Base-Promoted Internal Redox-Cyclisation Reactions

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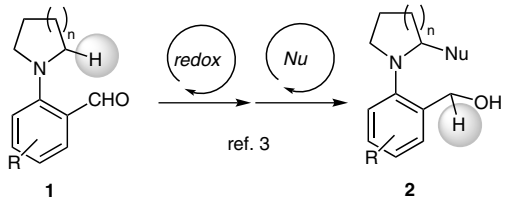
Received: 24.04.2013; Accepted after revision: 05.06.2013

Abstract: A new internal, base-mediated redox-cyclisation reaction has been discovered and developed. In this transformation, the sacrificial reduction of an alkynyl moiety to an alkene allows direct functionalisation of an α-amino C–H bond. This approach allows the preparation of several 1,3-oxazinane derivatives in an atom-efficient manner.

Key words: C–H activation, C–H functionalisation, redox, cyclisation, pyrrolidine

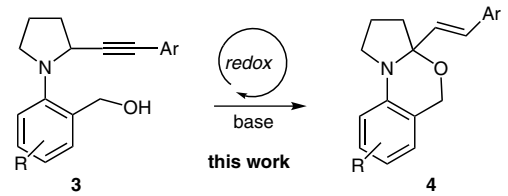
The direct functionalisation of C–H bonds is a current and highly attractive topic in contemporary organic synthesis.[1] Numerous creative and innovative C–H activation methods have been developed in the past decades. Recently, a novel approach to the functionalisation of sp^3 C–H bonds through internal hydride transfer has received a great deal of attention.[2] In contrast to traditional C–H activation reactions, such transformations proceed in the absence of external oxidants and generally hinge on an internal 1,5-hydride shift process.

Intrigued by this concept, we have developed a redox-triggered C–H functionalisation strategy (Scheme 1).[3] In this one-pot process, C–H bonds α to a pyrrolidine or piperidine moiety **1** are directly converted into C–C bonds, accompanied by concomitant reduction of a neighbouring carboxaldehyde group. Herein, we report the discovery and development of a base-promoted redox isomerisation of α-alkynyl pyrrolidines **3** that allows the deployment of sequential, iterative C–H functionalisation sequences (Scheme 2).

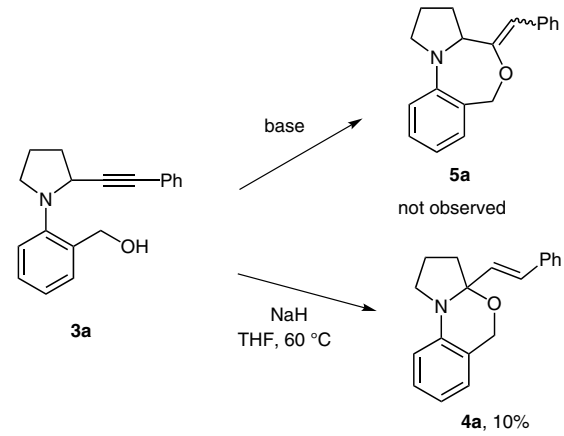


Scheme 1 Previously developed internal redox-triggered C–H functionalisation of amines

During our recent studies on redox-triggered C–H functionalisation, we attempted to transform adduct **3a** into **5a** by base-promoted 7-*exo-dig* cyclisation (Scheme 3).[4] To our surprise, while none of the oxepane **5a** was observed in these early attempts, *N*,*O*-acetal (aminal) **4a** was obtained in low (but reproducible) isolated yields when NaH was employed as base. In contrast to well-known Brønsted or Lewis acid catalyzed redox reactions,[2] this transformation piqued our interest since it proceeds under orthogonal conditions (in the presence of base rather than acid) and presented the potential to deliver compound **4a** in an atom-economical manner.[5] We thus decided to investigate this unexpected result further.



Scheme 2 Base-promoted redox cyclisation



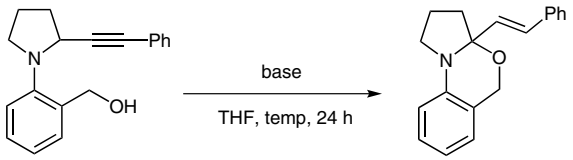
Scheme 3 Discovery of the base-promoted redox cyclisation

