The highly chemoselective transfer hydrogenation of the carbon–carbon double bond of conjugated nitroalkenes by a rhodium complex

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ABSTRACT

Chemoselective transfer hydrogenation of conjugated nitroalkenes catalyzed by [RhCl$_2$Cp*]$_2$–diamine complex (Cp*=η^5-C$_5$Me$_5$) using HCOOH/Et$_3$N (5:2) (TEAF) as a hydrogen source was realized. A variety of nitrostyrenes, β-methyl nitrostyrenes, and 3-methyl-4-nitro-5-alkenyl-isoxazoles were reduced smoothly in good to excellent yields in short reaction time. Other functional groups are inert under the reaction conditions.

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1. Introduction

Nitroalkanes have been proven to be valuable building blocks and intermediates in organic synthesis due to their easy conversion into versatile functionalities such as amines, carbonyl compounds, or denitrated compounds.[1,2] Moreover, they are very important precursors for carbon–carbon bond formation.[3] Selective reduction of conjugated nitroalkenes represents one of the most attractive routes for synthesis of nitroalkanes. Thus, considerable efforts have been made in this area and numerous reduction methodologies, such as hydride catalysis,[4,5] organocatalysis,[6,7] and biocatalysis[8] have been reported for this purpose.

On the other hand, transfer hydrogenation is a noteworthy method because of its simplification and safety. Recently, Noyori has achieved satisfactory results in transfer hydrogenation of ketones and imines by using chiral TsDPEN–Ru(II) [TsDPEN=N-(p-toluenesulfonyl)-1,2-diphenylethylenediamine] as catalysts and proposed a concerted mechanism.[9,10] In the previous studies, the α-nitro activated carbon–carbon or carbon–oxygen bond[11] and β,β-disubstituted nitroalkenes[12] have been also successfully reduced with this metal-to-ligand bifunctional catalyst. Katsumi Nanjo and

Minoru Sekiya[13] have reported the selective reduction of conjugated nitroolefins by using the triethylamine–formic acid azeotrope (TEAF) in N,N-dimethylformamide at 100–135 °C. However, the unsubstituted β-nitrostyrene failed to undergo the reduction due to its polymerization in such basic medium.

Herein, we reported a new method with high specific chemoselectivity, excellent substrates compatibility, and high catalytic efficiency for the transfer hydrogenation of the carbon–carbon double bond of conjugated nitroalkenes catalyzed by rhodium–diamine complex using triethylamine–formic acid azeotrope as hydrogen source.

2. Results and discussion

For exploratory experiments the unsubstituted β-nitrostyrene **1a** was used as a representative substrate. At first, we screened the influence of different transition metal precursors on the reaction rate. Generally, the precatalyst was generated in situ by treatment TsEN [TsEN=N-(p-toluenesulfonyl)-ethylenediamine] with the metal precursor in 1 mL methanol at 70 °C for 1 h. As summarized in the Table 1, with 1 mol% catalyst, all reactions could work smoothly. Poor yield of 15% could be obtained in the presence of [RuCl$_2$(p-cymene)]$_2$ (entry 1), while 87% yield could be gotten when [IrCl$_2$Cp*]$_2$ was employed as the metal precursor (entry 2).

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[RhCl$_2$Cp*]$_2$ complex proved to be the most effective catalyst in view of the reactivity, and using rhodium as metal source the reaction could be finished in 10 min with excellent yield over 99% at 28 °C. On the other hand, in the absence of TsEN ligand, the catalytic activity declined sharply with the corresponding decrease of the reduction product (entry 4). Therefore, [RhCl$_2$Cp*]$_2$ was chosen as the metal source along with the TsEN ligand for further investigation.

in Table 3, various reagents **1** with electron-rich and electron-poor substitution patterns on the benzene ring were equally good substrates (Table 3, entries 2–15, and entries 18, 19). We also verified that the more sterically demanding substrates **1l–o** and **1t** were viable for the transfer hydrogenation (Table 3, entry 12–15, and entry 20). Particularly, Compound **1p** containing hetero-aromatic ring also gave its corresponding product **2p** with good yield (Table 3, entry 16). More interestingly, the method was compatible with

Table 1
Transfer hydrogenation of β-nitrostyrene with different metal precursors[a]
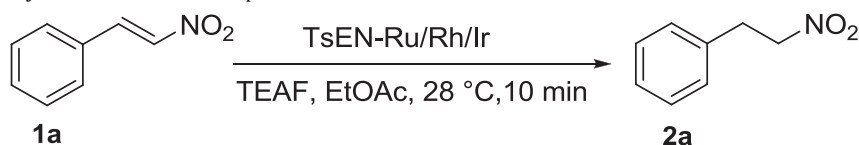
Entry	Metal	S/C	TEAF (mL)	T (°C)	Yield[b] (%)
1	[RuCl$_2$(*p*-cymene)]$_2$	100	0.2	28	15
2	[IrCl$_2$Cp*]$_2$	100	0.2	28	87
3	[RhCl$_2$Cp*]$_2$	100	0.2	28	>99
4[c]	[RhCl$_2$Cp*]$_2$	100	0.2	28	4.0

[a] Unless otherwise noted, the reaction was performed with 0.4 mmol of **1a**.
[b] Determined by ^{1}H NMR of the crude product, using dimethyl malonate as internal standard.
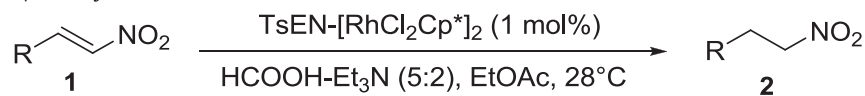[c] No TsEN was used.

Having identified the best catalytic complex, our attention focused on the optimization of the reaction conditions. It is well known that the type of solvent is an important parameter for obtaining reasonable quantities of product in transfer hydrogenations. Thus, we investigated frequently used solvents (Table 2). Obviously, it was revealed that the reaction could proceed in various solvents except water (Table 2). The failure of β-nitrostyrene to undergo the reduction in water was attributed to its indissolubility (Table 2, entry 1). Using DMF as solvent, compound **2a** was obtained smoothly in high to 93% yield (Table 2, entry 6). Among the solvents surveyed, EtOAc was the best suitable solvent for this transfer hydrogenation reaction, in which over 99% yield could be obtained (Table 2, entry 7).

1u in which R is represented by a cyclopropyl, with 91% yield (Table 3, entry 21). It was also worth noting that the halogen substituents were tolerant and the substrates could be reduced cleanly with good to excellent yields in a short time (Table 3, entries 5–7, entries 13, 14, entry 10, and entry 19).

