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Redox-Triggered α-C−H Functionalization of Pyrrolidines: Synthesis of Unsymmetrically 2,5-Disubstituted Pyrrolidines

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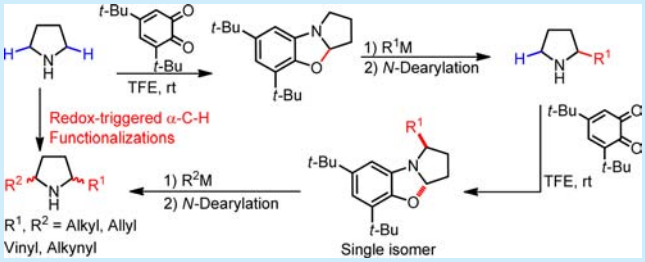
Supporting Information

ABSTRACT: By using *o*-benzoquinone as an internal oxidant, the regio- and diastereoselective functionalization of the secondary over the tertiary α-C−H bond of 2-substituted pyrrolidines is first realized. Subsequent intermolecular addition of a nucleophile to the generated *N,O*-acetal and cleavage of the aromatic substituent leads to 2,5-disubstituted pyrrolidines.



Unsymmetrically 2,5-disubstituted pyrrolidines (either in *trans*- or *cis*- form) are found in many natural products[1] and pharmaceuticals (Figure 1).[2] For example, pyrrolidine 225C, the

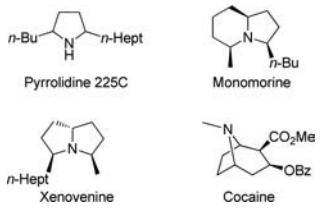


Figure 1. Unsymmetrically 2,5-disubstituted pyrrolidines.

trans isomer, was isolated from ant venom toxins of *Solenopsis punctaticeps*,[1a] and the *cis* isomer is a trail pheromone of the pharaoh ant, *Monomorium pharaonis*.[1b] Monomorine, which has also been isolated from *M. pharaonis*, is believed to be involved in defense against predators.[1c] Xenovenine, isolated from *Solenopsis xenoveneum*, inhibits the nicotinic acetylcholine response,[1d] and cocaine is a powerful analgesic and stimulant.[1e,f] The development of efficient methods for synthesizing structurally diverse unsymmetrically 2,5-disubstituted pyrrolidines is highly desirable.

Many efficient methods for direct functionalization of the α-C−H of pyrrolidines have been reported.[3−7] Among various elegant transformations, redox-neutral C−H functionalization reactions offer special redox and atom economy.[8] Most of these reactions proceed through a key 1,5-hydride transfer from the α-C of pyrrolidine to an intramolecular hydride acceptor (originally called the "*tert*-amino effect") to form an iminium ion, which is attacked by the reduced hydride-acceptor moiety, leading to a heterocyclic product in which the α-C−H bond functionalization of pyrrolidine is therefore realized.[4] Besides, Seidel et al. recently established the azomethine ylide-mediated α-C−H bond functionalization of pyrrolidines.[5−7] However, one of the challenges in this research field is the selective functionalization of the secondary over the tertiary α-C−H bond of 2-substituted pyrrolidines. The functionalization of the secondary α-C−H gives 2,5-disubstituted pyrrolidines, while the functionalization of the tertiary α-C−H gives 2,2-disubstituted pyrrolidines. Generally, selective functionalization of the tertiary α-C−H bond to afford 2,2-disubstituted pyrrolidines predominates because this transformation proceeds via the more thermodynamically stable intermediate.[6,9] There have been few reports in which secondary α-C−H functionalization were favored.[6d,7a]

In 2012, Maulide and co-workers successfully combined redox-neutral pyrrolidine α-C−H functionalization with subsequent intermolecular addition of a nucleophile to the generated intramolecularly α-oxygenated pyrrolidine. After cleavage of the aromatic substituent on the nitrogen atom, 2-substituted pyrrolidines with various functional groups (e.g., alkyl, vinyl, aryl, and alkynyl) were obtained in high yields (Scheme 1, eq 1).[9c] We envisioned that using *o*-benzoquinone, which has a higher oxidizing capability than benzaldehyde, as an internal oxidant would enable intramolecular redox-neutral C−H functionalization at ambient temperature in the absence of an acid.[10] Furthermore, steric effects on the formation of a five-membered-ring *N,O*-acetal in the present work should be larger than the effects on the formation of the six-membered-ring counterpart[6,9] in previous reports. Therefore, functionalization of the less substituted secondary α-C−H bond of 2-substituted pyrrolidines should be favored. Herein, we presented that based on the high regio- and diastereoselectivities of the intramolecular α-oxygenation of 2-substituted pyrrolidines, the redox-triggered C−H functionalization strategy for the synthesis of unsymmetri-