A selection of conditions that were surveyed is depicted in Table 1. According to our initial discovery, aminal **4a** was obtained in 10% yield, although full conversion of substrate **3a** was observed (Table 1, entry 1). Lowering the temperature from 60 to 50 °C significantly enhanced the selectivity, leading to a great improvement of the yield of **4a** (entry 2). The use of larger amounts of NaH or switching to potassium *tert*-butoxide as base did not lead to significant improvement (entries 3 and 4). In spite of numerous additional experiments (not shown), it was not possible to improve the yield of product **4a** further.[6]

With suitable conditions in hand, we then investigated the scope of this base-promoted redox reaction. Moderate to good yields of the desired 1,3-oxazinane derivatives were

SYNLETT 2013, 24, 1722–1724
Advanced online publication: 10.07.2013
DOI: 10.1055/s-0033-1339313; Art ID: ST-2013-D0383-L

Table 1 Optimisation of the Redox Reaction of **3a**[a]



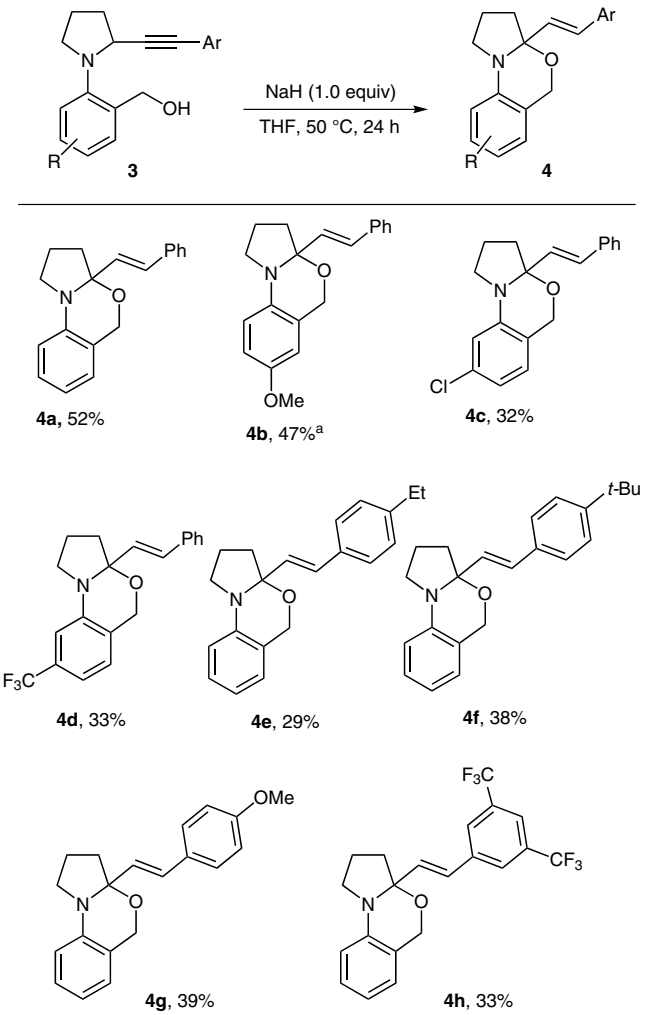
3a **4a**

Entry	Base	Temp (°C)	Yield (%)[b]
1	NaH (1.0 equiv)	60	10
2	NaH (1.0 equiv)	50	52
3	NaH (2.0 equiv)	50	trace
4	*t*-BuOK (1.0 equiv)	50	30

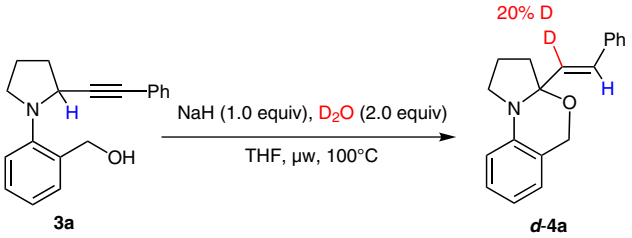
obtained for a range of substrates (Scheme 4). Substrate **3b**, bearing a *para*-methoxy substituent, proved to be unreactive under the optimised conditions. However, increasing the temperature to 100 °C led to a good yield of desired oxazinane **4b**. When substrates **3c** and **3d**, containing electron-deficient aromatic rings, were subjected to the redox cyclisation conditions, the desired 1,3-oxazinane derivatives **4c** and **4d** were also obtained albeit in lower yields. Substituents on the benzene of phenyl alkynes **3e**–**h** also led to slightly lower yields.