Further experiments included an examination of the rhodium–TsEN catalytic reduction of a series of β-methyl nitrostyrenes. Compared with β-nitrostyrenes, these substrates obviously suffered from more steric hindrance because their β-positions were disubstituted. Nevertheless, as summarized in Table 4, the β-methyl nitrostyrenes bearing electron-donating and electron-withdrawing at the benzene ring were all successfully reduced in good yields (Table 4, entries 1–11). Moreover, com-

Table 2
Transfer hydrogenation of β-nitrostyrene in different solvents[a]
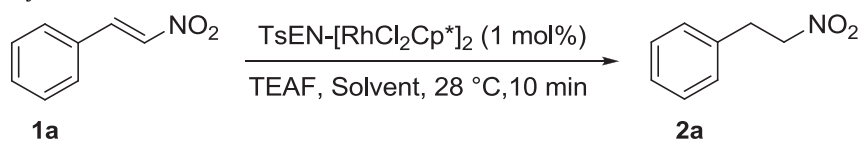
Entry	V_s (1 mL)	S/C	TEAF (mL)	T (°C)	Yield[b] (%)
1	H$_2$O	100	0.2	28	0
2	CH$_3$OH	100	0.2	28	3.5
3	Toluene	100	0.2	28	21
4	CH$_2$Cl$_2$	100	0.2	28	22
5	THF	100	0.2	28	57
6	DMF	100	0.2	28	93
7	EtOAc	100	0.2	28	>99

[a] Unless otherwise noted, the reaction was performed with 0.4 mmol of **1a**.
[b] Determined by ^{1}H NMR of the crude product, using dimethyl malonate as internal standard.
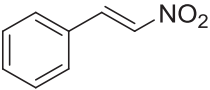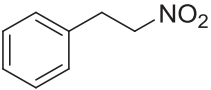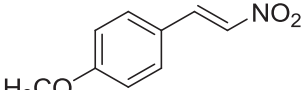
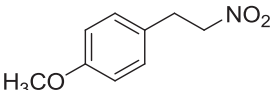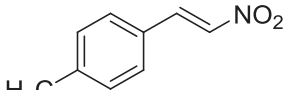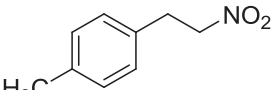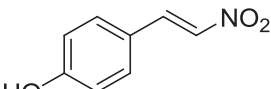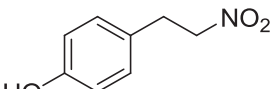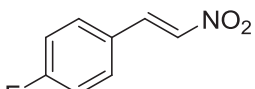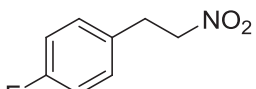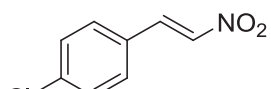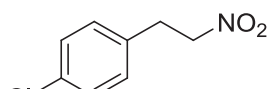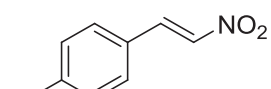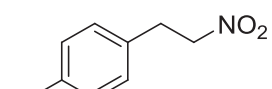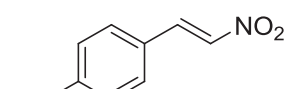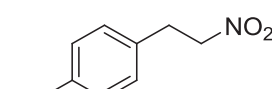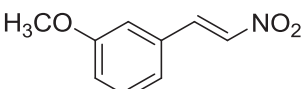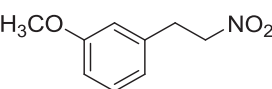In order to demonstrate the usefulness of our method, the rhodium–TsEN catalyst was tested in the selective reduction of the carbon–carbon double bond in varieties of conjugated nitroalkenes.

First, a wide range of β-nitrostyrenes were prepared[8d,14] and we then proceeded to examine the scope of these substrates. As shown

pound **3l**, in which R was substituted with furan group, was also converted to the corresponding nitroalkane **4l** in 91% yield (Table 4, entry 12).

Additionally, it is known that heterocycles play an important role in pharmaceutical science. Among the most widely employed nitrogen-containing five-membered rings are the isoxazoles.[15]

Table 3
Transfer hydrogenation of various β-nitrostyrenes[a]

$$R\diagup\diagdown NO_2 \quad \xrightarrow[\text{HCOOH-Et}_3\text{N (5:2), EtOAc, 28°C}]{\text{TsEN-[RhCl}_2\text{Cp*]}_2 \text{ (1 mol%)}} \quad R\diagup\diagdown NO_2$$

Entry	Substrate	Product	Time	Yield[b] (%)
1	**1a**	**2a**	10 min	>99
2	**1b**	**2b**	2 h	90
3	**1c**	**2c**	4 h	86
4	**1d**	**2d**	2 h	91
5	**1e**	**2e**	1 h	95
6	**1f**	**2f**	2 h	98
7	**1g**	**2g**	1 h	90
8	**1h**	**2h**	2 h	61
9	**1i**	**2i**	2 h	88

(continued on next page)

Table 3 (*continued*)
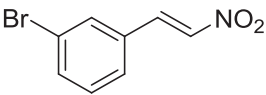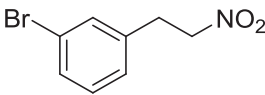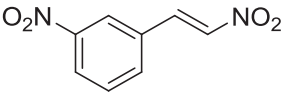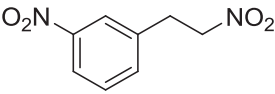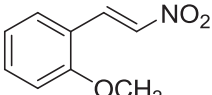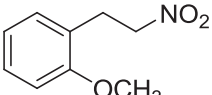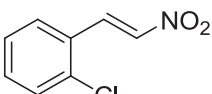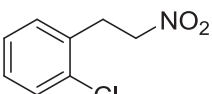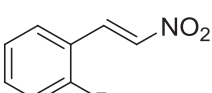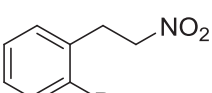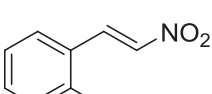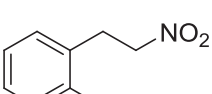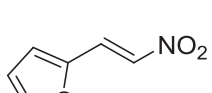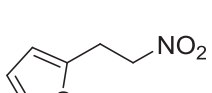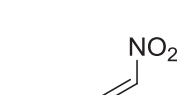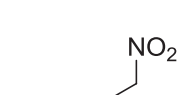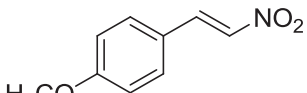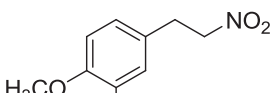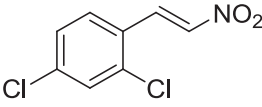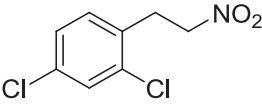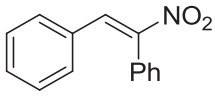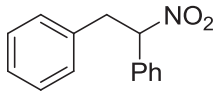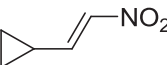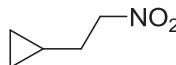
Entry	Substrate	Product	Time	Yield[b] (%)
10	**1j**	**2j**	15 h	88
11	**1k**	**2k**	1 h	97
12	**1l**	**2l**	1 h	88
13	**1m**	**2m**	1 h	94
14	**1n**	**2n**	1 h	94
15	**1o**	**2o**	1 h	93
16	**1p**	**2p**	3 h	84
17	**1q**	**2q**	4 h	86
18	**1r**	**2r**	4 h	77

Table 3 (continued)

Entry	Substrate	Product	Time	Yield[b] (%)
19	**1s**	**2s**	3 h	83
20	**1t**	**2t**	3 h	88
21	**1u**	**2u**	12 h	91

[a] Unless otherwise noted, the reaction was performed with 0.4 mmol of **1** and 0.2 mL TEAF.
[b] Isolated yield.