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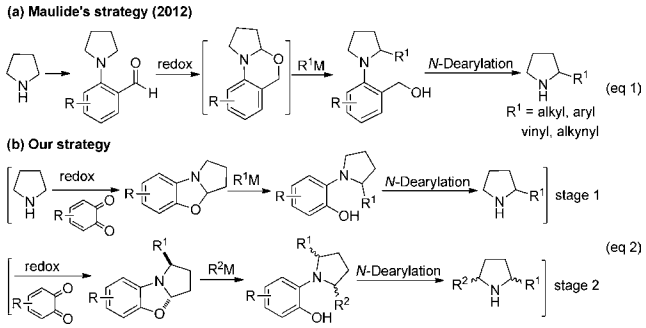
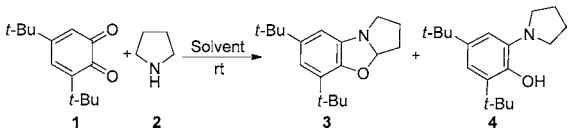
Scheme 1. Redox-Triggered α-C−H Functionalization of Pyrrolidine for Synthesis of (a) 2-Substituted Pyrrolidines and (b) Unsymmetrically 2,5-Disubstituted Pyrrolidines



cally 2,5-disubstituted pyrrolidines was realized (Scheme 1, eq 2).

We chose commercially available 3,5-di-*tert*-butyl-*o*-benzoquinone (**1**) and pyrrolidine **2** as substrates for a model reaction (Table 1; see the Supporting Information for the screening of the

Table 1. Pyrrolidine α-C−H Functionalization with *o*-Benzoquinone 1 in Various Solvents[a]



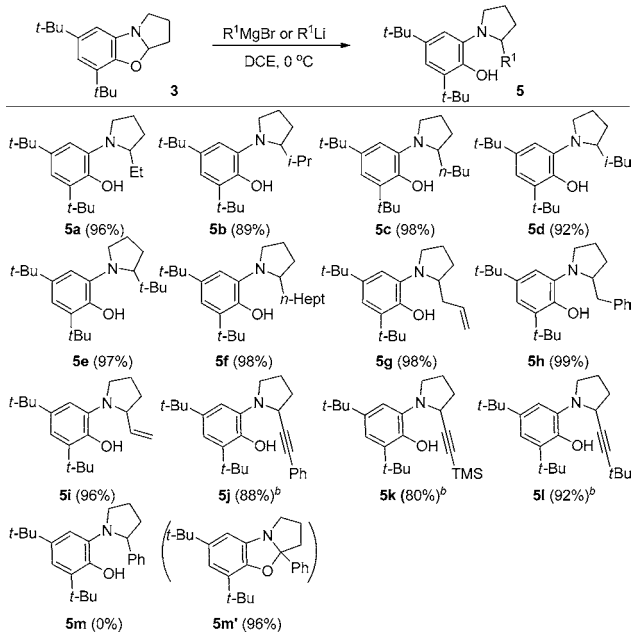
			yield[b] (%)	
entry	solvent	time (h)	3	4
1	PhMe	4	88	0
2	DCM	2	38	9
3	DCE	2	70	8
4	MeOH	0.2	84	4
5	TFE	0.5	89	0
6[c]	TFE	0.5	98	0

[a]Reactions were carried out with **1** (0.2 mmol) and **2** (0.24 mmol) in 1.0 mL of solvent at room temperature. [b]Isolated yields. [c]**1** (0.2 mmol, 0.5 M in TFE) was added to a solution of **2** (0.24 mmol) in TFE (0.6 mL) over the course of 5 min.

