facilitated the cleavage of the carbon-nitrogen bond of **3r** to provide **4r** in 65% and 67% yield, respectively (entries 19 and 20). The results of entries 18 and 19 indicated that the cleavage reaction of the carbon-nitrogen bond could proceed

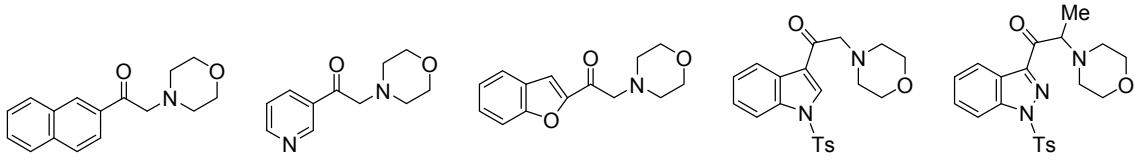
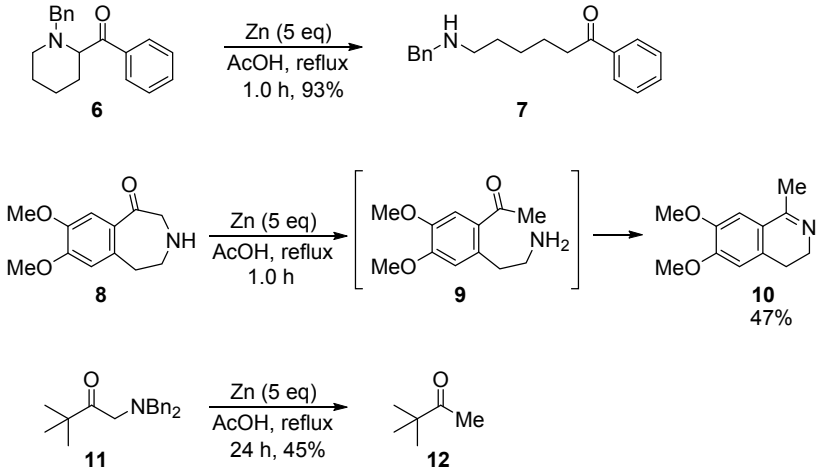


Figure 1. Structures of examined aryl or heteroaryl ketones **5**. The reaction time and the isolated yield are indicated in the parentheses. The asterisk "*" indicates the yield of 1-(pyridin-3-yl)ethan-1-ol.



Scheme 3. Reactions of benzoylpiperidine **6**, cyclic ketone **8**, and *t*-butyl ketone **11**

after the deprotection of the nitrogen by removal of the Boc group. Taken together, a basic α-amino group was essential in the reaction. Under the reaction conditions, the conversion of the amino group into the ammonium functionality, which is a better leaving group than an amino group, would be important for the reaction to progress. In the case of 4,5-epoxymorphinan derivative **1** (Scheme 1), the Troc group would be firstly removed under the reaction conditions and then the carbon-nitrogen bond would be cleaved. The carbon-nitrogen cleavage reaction was applicable to the ketones **3s**-**u** possessing substituents at the α-position (entries 21-24), however **3u** with the quaternary carbon center at the α-position required a large amount of zinc (entry 23) or reflux reaction conditions (entry 24).

We next examined the reaction of other aryl or heteroaryl ketones **5** (Figure 1). The reaction of **5** provided the corresponding ketones in moderate to good yields except for the case of **5b**. The treatment of **5b** with zinc and acetic acid gave 1-(pyridin-3-yl)ethan-1-ol in 54% yield. In the reaction of **5e**, the detosylation was observed to proceed concomitantly with the carbon-nitrogen bond cleavage. The reductive cleavage reaction of the carbon-nitrogen bond was also applicable to benzoylpiperidine **6**, cyclic ketone **8**, and *t*-butyl ketone **11**, although reflux reaction conditions were required (Scheme 3). After the cleavage of the carbon-nitrogen bond of **8**, the reaction further proceeded to provide imine **10** in 47% yield. Contrary to