Therefore, we also applied the rhodium–TsEN complex to the reduction of 3-methyl-4-nitro-5-alkenyl-isoxazoles. In Table 5, the carbon–carbon double bonds of 3-methyl-4-nitro-5-alkenyl-isoxazoles with varieties of substitutes were smoothly reduced in moderate to excellent yields, revealing the board substrate application of our catalytic complex.

In extensive studies, the amount of catalyst was also examined. In the transfer hydrogenation of the carbon–carbon double bond of conjugated nitroalkenes with rhodium–TsEN, a higher S/C ratio was proved to be feasible. Table 6 showed the results obtained for β-nitrostyrene, β-methyl nitrostyrene, and 3-methyl-4-nitro-5-styrylisoxazole, which were reduced with rhodium–TsEN at a higher S/C ratio of 500 and 1000. After a few hours, the reduction could be successfully completed with satisfactory yields.

3. Conclusion

In conclusion, the results presented in this paper showed that the rhodium–TsEN complex was excellent catalyst for the chemoselective transfer hydrogenation of a wide range of conjugated nitroalkenes including β-nitrostyrenes, β-methyl nitrostyrenes, and 3-methyl-4-nitro-5-alkenyl-isoxazoles, affording up to 99% yield. With high catalytic activity, excellent chemoselectivity and broad substrate application, this methodology provided a useful strategy for the synthesis of nitroalkane derivatives. Further studies to develop more efficient catalyst systems and the mechanism of the present reaction are now under investigation.

4. Experimental section

4.1. General information

Reagents and starting materials obtained from commercial suppliers were used without further purification unless otherwise stated. All reactions were conducted in a closed system with an atmosphere of air and were monitored by TLC. ^{1}H NMR and ^{13}C NMR spectra were performed on a Bruker-300 MHz spectrometer for products dissolved by CDCl$_3$ with tetramethylsilane (TMS) as an internal standard. Data for ^{1}H NMR are reported as follows: chemical shift (in ppm) and multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet). Splitting patterns that could not be clearly distinguished are designated as multiplets (m). Data for ^{13}C NMR are reported in parts per million. Electrospray

ionization high resolution mass spectra (ESI-HRMS) were recorded on a Bruker P-SIMS-Gly FT-ICR mass spectrometer.

4.2. General procedure for the transfer hydrogenation of conjugated nitroalkenes

A mixture of the TsEN ligand (0.0044 mmol), [RhCl$_2$Cp*]$_2$ (0.002 mmol), and triethylamine (11 μL, 0.08 mmol) was dissolved in1 mL methanol and heated at 70 °C for 1 h in a glass tube. After cooling down, the solvent was removed in vacuo. Nitroalkene substrate (0.4 mmol) in EtOAc (1.0 mL) and the azeotrope of formic acid/triethylamine (0.2 mL) were added in turn. The mixture was stirred at 28 °C for the corresponding time. After completion, the solution was washed with water. The aqueous layer was extracted with EtOAc (5 mL×3). The combined organic layer was dried over Na$_2$SO$_4$, filtered, and concentrated under reduced pressure to afford the crude product, which was purified by flash chromatography (PE/EtOAc) on silica gel to provide the pure reduction product.

4.2.1. (2-Nitroethyl)benzene (2a). Yellow oil, >99% yield. ^{1}H NMR (CDCl$_3$, 300 MHz) δ 7.38–7.29 (m, 3H), 7.24–7.21 (m, 2H), 4.61 (t, J=7.4 Hz, 2H), 3.32 (t, J=7.4 Hz, 2H). ^{13}C NMR (CDCl$_3$, 75 MHz) δ 135.6, 128.8, 128.5, 127.3, 76.2, 33.3.

4.2.2. 1-Methoxy-4-(2-nitroethyl)benzene (2b). Colorless oil, 90% yield. ^{1}H NMR (CDCl$_3$, 300 MHz) δ 7.12 (d, J=8.6 Hz, 2H), 6.87–6.84 (m, 2H), 4.56 (t, J=7.3 Hz, 2H), 3.78 (s, 3H), 3.24 (t, J=7.3 Hz, 2H). ^{13}C NMR data are in agreement with the literature.[6a,f]

4.2.3. 1-Methyl-4-(2-nitroethyl)benzene (2c). Pale yellow oil, 86% yield. ^{1}H NMR (CDCl$_3$, 300 MHz) δ 7.20 (d, J=8.0 Hz, 2H), 7.10 (d, J=8.0 Hz, 2H), 4.59 (t, J=7.4 Hz, 2H), 3.28 (t, J=7.4 Hz, 2H), 2.34 (s, 3H). ^{13}C NMR data is in agreement with the literature.[6a,f]

4.2.4. 4-(2-Nitroethyl)phenol (2d). Yellow oil, 91% yield. ^{1}H NMR (CDCl$_3$, 300 MHz) δ 7.05 (d, J=8.5 Hz, 2H), 6.80–6.75 (m, 2H), 5.93 (br s, 1H), 4.56 (t, J=7.2 Hz, 2H), 3.22 (t, J=7.2 Hz, 2H). ^{13}C NMR data are in agreement with the literature.[6f]
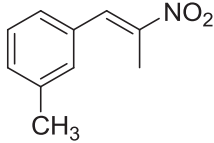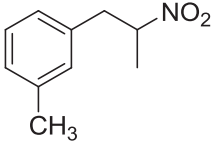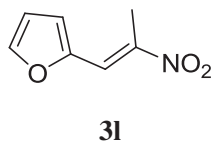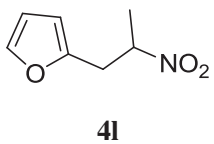
4.2.5. 1-Fluoro-4-(2-nitroethyl)benzene (2e). Pale yellow oil, 95% yield. ^{1}H NMR (CDCl$_3$, 300 MHz) δ 7.20–7.15 (m, 2H), 7.03–6.97 (m,

Table 4
Transfer hydrogenation of various β-methyl nitrostyrenes[a]

Entry	Substrate	Product	Time (h)	Yield[b] (%)
1	3a	4a	0.5	>99
2	3b	4b	5	88
3	3c	4c	3	99
4	3d	4d	12	75
5	3e	4e	2	85
6	3f	4f	3	64
7	3g	4g	2	99
8	3h	4h	2	82
9	3i	4i	2	98

Table 4 (continued)

Entry	Substrate	Product	Time (h)	Yield[b] (%)
10	**3j**	**4j**	2	87
11	**3k**	**4k**	2	65
12	**3l**	**4l**	52	91

[a] Unless otherwise noted, the reaction was performed with 0.4 mmol of **3** and 0.2 mL TEAF.
[b] Isolated yield.