o-benzoquinones). In room-temperature toluene in the absence of acid, the desired redox product *N,O*-acetal **3** was obtained in 88% yield after 4 h (Table 1, entry 1). Use of a chlorinated alkane solvent decreased the yield of the desired product and resulted in the formation of *o*-aminophenol **4** as a byproduct in low yield (Table 1, entries 2 and 3).[10c,11] Conducting the reaction in a polar protic solvent (methanol) markedly shortened the reaction time (Table 1, entry 4). 2,2,2-Trifluoroethanol (TFE) provided the highest yield of all of the tested solvents (Table 1, entry 5), and slow addition of **1** to the reaction mixture further increased the yield (Table 1, entry 6). When the reaction was carried out on a large scale (5.6 mmol of pyrrolidine), it was complete within 0.5 h and **3** was obtained in 98% yield. However, under these reaction conditions, piperidine reacted with **1** to yield mainly *o*-aminophenol.[10c,12]

We next investigated the nucleophilic addition of Grignard reagents to **3** (Scheme 2).[13] The C−C bond-forming reactions proved general for a broad range of nucleophiles. Therefore, alkyl, allyl, benzyl, vinyl, and alkynyl moieties could be introduced to the α-position of the pyrrolidine ring in high to excellent yields (**5a−l**). Even a bulky *tert*-butyl-substituted

Scheme 2. Nucleophilic Addition of *N,O*-Acetal 3[a]

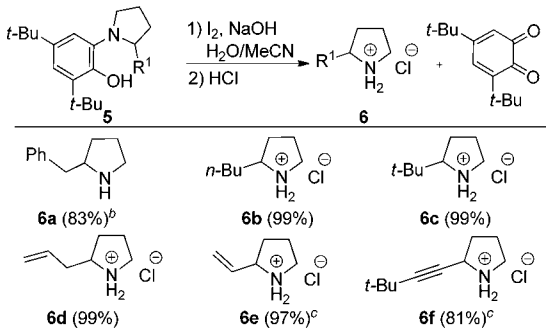


[a]Reaction conditions: *N,O*-acetal **3** (0.2 mmol) and R^1 MgBr or R^1Li (0.5 mmol) in DCE (2 mL) at 0 °C. [b]Carried out with R^1Li (1.0 mmol) in THF (3 mL) at −78 °C.

Grignard reagent was well tolerated (**5e**). The reaction of **3** with phenyl Grignard reagent afforded **5m′** (96%), presumably via air oxidation of **5m**.

Importantly, the *o*-hydroxy substituent on **5** facilitated removal of the aryl moiety. Among various oxidative cleavage conditions we tested, iodine in basic aqueous acetonitrile solution turned out to be efficient and also mild for the cleavage of the C−N bond.[14] Under these mild conditions, various 2-substituted pyrrolidines **6** were obtained in high yields (Scheme 3).

Scheme 3. Removal of the Aryl Moiety from 5[a]



[a]Reaction conditions: **5** (0.2 mmol), I_2 (0.22 mmol), NaOH (1 M, 7 mL), CH_3CN (14 mL). [b]The yield of free amine is reported only if it has a high boiling point. [c]7.0 mL of CH_3CN was used.

We then investigated the regio- and diastereoselectivity of α-C−H functionalization of 2-substituted pyrrolidines using 3,5-di-*tert*-butyl-*o*-benzoquinone (**1**) (Scheme 4). The secondary α-C−H bond of 2-methyl pyrrolidine was functionalized highly selectively to afford *trans*-substituted *N,O*-acetal **7a** in 95% isolated yield. The relative configuration of **7a** was unambiguously determined by X-ray crystallography.[15] Similar regio- and diastereoselectivities were observed for the reactions of 2-*n*-

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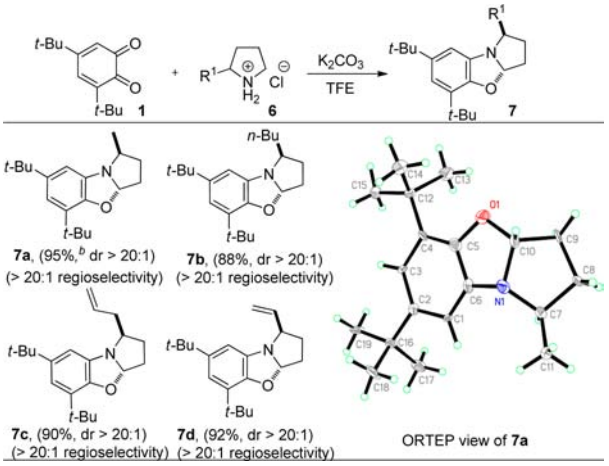
Scheme 4. Regio- and Diastereoselectivity of α-C−H Functionalization of 2-Substituted Pyrrolidines[a]