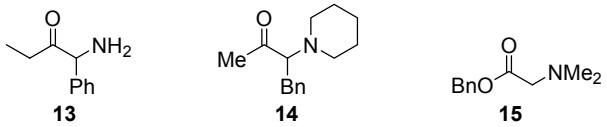
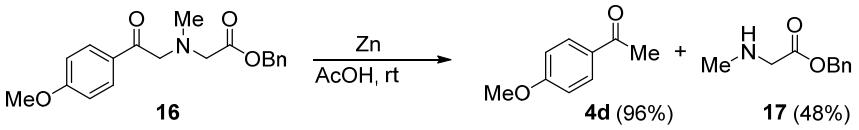


Figure 2. Structures of the investigated α-aminoalkyl alkyl ketones **13** and **14**, and α-aminoester **15**

the case of aryl or *t*-butyl ketones lacking protons at the α'-position, the reaction of alkyl ketones **13** and **14** with protons at the α'-position (Figure 2) were sluggish to the carbon-nitrogen cleavage reaction. The reaction of **13** or **14** in the presence of five equivalents of zinc at room temperature furnished the recovery of the starting ketones. The elevation of the reaction temperature to 118 ºC (a reflux temperature) decomposed the starting materials. Although the treatment of **14** with a large excess of zinc at room temperature for 12 hours afforded the corresponding ketone in 77% yield, the same treatment of **13** resulted in only a trace of the corresponding ketone with the bulk of the product being unreacted **13**, as observed by TLC analysis. Taking into account these results and the outcomes of α-acylamino or α-carbamoylketones (Table 1, entries 16-18), the progress of the reaction was critically affected by the α-amino functionality. The electron-withdrawing group generally lowers the energy of the LUMO of the carbonyl π bond and activates the carbonyl group for the nucleophilic or one-electron attack.[8] A strong electron withdrawing property of the quaternary ammonium group such as the methiodide[5i] or pyridinum[5e] group or a protonated amino group would sufficiently activate the carbonyl group, as compared with the acylamino or carbamoyl group.[9]

The α-aminoester **15** (Figure 2) also resisted the progress of the carbon-nitrogen cleavage reaction at room temperature. The treatment of **15** with zinc and acetic acid even at reflux temperature for 12 h gave a mixture of benzyl acetate and the starting ester **15** in 51% and 46% yield, respectively. This result was a clear contrast to that using samarium diiodide, which is known to cleave the carbon-nitrogen bond not only of α-aminoketones but also of α-aminoesters.[3l,4a,e] This result also suggests that the treatment with zinc-acetic acid can selectively cleave the carbon-nitrogen bond of α-aminoketones in the presence of α-aminoesters. Indeed, the treatment of compound **16**, which has α-aminoketone and α-aminoester moieties in a molecule, with zinc-acetic acid provided the corresponding ketone **4d** and α-aminoester **17** in 96% and 48% yield, respectively (Scheme 4). Benzyl acetate was not detected in the reaction mixture by TLC analysis.

In conclusion, we examined the scope and limitation of the zinc-acetic acid promoted reductive carbon-nitrogen bond cleavage reaction of α-aminoketones. The reaction was applicable to a wide range



Scheme 4. Reaction of compound **16**

of α-aminoalkyl aryl ketones possessing various substituents on the aromatic ring, α-position, or α-amino group. In the reaction, a basic α-amino group, which was converted into a protonated ammonium group under the acidic reaction conditions, would be essential because protection of an α-amino group by an acyl or alkoxycarbonyl group prevented the reaction from proceeding. On the other hand, α-aminoalkyl alkyl ketones with protons at the α'-position or α-aminoesters were sluggish to the carbon-nitrogen cleavage reaction.

EXPERIMENTAL

Nuclear magnetic resonance (NMR) spectra were recorded on an Agilent Technologies Mercury-300 or Agilent Technologies NMR System-400. Chemical shifts were reported as δ values (ppm) related to tetramethylsilane (TMS). Mass spectra (MS) were obtained on a JMS-100LP instrument by applying an electrospray ionization (ESI) or fast atom bombardment (FAB) method. Infrared (IR) spectra were recorded on a JASCO FT/IR-460Plus. The progress of the reaction was determined on Merck Silica Gel Art. 5715 (TLC). Column chromatographies were carried out using Kanto Silica Gel 60 N (40–100 μm). Zinc powder was used after the activation by a general procedure.[10]