2H), 4.59 (t, J=7.2 Hz, 2H), 3.28 (t, J=7.2 Hz, 2H). ^{13}C NMR data are in agreement with the literature.[6a]

4.2.6. 1-Chloro-4-(2-nitroethyl)benzene (2f). Pale yellow oil, 98% yield. ^{1}H NMR (CDCl$_3$, 300 MHz) δ 7.21 (d, J=8.3 Hz, 2H), 7.14 (d, J=8.3 Hz, 2H), 4.59 (t, J=7.2 Hz, 2H), 3.27 (t, J=7.2 Hz, 2H). ^{13}C NMR data are in agreement with the literature.[6a]

4.2.7. 1-Bromo-4-(2-nitroethyl)benzene (2g). White solid, 90% yield. ^{1}H NMR (CDCl$_3$, 300 MHz) δ 7.44 (d, J=8.3 Hz, 2H), 7.08 (d, J=8.3 Hz, 2H), 4.58 (t, J=7.2 Hz, 2H), 3.26 (t, J=7.2 Hz, 2H). ^{13}C NMR data are in agreement with the literature.[6f]

4.2.8. 1-Nitro-4-(2-nitroethyl)benzene (2h). White solid, 61% yield. ^{1}H NMR (CDCl$_3$, 300 MHz) δ 8.17 (d, J=8.7 Hz, 2H), 7.40 (d, J=8.6 Hz, 2H), 4.69 (t, J=7.0 Hz, 2H), 3.42 (t, J=7.0 Hz, 2H). ^{13}C NMR data are in agreement with the literature.[6a]

4.2.9. 1-Methoxy-3-(2-nitroethyl)benzene (2i). Colorless oil, 88% yield. ^{1}H NMR (CDCl$_3$, 300 MHz) δ 7.28–7.22 (m, 1H), 6.83–6.75 (m, 3H), 4.61 (t, J=7.4 Hz, 2H), 3.80 (s, 3H), 3.29 (t, J=7.4 Hz, 2H). ^{13}C NMR (CDCl$_3$, 75 MHz) δ 159.8, 137.1, 129.9, 120.7, 114.3, 112.6, 76.1, 55.1, 33.3.

4.2.10. 1-Bromo-3-(2-nitroethyl)benzene (2j). Pale yellow oil, 88% yield. ^{1}H NMR (CDCl$_3$, 300 MHz) δ 7.42–7.37 (m, 2H), 7.23–7.13 (m, 2H), 4.61 (t, J=7.3 Hz, 2H), 3.29 (t, J=7.3 Hz, 2H). ^{13}C NMR (CDCl$_3$, 75 MHz) δ 137.8, 131.6, 130.6, 130.5, 127.2, 122.8, 75.7, 32.8.

4.2.11. 1-Nitro-3-(2-nitroethyl)benzene (2k). White solid, 97% yield. ^{1}H NMR (CDCl$_3$, 300 MHz) δ 8.12 (d, J=9.8 Hz, 2H), 7.59–7.49 (m, 2H), 4.70 (t, J=6.8 Hz, 2H), 3.43 (t, J=7.0 Hz, 2H). ^{13}C NMR (CDCl$_3$, 75 MHz) δ 137.7, 134.8, 130.0, 123.5, 122.6, 65.5, 32.7.

4.2.12. 1-Methoxy-2-(2-nitroethyl)benzene (2l). Colorless oil, 88% yield. ^{1}H NMR (CDCl$_3$, 300 MHz) δ 7.30–7.25 (m, 1H), 7.16 (d, J=7.2 Hz, 1H), 6.93–6.87 (m, 2H), 4.61 (t, J=7.3 Hz, 2H), 3.85

(s, 3H), 3.31 (t, J=7.3 Hz, 2H). ^{13}C NMR data are in agreement with the literature.[6f]

4.2.13. 1-Chloro-2-(2-nitroethyl)benzene (2m). Yellow oil, 94% yield. ^{1}H NMR (CDCl$_3$, 300 MHz) δ 7.40–7.37 (m, 1H), 7.28–7.21 (m, 3H), 4.65 (t, J=7.3 Hz, 2H), 3.44 (t, J=7.3 Hz, 2H). ^{13}C NMR data are in agreement with the literature.[6a]
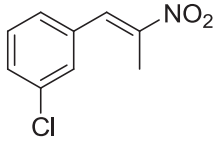
4.2.14. 1-Bromo-2-(2-nitroethyl)benzene (2n). Colorless oil, 94% yield. ^{1}H NMR (CDCl$_3$, 300 MHz) δ 7.57 (d, J=7.9 Hz, 1H), 7.28–7.24 (m, 2H), 7.18–7.13 (m, 1H), 4.65 (t, J=7.3 Hz, 2H), 3.45 (t, J=7.3 Hz, 2H). ^{13}C NMR (CDCl$_3$, 75 MHz) δ 134.9, 133.1, 131.1, 129.3, 127.9, 124.2, 74.2, 33.7.

4.2.15. 1-Nitro-2-(2-nitroethyl)benzene (2o). Orange oil, 93% yield. ^{1}H NMR (CDCl$_3$, 300 MHz) δ 8.07–8.04 (m, 1H), 7.62–7.57 (m, 1H), 7.50–7.48 (m, 1H), 7.45–7.38 (m, 1H), 4.77 (t, J=6.8 Hz, 2H), 3.59 (t, J=6.8 Hz, 2H). ^{13}C NMR data are in agreement with the literature.[6a]
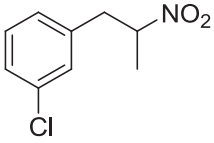
4.2.16. 2-(2-Nitroethyl)thiophene (2p). Yellow oil, 84% yield. ^{1}H NMR (CDCl$_3$, 300 MHz) δ 7.26–7.20 (m, 1H), 6.97–6.94 (m, 1H), 6.89 (d, J=2.6 Hz, 1H), 4.63 (t, J=7.1 Hz, 2H), 3.54 (t, J=7.1 Hz, 2H). ^{13}C NMR data are in agreement with the literature.[6a]

4.2.17. 1-(2-Nitroethyl)naphthalene (2q). White solid, 86% yield. ^{1}H NMR (CDCl$_3$, 300 MHz) δ 8.00 (d, J=8.2 Hz, 1H), 7.91 (d, J=7.8 Hz, 1H), 7.82 (d, J=8.0 Hz, 1H), 7.62–7.52 (m, 2H), 7.46–7.36 (m, 2H), 4.73 (t, J=7.7 Hz, 2H), 3.80 (t, J=7.7 Hz, 2H). ^{13}C NMR data are in agreement with the literature.[6a]