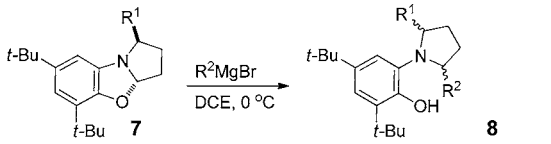


[a]Reaction conditions: **1** (0.2 mmol), **6** (0.24 mmol), K_2CO_3 (0.3 mmol), TFE (1.0 mL), room temperature. [b]Free 2-methylpyrrolidine was used; no K_2CO_3 was added.

butylpyrrolidine hydrochloride (**6b**) and 2-allylpyrrolidine hydrochloride (**6d**); **7b** and **7c**, respectively, were isolated as single isomers. Note that excellent regioselectivity was also observed for 2-vinyl-substituted pyrrolidine **6e**, which bears an allylic α-C−H bond; **7d** was the only product isolated.

Nucleophilic addition of Grignard reagents to *N,O*-acetal **7** yielded 2,5-difunctionalized products **8** in excellent yields, but the diastereoselectivity varied (Scheme 5). *Trans*-disubstituted

Scheme 5. Nucleophilic Addition Reactions of *N,O*-acetal 7

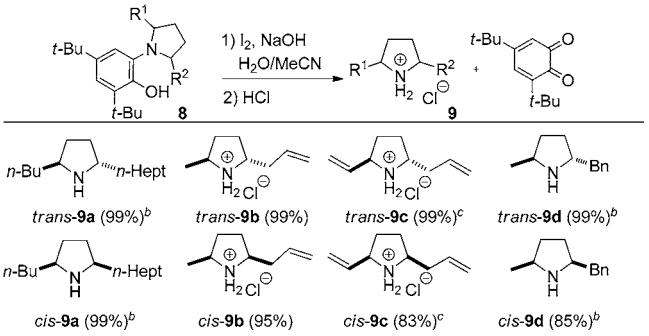


8a, $R^1 = R^2 =$ Me (99%) [*trans*-**8a** (58%); *cis*-**8a** (41%)]
8b, R^1 = Me, R^2 = allyl (95%) [*trans*-**8b** (86%); *cis*-**8b** (9%)]
8c, R^1 = Me, R^2 = Bn (94%) [*trans*-**8c** (90%); *cis*-**8c** (4%)]
8d, R^1 = *n*-Bu, R^2 = *n*-Pr (95%) [*trans*-**8d** (63%); *cis*-**8d** (32%)]
8e, R^1 = *n*-Bu, R^2 = *t*-Bu (93%) [*trans*-**8e** (62%); *cis*-**8e** (31%)]
8f, R^1 = *n*-Bu, R^2 = *n*-Hept (95%) [*trans*-**8f** (30%); *cis*-**8f** (65%)]
8g, R^1 = allyl, R^2 = vinyl (91%) [*trans*-**8g** (52%); *cis*-**8g** (39%)]

products were favored in most of the addition reactions[13c−e] However, it was mysterious that **7b** reacted with *n*-heptylmagnesium bromide to give more *cis* product, while it gave more *trans* product in its reaction with *n*-propylmagnesium bromide and *tert*-butylmagnesium bromide. Fortunately, the *trans* and *cis* diastereomers could be readily separated by column chromatography. When $R^1 \neq R^2$, the ^{1}H NMR spectra of *trans*-**8b**−**8g** were ambiguous because of the restricted rotation of the disubstituted pyrrolidine moiety. Variable-temperature ^{1}H NMR studies of *trans*-**8b** in DMSO-d_6 revealed that the two set of signals broadened and began to coalesce at 333 K.[16]

To synthesize 2,5-disubstituted pyrrolidines, we removed the aryl moieties of **8** under oxidative cleavage conditions similar to those used for *N*-dearylation of **5** (Scheme 6). The racemic *trans*- and *cis*- pyrrolidine alkaloid 225C (**9a**) were obtained in high yields.[17] This represents the first synthesis of these pyrrolidine alkaloids by means of sequential C−H functionalization. 2,5-

Scheme 6. Removal of Aryl Moiety[a]