Registry numbers of the described products are following; **3a** (613-89-8), **3b** (3319-03-7), **3c** (80354-58-1), **3d** (53250-07-0), **3e** (709-23-9), **3f** (1266166-47-5), **3g** (99985-55-4), **3h** (31543-50-7), **3i** (1266216-21-0), **3j·HCl** (3883-94-1), **3k·HCl** (29705-80-4), **3l** (6037-64-5), **3m** (108976-12-1), **3n** (140420-07-1), **3o** (20099-92-7), **3p** (3755-89-3), **3q** (178888-27-2), **3r** (778617-61-1), **3s** (91564-39-5), **3t** (794-06-9), **3u** (119313-12-1), **4a** (98-86-2), **4c** (122-00-9), **4d** (100-06-1), **4e** (403-42-9), **4f** (709-63-7), **4g** (586-37-8), **4h** (579-74-8), **4i** (3609-53-8), **4t** (451-40-1), **5a** (119270-39-2), **5b** (46440-89-5), **5c** (106272-36-0), **6** (729553-31-5), **8** (1416064-72-6), **10** (4721-98-6), **11** (1338492-73-1), **12** (75-97-8), **13·HCl** (19389-43-6), **14** (19134-47-5), **15** (30379-57-8), **17** (54384-05-3), 1-(naphthalen-2-yl)ethan-1-one (93-08-3), 1-(pyridin-3-yl)ethan-1-ol (4754-27-2), 1-(benzofuran-2-yl)ethan-1-one (1646-26-0), and benzyl acetate (140-11-4).

General procedure of reductive carbon-nitrogen bond cleavage reaction

To a solution of an α-aminoketone in acetic acid (2 mL) was added zinc powder (5.0 mmol) and stirred at

the indicated temperature for the indicated time. After a filtration, the reaction mixture was poured into a saturated aqueous solution of sodium hydrogen carbonate and extracted with Et_2O. The combined organic layers were washed with brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give the corresponding ketone in the indicated yield.

2-Benzyl-1-(4-morpholinophenyl)butan-1-one (4u)

IR (neat, cm^{-1}): 3083, 3460, 3026, 2962, 2926, 2895, 2856, 1661, 1598, 1567, 1554, 1517, 1495, 1451, 1427, 1383, 1304, 1267, 1223, 1193, 1182, 1123, 1115, 1070, 1051, 1029, 1013, 930, 832, 804, 757, 741, 700, 647. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.86 (t, J = 7.4 Hz, 3H), 1.66-1.50 (m, 1H), 1.88-1.70 (m, 1H), 2.74 (dd, J = 6.8, 13.7 Hz, 1H), 3.08 (dd, J = 7.4, 13.7 Hz, 1H), 3.28 (t, J = 5.0 Hz, 4H), 3.64-3.55 (m, 1H), 3.84 (t, J = 5.0 Hz, 4H), 6.83 (d, J = 9.0 Hz, 2H), 7.26-7.10 (m, 5H), 7.84 (d, J = 7.2 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 12.0, 25.7, 38.2, 202.1, 154.3, 140.6, 130.5, 129.3, 128.6, 128.5, 126.2, 113.5, 66.8, 49.2, 47.7, 38.2, 25.7, 12.0. HR-MS (ESI): $[M+Na]^+$ Calcd for $C_{21}H_{25}NNaO_2$: 346.1783. Found: 346.1792.

1-(1*H*-Indazol-3-yl)propan-1-one

IR (KBr, cm^{-1}): 3292, 2929, 1724, 1677, 1465, 1380, 1287, 1179, 1129, 1073, 936, 897, 748, 424, 408. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.30 (t, J = 7.4 Hz, 3H), 3.23 (q, J = 7.4 Hz, 2H), 7.31-7.38 (m, 1H), 7.42-7.49 (m, 1H), 7.55 (d, J = 8.4 Hz, 1H), 8.41 (d, J = 8.1 Hz, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 8.2, 32.3, 109.8, 122.8, 123.7, 127.1, 127.5, 130.2, 141.1, 198.1. HR-MS (EI): $[M]^+$ Calcd for $C_{10}H_{10}N_2O$: 174.2030. Found: 174.0795.