4.2.18. 1,2-Dimethoxy-4-(2-nitroethyl)benzene (2r). Pale yellow oil, 77% yield. ^{1}H NMR (CDCl$_3$, 300 MHz) δ 6.81–6.69 (m, 3H), 4.57 (t, J=7.2 Hz, 2H), 3.85 (s, 3H), 3.84 (s, 3H), 3.24 (t, J=7.2 Hz, 2H). ^{13}C NMR data is in agreement with the literature.[6a]
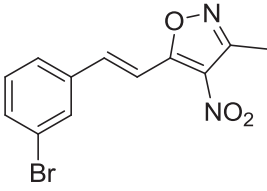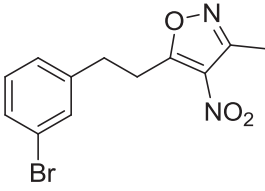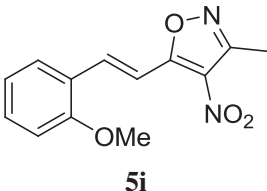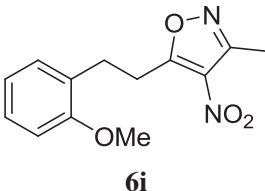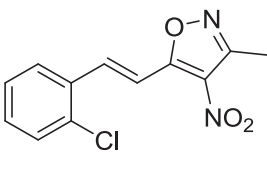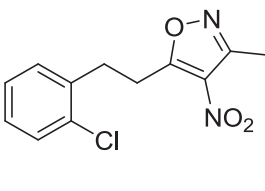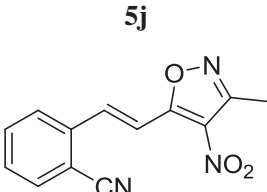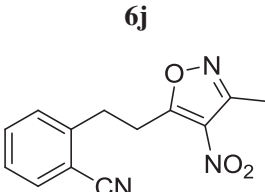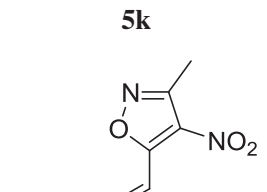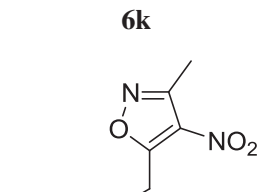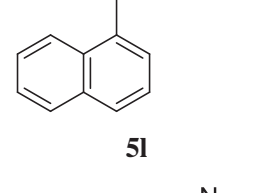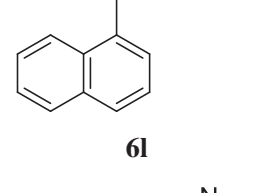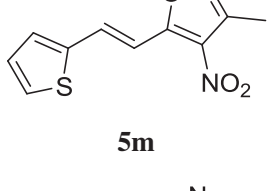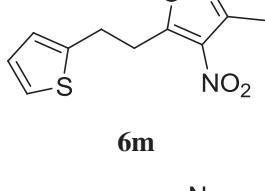
4.2.19. 2,4-Dichloro-1-(2-nitroethyl)benzene (2s). Pale yellow oil, 83% yield. ^{1}H NMR (CDCl$_3$, 300 MHz) δ 7.40 (s, 1H), 7.26–7.17 (m,

Table 5
Transfer hydrogenation of various 3-methyl-4-nitro-5-alkenyl-isoxazoles[a]
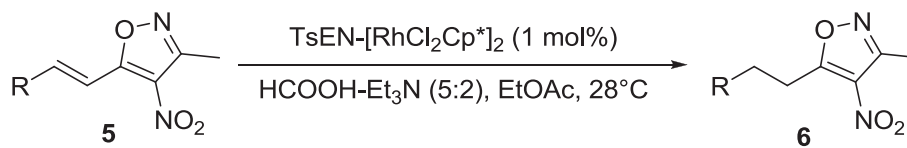
Entry	Substrate	Product	Time (h)	Yield[b] (%)
1	5a	6a	3	95
2	5b	6b	5	84
3	5c	6c	3.5	81
4	5d	6d	4	91
5	5e	6e	2	90
6	5f	6f	3	94
7	5g	6g	2	81

Table 5 (*continued*)

Entry	Substrate	Product	Time (h)	Yield[b] (%)
8	**5h**	**6h**	2	83
9	**5i**	**6i**	24	80
10	**5j**	**6j**	24	83
11	**5k**	**6k**	2	63
12	**5l**	**6l**	20	54
13	**5m**	**6m**	18	92
14	**5n**	**6n**	3	87

[a] Unless otherwise noted, the reaction was performed with 0.4 mmol of **5** and 0.2 mL TEAF.
[b] Isolated yield.

Table 6
Transfer hydrogenation of conjugated nitroalkenes by TEAF with Rh−TsEN at a higher S/C ratio
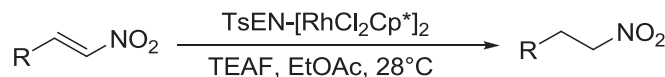
Entry	Substrate	Product	S/C	Time (h)	Yield[a] (%)
1			500	6	93
			1000	22	91
2			500	8	96
			1000	32	91
3			500	12	90
			1000	85	81

[a] Isolated yield.

2H), 4.63 (t, J=7.1 Hz, 2H), 3.40 (t, J=7.1 Hz, 2H). ^{13}C NMR (CDCl$_3$, 75 MHz) δ 134.6, 134.2, 131.9, 129.6, 127.6, 73.9, 30.8.

*4.2.20. (1-Nitroethane-1,2-diyl)dibenzene (**2t**).* Colorless oil, 88% yield. ^{1}H NMR (CDCl$_3$, 300 MHz) δ 7.56−7.53 (m, 2H), 7.45−7.42 (m, 3H), 7.34−7.27 (m, 3H), 7.22−7.19 (m, 2H), 5.74 (dd, J_1=9.4 Hz, J_2=5.8 Hz, 1H), 3.83 (dd, J_1=14.3 Hz, J_2=9.4 Hz, 1H), 3.37 (dd, J_1=14.3 Hz, J_2=5.8 Hz, 1H). ^{13}C NMR (CDCl$_3$, 75 MHz) δ 135.3, 134.1, 129.9, 128.9, 128.8, 128.7, 127.6, 127.3, 92.5, 40.0.

*4.2.21. (2-Nitroethyl)cyclopropane (**2u**).* Pale yellow oil, 91% yield. ^{1}H NMR (CDCl$_3$, 300 MHz) δ 3.29 (t, J=7.5 Hz, 2H), 1.72−1.65 (m, 2H), 0.78−0.73 (m, 1H), 0.48−0.44 (m, 2H), 0.09−0.04 (m, 2H). ^{13}C NMR (CDCl$_3$, 75 MHz) δ 31.7, 27.9, 11.7, 10.5, 4.6.