To acquire further insight into the mechanism of this reaction, a deuterium labelling experiment was performed as shown in Scheme 5. When the reaction of **3a** was conducted with NaH (1.0 equiv) and deuterium oxide (2.0 equiv),[7] the product *d*-**4a** was isolated containing 20% of the deuterium label at the indicated position. Based on this experiment, we can tentatively propose a mechanism for this base-promoted redox-cyclisation (Scheme 6).

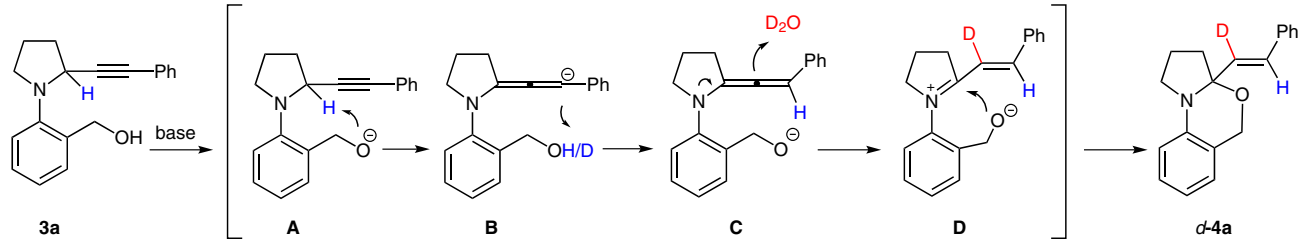
At the outset, deprotonation of the alcohol functionality in **3a** gives alkoxide **A**, which may trigger an internal deprotonation of the propargylic α-amine moiety, leading to the formation of intermediate **B**. The allenic anion **B** (bearing an OH or OD residue) thus generated is internally quenched by the alcohol, providing allenamine intermediate **C**.[8] Isomerisation of allenamine **C** (assisted by D_2O) then leads to iminium intermediate **D**, the nucleophilic trapping of which furnishes deuterated oxazinane derivative *d*-**4a**.



Scheme 4 Substrate scope for the base-promoted redox C–H functionalisation. *Reagents and conditions*: amino alcohol **2** (0.1 mmol), THF (2.5 mL), NaH (4.0 mg), 50 °C, 24 h.[7] [a] Reaction performed at 100 °C in a microwave reactor for 16 h.

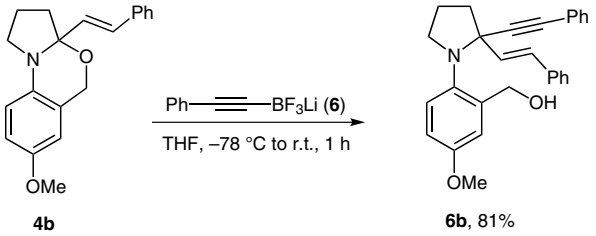


Scheme 5 Labelling experiment



Scheme 6 Plausible mechanism for the base-promoted redox C–H functionalisation

The obtained 1,3-oxazinane derivatives possess an additional *N*,*O*-acetal moiety, which suggests further possibilities for functionalisation. To this end, we attempted to further elaborate product **4b** by reaction with another nucleophile (Scheme 7). In the event, it was found that lithium alkynyltrifluoroborate **6** reacted smoothly with **4b**, affording the aminoenyne **6b** in 81% yield. Notably, **6b** contains both alkynyl- and alkenyl fragments at the α-position of the pyrrolidine moiety, introduced sequentially in a redox-based fashion.



Scheme 7 Elaboration of compound **4b**

In summary, we have discovered and developed a base-promoted redox cyclisation providing a series of 1,3-oxazinane derivatives in moderate to good yields.[9] In this process, a C–H bond α to an amine moiety is transformed into a C–O bond through a redox process whereupon an alkyne fragment is simultaneously reduced to an alkene. Further mechanistic investigations, exploration of synthetic applications, and development of redox reactions as tools for C–H functionalisation are ongoing in our group.

Acknowledgment

We are highly indebted to the Max-Planck Society and the Max-Planck-Institut für Kohlenforschung for generous funding of our research programs.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(6) The remainder of the mass balance in these reactions was typically composed of a mixture of oligomeric material, decomposition products and (occasionally) small amounts of cyclisation products isomeric or akin to **5a** (Scheme 3).

(7) No reaction occurred under the optimised conditions; however, when the reaction temperature was raised to 100 °C, the product *d*-**4a** was isolated containing 20% deuterium at the indicated position.

(8) Wei, L.-L.; Xiong, H.; Douglas, C. J.; Hsung, R. P. *Tetrahedron Lett.* **1999**, *40*, 6903.