Preparation of 2-morpholino-1-(1-tosyl-1*H*-indol-3-yl)ethanone (5d)

To a solution of 1-(1-tosyl-1*H*-indol-3-yl)ethanone[11] (387.2 mg, 1.23 mmol) in MeCN (5 mL) were added iodobenzene (27 μL, 0.25 mmol), *p*-toluenesulfonic acid monohydrate (293 mg, 1.54 mmol), and *m*CPBA (65%, 409 mg, 1.54 mmol), and stirred at 50 ºC for 12 h.[12] The reaction mixture was poured into a saturated aqueous sodium hydrogen carbonate solution and extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure to give a crude product (590 mg) as a brown amorphous solid. To a solution of the crude product (590 mg) in THF (3 mL) was added morpholine (1 mL, 11.2 mmol) and the mixture was stirred at rt for 12 h. The reaction mixture was poured into a 4 M aqueous solution of sodium hydroxide and extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate,

and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give **5d** (98 mg, 20%) as a brown amorphous solid.

IR (neat, cm^{-1}): 2854, 1661, 1596, 1535, 1445, 1379, 1296, 1173, 1135, 1117, 1089, 984, 942, 914, 866, 813, 751, 705, 664, 572. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.37 (s, 3H), 2.61 (t, J = 4.5 Hz, 4H), 3.66 (s, 2H), 3.78 (t, J = 4.7 Hz, 4H), 7.24-7.40 (m, 4H), 7.85 (d, J = 8.4 Hz, 2H), 7.94 (d, J = 7.4 Hz, 1H), 8.31-8.35 (m, 1H), 8.66 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 22.2, 54.4, 67.4, 67.5, 113.6, 119.9, 123.6, 125.5, 126.3, 127.7, 127.9, 128.4, 130.4, 130.8, 133.3, 135.07, 135.13, 146.6, 193.5. HR-MS (ESI): $[M+Na]^+$ Calcd for $C_{21}H_{22}N_2NaO_4S$: 421.1198. Found: 421.1233.

Preparation of 2-morpholino-1-(1-tosyl-1*H*-indazol-3-yl)propan-1-one (5e)

Under an Ar atmosphere, to a solution of *N*-methoxy-*N*-methyl-1*H*-indazole-3-carboxamide[13] (313 mg, 1.5 mmol) in THF (5 mL) was added a prepared 1.14 M solution of ethylmagnesium bromide in Et_2O (6.6 mL, 7.5 mmol) at 0 ºC. The mixture was stirred at the same temperature for 80 min, and further stirred at rt for 12 h. The reaction mixture was poured into a 2 M hydrochloric acid and the aqueous layer was washed with EtOAc. The pH of the aqueous layer was adjusted to basic by a 4 M aqueous solution of sodium hydroxide and extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give 1-(1*H*-indazol-3-yl)propan-1-one (228 mg, 87%) as a white amorphous solid. To a solution of 1-(1*H*-indazol-3-yl)propan-1-one (487 mg, 2.8 mmol) in THF (5 mL) were added tosyl chloride (800 mg, 4.2 mmol) and triethylamine (1.9 mL, 14 mmol), and the mixture was stirred at rt for 12 h. The reaction mixture was poured into a 4 M aqueous solution of sodium hydroxide and extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give 1-(1-tosyl-1*H*-indazol-3-yl)propan-1-one (824 mg, 90%) as a white amorphous solid.

IR (KBr, cm^{-1}): 2982, 2940, 1933, 1693, 1594, 1491, 1476, 1458, 1413, 1380, 1332, 1296, 1253, 1192, 1175, 1128, 1090, 1015, 993, 910, 818, 750, 703, 680, 657, 580, 565, 539, 492, 420. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.23 (t, J = 7.3 Hz, 3H), 2.38 (s, 3H), 3.21 (q, J = 7.3 Hz, 2H), 7.28 (d, J = 4.0 Hz, 2H), 7.42 (t, J = 7.6 Hz, 1H), 7.58 (t, J = 7.9 Hz, 1H), 7.92 (d, J = 8.4 Hz, 2H), 8.21 (d, J = 8.5 Hz, 1H), 8.32 (d, J = 8.1 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 8.3, 22.3, 33.2, 113.5, 123.8, 124.1, 126.2, 128.3, 130.1, 130.6, 134.8, 141.9, 146.6, 147.5, 198.4. HR-MS (ESI): $[M+Na]^+$ Calcd for $C_{17}H_{16}N_2NaO_3S$: 351.0779. Found: 351.0756.