*4.2.22. (2-Nitropropyl)benzene (**4a**).* Yellow oil, >99% yield. ^{1}H NMR (CDCl$_3$, 300 MHz) δ 7.36−7.25 (m, 3H), 7.19−7.17 (m, 2H), 4.85−4.73 (m, 1H), 3.33 (dd, J_1=14.0 Hz, J_2=7.5 Hz, 1H), 3.02 (dd, J_1=14.0 Hz, J_2=6.8 Hz, 1H), 1.55 (d, J=6.7 Hz, 3H). ^{13}C NMR (CDCl$_3$, 75 MHz) δ 135.4, 128.9, 128.7, 127.3, 84.4, 41.1, 18.7.

*4.2.23. 1-Methoxy-4-(2-nitropropyl)benzene (**4b**).* Colorless oil, 88% yield. ^{1}H NMR (CDCl$_3$, 300 MHz) δ 7.08 (d, J=8.7 Hz, 2H), 6.86−6.83 (m, 2H), 4.77−4.70 (m, 1H), 3.78 (s, 3H), 3.24 (dd, J_1=14.0 Hz, J_2=7.6 Hz, 1H), 2.95 (dd, J_1=14.0 Hz, J_2=6.6 Hz, 1H), 1.53 (d, J=6.6 Hz, 3H). ^{13}C NMR (CDCl$_3$, 75 MHz) δ 158.7, 129.9, 127.4, 114.0, 84.6, 55.1, 40.3, 18.6.

*4.2.24. 1-Methyl-4-(2-nitropropyl)benzene (**4c**).* Colorless oil, 99% yield. ^{1}H NMR (CDCl$_3$, 300 MHz) δ 7.14 (d, J=7.9 Hz, 2H), 7.07 (d, J=8.0 Hz, 2H), 4.80−4.74 (m, 1H), 3.29 (dd, J_1=13.9 Hz, J_2=7.4 Hz, 1H), 2.99 (dd, J_1=13.9 Hz, J_2=6.8 Hz, 1H), 2.37 (s, 3H), 1.55 (d, J=6.6 Hz, 3H). ^{13}C NMR (CDCl$_3$, 75 MHz) δ 136.9, 132.3, 129.5, 129.4, 128.7, 127.5, 84.5, 40.7, 20.9, 18.6.

*4.2.25. 4-(2-Nitropropyl)phenol (**4d**).* Pale yellow oil, 75% yield. ^{1}H NMR (CDCl$_3$, 300 MHz) δ 7.01 (d, J=8.5 Hz, 2H), 6.77−6.74 (m, 2H), 5.50 (br s, 1H), 4.79−4.68 (m, 1H), 3.22 (dd, J_1=14.1 Hz, J_2=7.7 Hz, 1H), 2.95 (dd, J_1=14.1 Hz, J_2=6.5 Hz, 1H), 1.53 (d, J=6.7 Hz, 3H). ^{13}C NMR (CDCl$_3$, 75 MHz) δ 154.8, 130.2, 127.4, 115.6, 84.8, 40.3, 18.7.

*4.2.26. 1-Fluoro-4-(2-nitropropyl)benzene (**4e**).* Pale yellow oil, 85% yield. ^{1}H NMR (CDCl$_3$, 300 MHz) δ 7.15−7.10 (m, 2H), 7.02−6.96

(m, 2H), 4.81−4.69 (m, 1H), 3.27 (dd, J_1=14.1 Hz, J_2=7.9 Hz, 1H), 2.99 (dd, J_1=14.2 Hz, J_2=6.3 Hz, 1H), 1.54 (d, J=6.7 Hz, 3H). ^{13}C NMR (CDCl$_3$, 75 MHz) δ 163.6, 160.4, 131.2, 131.1, 130.5, 130.4, 115.8, 115.5, 84.4, 40.2, 18.7.

*4.2.27. 1-Chloro-4-(2-nitropropyl)benzene (**4f**).* Colorless oil, 64% yield. ^{1}H NMR (CDCl$_3$, 300 MHz) δ 7.29 (d, J=8.3 Hz, 2H), 7.10 (d, J=8.3 Hz, 2H), 4.79−4.69 (m, 1H), 3.29 (dd, J_1=14.1 Hz, J_2=7.8 Hz, 1H), 2.99 (dd, J_1=14.1 Hz, J_2=6.4 Hz, 1H), 1.55 (d, J=6.7 Hz, 3H). ^{13}C NMR (CDCl$_3$, 75 MHz) δ 133.9, 133.4, 130.3, 129.0, 84.2, 40.4, 18.8.

*4.2.28. 4-(2-Nitropropyl)benzonitrile (**4g**).* Pale yellow oil, 99% yield. ^{1}H NMR (CDCl$_3$, 300 MHz) δ 7.59 (d, J=8.2 Hz, 2H), 7.28 (d, J=8.1 Hz, 2H), 4.83−4.76 (m, 1H), 3.33 (dd, J_1=14.2 Hz, J_2=8.4 Hz, 1H), 3.08 (dd, J_1=14.2 Hz, J_2=5.8 Hz, 1H), 1.57 (d, J=6.7 Hz, 3H). ^{13}C NMR (CDCl$_3$, 75 MHz) δ 140.8, 132.4, 129.7, 118.4, 111.2, 83.7, 40.6, 18.9.

*4.2.29. 1-Fluoro-2-(2-nitropropyl)benzene (**4h**).* Pale yellow oil, 82% yield. ^{1}H NMR (CDCl$_3$, 300 MHz) δ 7.40−7.34 (m, 1H), 7.26−7.15 (m, 3H), 4.99−4.87 (m, 1H), 3.39 (dd, J_1=14.0 Hz, J_2=8.2 Hz, 1H), 3.19 (dd, J_1=14.0 Hz, J_2=6.0 Hz, 1H), 1.59 (d, J=6.7 Hz, 3H). ^{13}C NMR (CDCl$_3$, 75 MHz) δ 134.0, 133.3, 131.3, 129.7, 129.0, 127.2, 82.6, 38.8, 19.1.

*4.2.30. 1-Chloro-2-(2-nitropropyl)benzene (**4i**).* Colorless oil, 98% yield. ^{1}H NMR (CDCl$_3$, 300 MHz) δ 7.39−7.36 (m, 1H), 7.26−7.15 (m, 3H), 4.99−4.87 (m, 1H), 3.39 (dd, J_1=14.0 Hz, J_2=8.2 Hz, 1H), 3.19 (dd, J_1=14.0 Hz, J_2=6.0 Hz, 1H), 1.59 (d, J=6.7 Hz, 3H). ^{13}C NMR (CDCl$_3$, 75 MHz) δ 134.0, 133.3, 131.3, 129.7, 129.0, 127.1, 82.6, 38.7, 19.1.