(9) **Typical Procedure; Synthesis of 1,3-Oxazine 4a:** To a solution of amino alcohol **3a** (62 mg, 0.22 mmol) in THF (5 mL) was added NaH (60% w/w, 1.0 equiv, 8.8 mg, 0.22 mmol) under argon at room temperature and the mixture was stirred at 50 °C overnight. The reaction mixture was then cooled to room temperature, quenched with sat. aq NH_4Cl, extracted with EtOAc (3×), dried (Na_2SO_4), and concentrated under reduced pressure. Purification by column chromatography (pentane–EtOAc, 9:1) afforded the desired product 1,3-oxazinane **4a**.

3a-Styryl-2,3,3a,5-tetrahydro-1*H*-benzo[*d*]pyrrolo[2,1-*b*][1,3]oxazine (4a): Yield: 52%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.33 (m, 2 H), 7.30–7.27 (m, 2 H), 7.23–7.16 (m, 2 H), 6.88 (d, *J* = 7.2 Hz, 1 H), 6.74 (d, *J* = 8.1 Hz, 1 H), 6.71–6.67 (m, 1 H), 6.41 (d, *J* = 15.7 Hz, 1 H), 6.19 (d, *J* = 15.7 Hz, 1 H), 4.88 (d, *J* = 14.6 Hz, 1 H), 4.62 (d, *J* = 14.6 Hz, 1 H), 3.79 (td, *J* = 8.9, 1.8 Hz, 1 H), 3.36 (ddd, *J* = 9.8, 8.8, 6.7 Hz, 1 H), 2.25–2.20 (m, 1 H), 2.16–2.09 (m, 1 H), 2.05–1.91 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 142.4, 136.1, 133.8, 130.4, 128.5, 127.8, 127.7, 126.8, 124.5, 120.1, 116.7, 113.3, 93.6, 63.5, 50.0, 39.3, 21.3. IR (neat): 3024 (w), 2970 (w), 2841 (w), 1881 (w), 1607 (s), 1497 (s), 1361 (s), 1196 (m), 1029 (m), 973 (m), 747 (s) cm^{-1}. HRMS: *m*/*z* calcd for $[C_{19}H_{19}NO + H]^+$: 278.1545; found: 278.1539.

Typical Procedure; Synthesis of 1,3-Oxazine 4f: To a solution of amino alcohol **3f** (50 mg, 0.15 mmol) in THF (4 mL), NaH (60% w/w, 1.0 equiv, 6.2 mg, 0.15 mmol) was added under argon at room temperature and the mixture was stirred at 50 °C overnight. The reaction mixture was cooled to room temperature, quenched with sat. aq NH_4Cl, extracted with EtOAc (3×), dried (Na_2SO_4), and concentrated under reduced pressure. Purification by column chromatography (pentane–EtOAc, 19:1) afforded the desired 1,3-oxazinane **4f**.

3a-[4-(*tert*-Butyl)styryl]-2,3,3a,5-tetrahydro-1*H*-benzo[*d*]pyrrolo[2,1-*b*][1,3]oxazine (3f): Yield: 38%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.28–7.25 (m, 4 H), 7.12–7.09 (m, 2 H), 6.81–6.77 (m, 1 H), 6.80 (d, *J* = 7.6 Hz, 1 H), 6.72 (d, *J* = 8.2 Hz, 1 H), 6.62–6.59 (m, 1 H), 6.31 (d, *J* = 15.7 Hz, 1 H), 6.08 (d, *J* = 15.4 Hz, 1 H), 4.80 (d, *J* = 14.8 Hz, 1 H), 4.54 (d, *J* = 15.8 Hz, 1 H), 3.71 (td, *J* = 8.5 Hz, *J* = 8.4 Hz, 1 H), 3.36 (m, 1 H), 2.16–2.11 (m, 1 H), 2.08–2.02 (m, 1 H), 1.91–1.95 (m,1 H), 1.89–1.82 (m, 1 H), 1.25–1.22 (s, 9 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 133.6, 133.1, 129.7, 127.8, 126.8, 125.7, 124.5, 120.3, 116.7, 113.2, 96.6, 93.8, 63.5, 50.3, 39.4, 34.6, 30.9, 21.2. IR (neat): 3024 (w), 2970 (w), 2841 (w), 1830 (w), 1698 (s), 1498 (s), 1362 (s), 1263 (m), 1029 (m), 815 (m), 749 (s) cm^{-1}. HRMS: *m*/*z* calcd for $[C_{23}H_{27}NO + H]^+$: 334.2167; found: 334.2165.