To a solution of 1-(1-tosyl-1*H*-indazol-3-yl)propan-1-one (560 mg, 1.7 mmol) in MeCN (5 mL) were

added iodobenzene (48.6 μL, 0.44 mmol), *p*-toluenesulfonic acid monohydrate (518 mg, 2.7 mmol), and *m*CPBA (65%, 723 mg, 2.7 mmol) and the mixture was stirred at 50 ºC for 12 h.[12] The reaction mixture was poured into a saturated aqueous solution of sodium hydrogen carbonate and extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give 1-oxo-1-(1-tosyl-1*H*-indazol-3-yl)propan-2-yl 4-methylbenzenesulfonate (550 mg, 65%) as a white amorphous solid.

IR (KBr, cm^{-1}): 3388, 1706, 1596, 1476, 1392, 1366, 1295, 1251, 1193, 1178, 1129, 1085, 1000, 936, 893, 815, 756, 705, 689, 663, 582, 565, 550, 539. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.61 (d, J = 6.9 Hz, 3H), 2.33 (s, 3H), 2.39 (s, 3H), 6.11 (q, J = 7.0 Hz, 1H), 7.19 (d, J = 8.0 Hz, 2H), 7.33 (d, J = 8.0 Hz, 2H), 7.39-7.46 (m, 1H), 7.57-7.64 (m, 1H), 7.74 (d, J = 8.4 Hz, 2H), 7.96 (d, J = 8.4 Hz, 2H), 8.17-8.26 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 19.3, 22.1, 22.3, 77.2, 113.6, 123.5, 124.1, 126.6, 128.5, 128.7, 130.3, 130.5, 130.8, 133.9, 134.5, 141.6, 144.6, 145.5, 147.1, 191.0. HR-MS (ESI): $[M+Na]^+$ Calcd for $C_{24}H_{22}N_2NaO_6S_2$: 521.0817. Found: 521.0769.

To a solution of 1-oxo-1-(1-tosyl-1*H*-indazol-3-yl)propan-2-yl 4-methylbenzenesulfonate (140 mg, 0.28 mmol) in THF (3 mL) was added morpholine (0.5 mL, 5.6 mmol) and the mixture was stirred at rt for 12 h. The reaction mixture was poured into distillated water and extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give **5e** (99 mg, 85%) as a brown amorphous solid.

IR (neat, cm^{-1}): 2855, 1692, 1596, 1474, 1386, 1292, 1253, 1193, 1179, 1118, 1078, 1000, 957, 901, 853, 814, 754, 704, 685, 663, 580, 564, 538. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.33 (d, J = 7.0 Hz, 3H), 2.38 (s, 3H), 2.52-2.69 (m, 4H), 3.57-3.70 (m, 4H), 4.63 (q, J = 7.0 Hz, 1H), 7.28 (d, J = 8.4 Hz, 2H), 7.41-7.47 (m, 1H), 7.57-7.66 (m, 1H), 7.91 (d, J = 8.5 Hz, 2H), 8.23 (d, J = 8.6 Hz, 1H), 8.32 (d, J = 8.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 13.4, 22.3, 50.7, 63.4, 67.9, 113.6, 123.8, 124.3, 126.4, 128.4, 130.6, 134.8, 141.9, 146.7, 197.2. HR-MS (ESI): $[M+Na]^+$ Calcd for $C_{21}H_{23}N_3NaO_4S_1$: 436.1307. Found: 436.1312.

Reaction of 6

To a solution of **6**[14] (9.3 mg, 0.033 mmol) in acetic acid (3 mL) was added zinc powder (33 mg, 0.50 mmol) and the mixture was stirred for 1 h with refluxing. After a filtration, the reaction mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give **7** (8.6 mg, 93%) as a brown amorphous solid.