*4.2.31. 1-Methyl-3-(2-nitropropyl)benzene (**4j**).* Pale yellow oil, 87% yield. ^{1}H NMR (CDCl$_3$, 300 MHz) δ 7.26−7.19 (m, 1H), 7.09 (d, J=7.5 Hz, 1H), 6.98 (d, J=7.8 Hz, 2H), 4.84−4.73 (m, 1H), 3.30 (dd, J_1=13.9 Hz, J_2=7.5 Hz, 1H), 2.97 (dd, J_1=13.9 Hz, J_2=6.8 Hz, 1H), 2.34 (s, 3H), 1.55 (d, J=6.6 Hz, 3H). ^{13}C NMR (CDCl$_3$, 75 MHz) δ 138.4, 135.4, 129.7, 128.6, 128.1, 125.9, 84.4, 41.0, 21.3, 18.7.

*4.2.32. 1-Chloro-3-(2-nitropropyl)benzene (**4k**).* Pale yellow oil, 65% yield. ^{1}H NMR (CDCl$_3$, 300 MHz) δ 7.25−7.21 (m, 2H), 7.17 (s, 1H), 7.06−7.03 (m, 1H), 4.82−4.71 (m, 1H), 3.29 (dd, J_1=14.1 Hz, J_2=7.8 Hz, 1H), 2.98 (dd, J_1=14.1 Hz, J_2=6.4 Hz, 1H), 1.56 (d, J=6.7 Hz,

3H). ^{13}C NMR (CDCl$_3$, 75 MHz) δ 137.4, 134.5, 130.0, 129.0, 127.6, 127.1, 84.0, 40.5, 18.8.

*4.2.33. 2-(2-Nitropropyl)furan (**4l**).* Pale yellow oil, 91% yield. ^{1}H NMR (CDCl$_3$, 300 MHz) δ 7.33 (d, $J=0.8$ Hz, 1H), 6.29 (d, $J=1.8$ Hz, 1H), 6.12 (d, $J=3.1$ Hz, 1H), 4.88–4.81 (m, 1H), 3.36 (dd, $J_1=15.2$ Hz, $J_2=7.3$ Hz, 1H), 3.08 (dd, $J_1=15.2$ Hz, $J_2=6.5$ Hz, 1H), 1.57 (d, $J=6.7$ Hz, 3H). ^{13}C NMR (CDCl$_3$, 75 MHz) δ 149.3, 142.3, 110.5, 108.0, 81.8, 33.4, 18.8.

*4.2.34. 3-Methyl-4-nitro-5-phenethylisoxazole (**6a**).* White solid, 95% yield. ^{1}H NMR (CDCl$_3$, 300 MHz) δ 7.34–7.30 (m, 2H), 7.26–7.22 (m, 3H), 3.53–3.48 (m, 2H), 3.13–3.07 (m, 2H), 2.55 (s, 3H). ^{13}C NMR (CDCl$_3$, 75 MHz) δ 174.1, 155.6, 138.9, 128.7, 128.2, 126.7, 32.2, 29.5, 11.6. HRMS (ESI) calcd for C$_{12}$H$_{12}$N$_2$NaO$_3$ [M+Na]$^+$: 255.0746, found: 255.0736.

*4.2.35. 5-(4-Methoxyphenethyl)-3-methyl-4-nitroisoxazole (**6b**).* Yellow solid, 84% yield. ^{1}H NMR (CDCl$_3$, 300 MHz) δ 7.13 (d, $J=8.4$ Hz, 2H), 6.83 (d, $J=8.5$ Hz, 2H), 3.78 (s, 3H), 3.48–3.43 (m, 2H), 3.06–3.00 (m, 2H), 2.54 (s, 3H). ^{13}C NMR (CDCl$_3$, 75 MHz) δ 174.3, 158.3, 155.6, 130.9, 129.2, 114.0, 55.2, 31.4, 29.8, 11.6. HRMS (ESI) calcd for C$_{13}$H$_{14}$N$_2$NaO$_4$ [M+Na]$^+$: 285.0851, found: 285.0836.

*4.2.36. 3-Methyl-5-(4-methylphenethyl)-4-nitroisoxazole (**6c**).* White solid, 81% yield. ^{1}H NMR (CDCl$_3$, 300 MHz) δ 7.12 (m, 4H), 3.51–3.45 (m, 2H), 3.09–3.03 (m, 2H), 2.56 (s, 3H), 2.33 (s, 3H). ^{13}C NMR (CDCl$_3$, 75 MHz) δ 174.3, 155.5, 136.3, 135.8, 129.3, 128.1, 31.8, 29.6, 20.9, 11.6. HRMS (ESI) calcd for C$_{13}$H$_{14}$N$_2$NaO$_3$ [M+Na]$^+$: 269.0902, found: 269.0893.

*4.2.37. 5-(4-Fluorophenethyl)-3-methyl-4-nitroisoxazole (**6d**).* White solid, 91% yield. ^{1}H NMR (CDCl$_3$, 300 MHz) δ 7.19–7.15 (m, 2H), 6.97 (t, $J=8.7$ Hz, 2H), 3.49–3.44 (m, 2H), 3.09–3.04 (m, 2H), 2.53 (s, 3H). ^{13}C NMR (CDCl$_3$, 75 MHz) δ 173.9, 163.2, 160.0, 155.5, 134.6, 134.5, 129.8, 129.6, 115.6, 115.3, 31.4, 29.5, 11.5. HRMS (ESI) calcd for C$_{12}$H$_{11}$FN$_2$NaO$_3$ [M+Na]$^+$: 273.0651, found: 273.0643.

*4.2.38. 5-(4-Chlorophenethyl)-3-methyl-4-nitroisoxazole (**6e**).* White solid, 90% yield. ^{1}H NMR (CDCl$_3$, 300 MHz) δ 7.26 (d, $J=8.4$ Hz, 2H), 7.14 (d, $J=8.4$ Hz, 2H), 3.49–3.44 (m, 2H), 3.09–3.03 (m, 2H), 2.53 (s, 3H). ^{13}C NMR (CDCl$_3$, 75 MHz) δ 173.7, 155.6, 137.3, 132.5, 129.6, 128.7, 31.5, 29.3, 11.5. HRMS (ESI) calcd for C$_{12}$H$_{11}$ClN$_2$NaO$_3$ [M+Na]$^+$: 289.0356, found: 289.0352.

*4.2.39. 5-(4-Bromophenethyl)-3-methyl-4-nitroisoxazole (**6f**).* White solid, 94% yield. ^{1}H NMR (CDCl$_3$, 300 MHz) δ 7.41 (d, $J=8.3$ Hz, 2H), 7.09 (d, $J=8.3$ Hz, 2H), 3.49–3.44 (m, 2H), 3.07–3.02 (m, 2H), 2.54 (s, 3H). ^{13}C NMR (CDCl$_3$, 75 MHz) δ 173.7, 155.6, 137.8, 131.7, 130.0, 120.6, 31.6, 29.2, 11.2. HRMS (ESI) calcd for C$_{12}$H$_{11}$BrN$_2$NaO$_3$ [M+Na]$^+$: 332.9851, found: 332.9846.