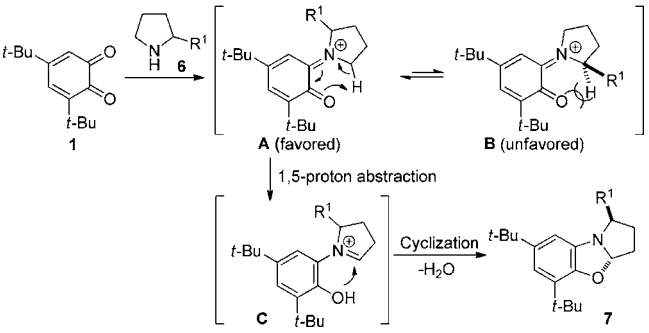


[a]Reaction conditions: **8** (0.2 mmol) and I_2 (0.22 mmol), aq NaOH (1 M, 7.0 mL), CH_3CN (14 mL). [b]The yield of free amine is reported only if it has a high boiling point. [c]7.0 mL of CH_3CN was used.

Disubstituted pyrrolidines **9b** and **9c** were also obtained in high yields, and their double bonds can be expected to enable the preparation of more complicated pyrrolidine alkaloids.[18]

We propose the following mechanism for the redox transformation (Scheme 7). First, 3,5-di-*tert*-butyl-*o*-benzoquinone

Scheme 7. Proposed Mechanism for Regio- and Diastereoselective α-Functionalization of 2-Substituted Pyrrolidines 6



(**1**) reacts with 2-pyrrolidines (**6**) to give iminium ion **A**. Owing to the steric bulk of the R^1 group, **A** preferentially undergoes 1,5-proton abstraction to form iminium ion **C**. Subsequent cyclization of **C** occurs from the less hindered face, leading to *trans*-substituted *N,O*-acetal **7**.

In summary, we developed an efficient, practical method for the synthesis of structurally diverse 2-substituted and 2,5-disubstituted pyrrolidines from pyrrolidine. The intramolecular redox-neutral α-functionalization of 2-substituted pyrrolidine was highly regio- and diastereoselective. The two substituents at the α-position of the pyrrolidines could be varied easily by the choice of appropriate Grignard reagents.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02298.

Experimental details, characterization data for new compounds, NMR spectra, and HRMS data (PDF)
X-ray crystallographic data for **7a** (CIF)

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Notes

The authors declare no competing financial interest.

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(11) The byproduct *o*-aminophenol **4** was likely formed by the reduction of the intermediate **A** or **C** by pyrrolidine in the reaction mixture.

(12) Piperidine could react with **1** but the reaction mainly gave *o*-aminophenol type product (formed in a similar way as *o*-aminophenol **4**) and it could not be converted to the corresponding *N*,*O*-acetal using the method described in ref 10c.

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(14) Selection of appropriate reaction conditions is described in the Supporting Information.

(15) CCDC-1405127 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB21EZ, UK; fax: (+44) 1223−336−033; or deposit@ccdc.cam.ac.uk).

(16) See Supporting Information for details.

(17) For selected previous reports on the synthesis of racemic pyrrolidine 225C, see: (a) Weidner, K.; Giroult, A.; Panchaud, P.; Renaud, P. *J. Am. Chem. Soc.* **2010**, *132*, 17511−17515. (b) Tufariello, J. J.; Puglis, J. M. *Tetrahedron Lett.* **1986**, *27*, 1489−1492. (c) Gessner, W.; Takahashi, K.; Brossi, A.; Kowalski, M.; Kaliner, M. A. *Helv. Chim. Acta* **1987**, *70*, 2003−2010. (d) Miyashita, M.; Awen, B. Z. E.; Yoshikoshi, A. *Tetrahedron* **1990**, *46*, 7569−7586. For selected previous reports on asymmetric synthesis of pyrrolidine 225c, see: (e) Davis, F. A.; Xu, H.; Wu, Y.; Zhang, J. *Org. Lett.* **2006**, *8*, 2273−2276. (f) Gärtner, M.; Weihofen, R.; Helmchen, G. *Chem. - Eur. J.* **2011**, *17*, 7605−7622. (g) Dübon, P.; Farwick, A.; Helmchen, G. *Synlett* **2009**, *9*, 1413−1416. (h) Arredondo, V. M.; Tian, S.; McDonald, F. E.; Marks, T. J. *J. Am. Chem. Soc.* **1999**, *121*, 3633−3639.

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