IR (KBr, cm^{-1}): 3905, 3855, 3842, 3822, 3752, 3737, 3713, 3691, 3678, 3651, 3400, 3061, 3029, 2944, 2801, 2572, 2411, 1813, 1736, 1689,1655, 1579, 1498, 1449, 1435, 1410. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.33-1.47 (m, 2H), 1.57-1.80 (m, 4H), 2.70 (t, J = 7.6 Hz, 2H), 2.95 (t, J = 7.3 Hz, 2H), 3.87 (s, 2H), 7.22-7.63 (m, 8H), 7.94 (d, J = 7.4 Hz, 2H). ^{13}C NMR (100 MHz $CDCl_3$) δ: 23.8, 26.7, 28.1, 38.3, 47.6, 52.4, 127.9, 128.0, 128.6, 128.7, 128.9, 133.0, 136.4, 137.0, 200.2. HR-MS (ESI): $[M+H]^+$ Calcd for $C_{19}H_{24}NO$: 282.1858. Found: 282.1869.

Reaction of 8

To a solution of **8**[15] (74 mg, 0.29 mmol) in acetic acid (3 mL) was added zinc powder (93 mg, 1.4 mmol) and the mixture was stirred for 1 h with refluxing. After a filtration, the reaction mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography and preparative TLC to give **10** (27 mg, 47%) as a brown amorphous solid. ^{1}H NMR data of compound **10** were identical to those of the literature.[16]

Reaction of 14

To a solution of **14** (32.6 mg, 0.14 mmol) in acetic acid (2 mL) was added zinc powder (622 mg, 9.52 mmol) and the mixture was stirred at rt for 12 h. After a filtration, the reaction mixture was poured into a 4M aqueous solution of sodium hydroxide and extracted with Et_2O. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give 4-phenylbutan-2-one (15.9 mg, 77%) as a pale yellow oil.

Reaction of 15

To a solution of **15** (116 mg, 0.6 mmol) in acetic acid (3 mL) was added zinc powder (196 mg, 3.0 mmol) and the mixture was stirred for 12 h with refluxing. After a filtration, the reaction mixture was poured into a 4 M aqueous solution of sodium hydroxide and extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give benzyl acetate (46 mg, 51%) as a colorless oil and recovered **15** (54 mg, 46%).

Preparation of benzyl 2-((2-(4-methoxyphenyl)-2-oxoethyl)(methyl)amino)acetate (16)

To a solution of benzyl 2-(methylamino)acetate **17** (81 mg, 0.45 mmol) in THF (2 mL) were added 4'-methoxyphenacyl bromide (113 mg, 0.50 mmol) and triethylamine (0.19 mL, 1.35 mmol) at 0 ºC and the mixture was stirred at rt for 4 h. The reaction mixture was poured into a saturated aqueous solution of

sodium hydrogen carbonate and extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by preparative TLC to give **16** (47 mg, 32%) as a yellow oil.

IR (neat, cm^{-1}): 2937, 1742, 1681, 1600, 1511, 1455, 1257, 1171, 1027, 834, 698, 440, 408. ^1H NMR (400 MHz, $CDCl_3$) δ: 2.56 (s, 3H), 3.61(s, 2H), 3.86 (s, 3H), 4.10 (s, 2H), 5.17(s, 2H), 6.89-6.94 (m, 2H), 7.31-7.42 (m, 5H), 7.95-8.05 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 42.5, 55.5, 57.5, 61.6, 66.3, 113.7, 128.3, 128.6, 128.8, 130.4, 132.1, 135.6, 163.6, 170.7, 195.5. HR-MS (FAB): $[M+H]^+$ Calcd for $C_{19}H_{22}NO_4$: 328.38. Found: 328.1545.

Reaction of 16

To a solution of **16** (103 mg, 0.31 mmol) in acetic acid (3 mL) was added zinc powder (405 mg, 6.2 mmol) and the mixture was stirred at rt. After 1 h with stirring, benzyl acetate was not detected in the reaction mixture by TLC analysis. After a filtration, the reaction mixture was concentrated under reduced pressure. To the residue was added a saturated aqueous solution of potassium carbonate and extracted with EtOAc.The residue was purified by silica gel column chromatography to give **4d** (45 mg, 96%) as a brown oil and **17** (27 mg, 48%) as a brown oil.

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