*4.2.40. 5-(3-Fluorophenethyl)-3-methyl-4-nitroisoxazole (**6g**).* White solid, 81% yield. ^{1}H NMR (CDCl$_3$, 300 MHz) δ 7.30–7.23 (m, 1H), 6.99 (d, $J=7.7$ Hz, 1H), 6.95–6.90 (m, 2H), 3.52–3.46 (m, 2H), 3.12–3.07 (m, 2H), 2.55 (s, 3H). ^{13}C NMR (CDCl$_3$, 75 MHz) δ 173.7, 164.4, 161.2, 155.6, 141.3, 141.2, 130.2, 130.1, 123.9, 123.8, 115.3, 115.0, 113.8, 113.6, 31.8, 29.2, 11.5. HRMS (ESI) calcd for C$_{12}$H$_{11}$FN$_2$NaO$_3$ [M+Na]$^+$: 273.0651, found: 273.0648.

*4.2.41. 5-(3-Bromophenethyl)-3-methyl-4-nitroisoxazole (**6h**).* White solid, 83% yield. ^{1}H NMR (CDCl$_3$, 300 MHz) δ 7.37–7.35 (m, 2H), 7.20–7.13 (m, 2H), 3.50–3.45 (m, 2H), 3.08–3.03 (m, 2H), 2.54 (s, 3H). ^{13}C NMR (CDCl$_3$, 75 MHz) δ 173.6, 155.6, 141.1, 131.3, 130.2, 129.9,

126.9, 122.6, 31.7, 29.2, 11.5. HRMS (ESI) calcd for C$_{12}$H$_{11}$BrN$_2$NaO$_3$ [M+Na]$^+$: 332.9851, found: 332.9848.

*4.2.42. 5-(2-Methoxyphenethyl)-3-methyl-4-nitroisoxazole (**6i**).* Yellow solid, 80% yield. ^{1}H NMR (CDCl$_3$, 300 MHz) δ 7.26–7.19 (m, 1H), 7.12–7.09 (m, 1H), 6.89–6.84 (m, 2H), 3.82 (s, 3H), 3.51–3.46 (m, 2H), 3.12–3.07 (m, 2H), 2.54 (s, 3H). ^{13}C NMR (CDCl$_3$, 75 MHz) δ 174.9, 157.3, 155.4, 129.9, 128.1, 127.1, 120.4, 110.1, 55.1, 27.7, 27.5, 11.6. HRMS (ESI) calcd for C$_{13}$H$_{14}$N$_2$NaO$_4$ [M+Na]$^+$: 285.0851, found: 285.0841.

*4.2.43. 5-(2-Chlorophenethyl)-3-methyl-4-nitroisoxazole (**6j**).* White solid, 83% yield. ^{1}H NMR (CDCl$_3$, 300 MHz) δ 7.38–7.34 (m, 1H), 7.20–7.17 (m, 3H), 3.54–3.49 (m, 2H), 3.24–3.19 (m, 2H), 2.55 (s, 3H). ^{13}C NMR (CDCl$_3$, 75 MHz) δ 173.8, 155.6, 136.5, 133.9, 130.4, 129.7, 128.4, 127.1, 30.2, 27.6, 11.6. HRMS (ESI) calcd for C$_{12}$H$_{11}$ClN$_2$NaO$_3$ [M+Na]$^+$: 289.0356, found: 289.0349.

*4.2.44. 2-(2-(3-Methyl-4-nitroisoxazol-5-yl)ethyl)benzonitrile (**6k**).* White solid, 63% yield. ^{1}H NMR (CDCl$_3$, 300 MHz) δ 7.61–7.58 (m, 2H), 7.35–7.32 (m, 2H), 3.54–3.49 (m, 2H), 3.19–3.14 (m, 2H), 2.54 (s, 3H). ^{13}C NMR (CDCl$_3$, 75 MHz) δ 173.1, 155.6, 144.3, 132.5, 129.1, 118.6, 110.7, 32.1, 28.8, 11.5. HRMS (ESI) calcd for C$_{13}$H$_{11}$N$_3$NaO$_3$ [M+Na]$^+$: 280.0698, found: 280.0696.

*4.2.45. 3-Methyl-5-(2-(naphthalen-1-yl)ethyl)-4-nitroisoxazole (**6l**).* White solid, 54% yield. ^{1}H NMR (CDCl$_3$, 300 MHz) δ 8.12 (d, $J=8.3$ Hz, 1H), 7.89 (d, $J=7.9$ Hz, 1H), 7.78 (d, $J=7.8$ Hz, 1H), 7.62–7.50 (m, 2H), 7.45–7.36 (m, 2H), 3.64–3.51 (m, 4H), 2.57 (s, 3H). ^{13}C NMR (CDCl$_3$, 75 MHz) δ 174.2, 155.7, 135.0, 133.8, 131.3, 129.0, 127.7, 126.4, 126.3, 125.8, 125.5, 123.0, 29.7, 28.9, 11.6. HRMS (ESI) calcd for C$_{16}$H$_{14}$N$_2$NaO$_3$ [M+Na]$^+$: 305.0902, found: 305.0893.

*4.2.46. 3-Methyl-4-nitro-5-(2-(thiophen-2-yl)ethyl)isoxazole (**6m**).* Pale yellow solid, 92% yield. ^{1}H NMR (CDCl$_3$, 300 MHz) δ 7.15 (d, $J=5.1$ Hz, 1H), 6.93–6.90 (m, 1H), 6.84 (d, $J=2.2$ Hz, 1H), 3.58–3.53 (m, 2H), 3.36–3.31 (m, 2H), 2.55 (s, 3H). ^{13}C NMR (CDCl$_3$, 75 MHz) δ 173.4, 155.6, 141.1, 127.0, 125.2, 124.2, 29.7, 26.3, 11.6. HRMS (ESI) calcd for C$_{10}$H$_{10}$N$_2$NaO$_3$S [M+Na]$^+$: 261.0310, found: 261.0307.

*4.2.47. 5-(2-Cyclopropylethyl)-3-methyl-4-nitroisoxazole (**6n**).* Yellow oil, 87% yield. ^{1}H NMR (CDCl$_3$, 300 MHz) δ 3.29–3.24 (m, 2H), 2.53 (s, 3H), 1.70–1.63 (m, 2H), 0.74–0.71 (m, 1H), 0.47–0.41 (m, 2H), 0.06–0.03 (m, 2H). ^{13}C NMR (CDCl$_3$, 75 MHz) δ 175.3, 155.5, 31.6, 27.8, 11.6, 10.4, 4.5. HRMS (ESI) calcd for C$_9$H$_{12}$N$_2$NaO$_3$ [M+Na]$^+$: 219.0746, found: 219.0745.

Acknowledgements

Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2012.04.028.

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