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Unusual biaryl torsional strain promotes reactivity in Cu-catalyzed Sommelet–Hauser rearrangement†

Chongqing Pan, Wenjing Guo and Zhenhua Gu *

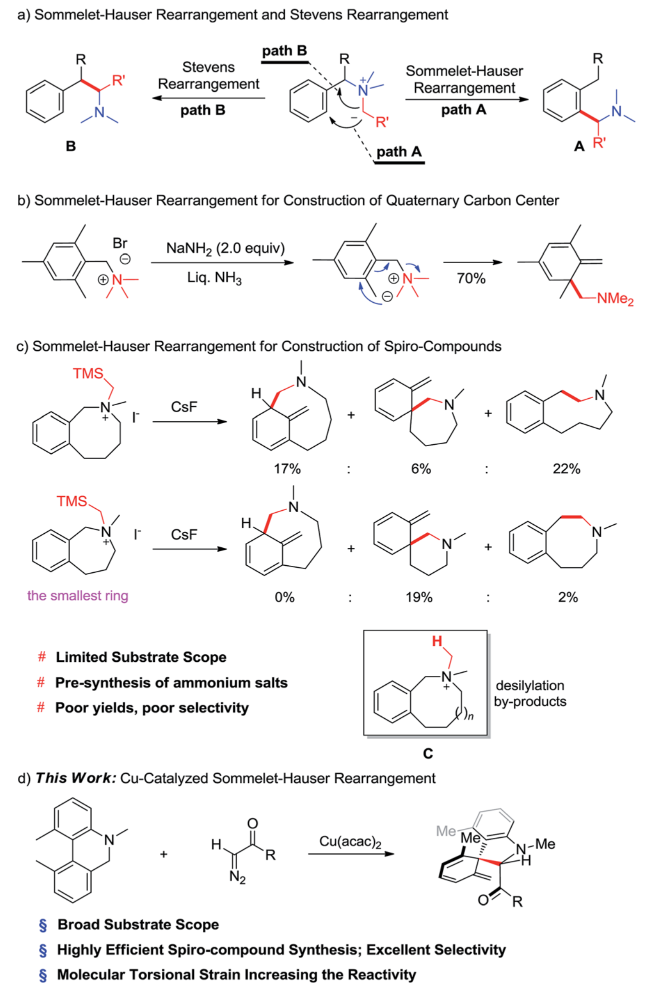
A Cu-catalyzed Sommelet–Hauser dearomatization of dihydrophenanthridine and diazo compounds is reported for the synthesis of spiro-indolines. A spiro-structure with adjacent quaternary and tertiary carbon centers was constructed in one step as a single isomer. Increasing steric hindrance by introducing *ortho*-substituents dramatically improved substrate reactivity in this transformation.

Introduction

Dearomatization is a robust method for the construction of polyfunctionalized cyclic compounds; it can generate quaternary carbon centers and multi-substituted C=C double bonds in one or two steps. Due to the high stabilization of aromaticity, dearomatization reactions are traditionally performed under harsh conditions, such as oxidation in the presence of hypervalent iodine,[1] Birch reduction,[2] enzymatic conditions,[3] or other conditions.[4] Dearomatization has recently been achieved using photochemistry and transition metal catalysis. In particular, catalytic asymmetric dearomatization (CADA) has attracted substantial attention, such as from the You group, for constructing optically pure molecules from arenes.[5]

The Sommelet–Hauser reaction is an intramolecular rearrangement of benzyl ammonium salts to give *ortho*-substituted benzylamines (Scheme 1a, **path A**).[6–8] Sommelet–Hauser dearomatization can efficiently generate valuable three-dimensional compounds bearing quaternary carbon centers if the two *ortho* positions have non-hydrogen substituents (Scheme 1b). In a variation known as thio-Sommelet rearrangement, dearomatized compounds bearing thioether functionalities can be prepared by replacing the ammonium ylides with sulfur ylides.[9,10]

A challenge to exploiting the Sommelet–Hauser reaction is preventing competitive Stevens rearrangement,[11,12] in which formal intramolecular nucleophilic attack at the benzylic position affords 2-phenylethanamine analogues (Scheme 1a, **path B**). Singleton has argued that these two types of rearrangements compete dynamically because they can occur *via* the same transition state.[13]



Scheme 1 The Sommelet–Hauser rearrangement.

Department of Chemistry, Center for Excellence in Molecular Synthesis, Hefei National Laboratory for Physical Sciences at the Microscale, University of Science and Technology of China, 96 Jinzhai Road, Hefei, Anhui 230026, China. E-mail: zhgu@ustc.edu.cn

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Sommelet–Hauser rearrangement can be used to produce spiro-compounds from benzocyclic ammonium salts, but the reported reactions usually give low yields and wide product distribution.[14] For example, the reaction usually produces two regioisomers together with ring-enlarged products from Stevens rearrangement (Scheme 1c). Ring strain in seven- and eight-membered structures lowers the rearrangement rate, significantly increasing the yields of desilylation by-products **C**. In addition, the requirement for pre-synthesized ammonium salts considerably limits the substrate scope of the reaction. Third, the Sommelet–Hauser rearrangement appears incompatible with ammonium salts with fewer than seven members. As a result, the reaction cannot generate rings smaller than six-membered N-heterocycles (Scheme 1c).

Herein we report the copper-catalyzed generation of nitrogen ylide intermediates capable of Sommelet–Hauser rearrangement, in which N-containing six-membered rings efficiently participate. We further report that molecular torsional strain in biaryl substrates increases their reactivity in this rearrangement.

We wondered whether we could adapt dearomatization *via* Sommelet–Hauser rearrangement to generate the important spirocyclohexaneindoline structural motif, found in several natural products including gelsemine,[15] 21-oxogelsemine[16] and koumine (Fig. 1).[17] It also comprises the core structural unit of various biologically active molecules.[18]

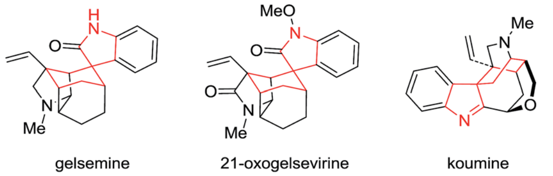


Fig. 1 Natural products containing a spirocyclohexaneindoline skeleton.

Results and discussion

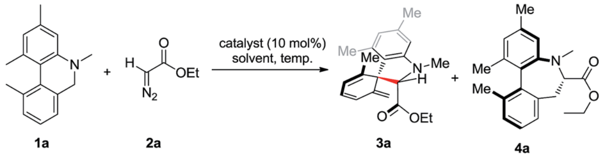
Optimization

We were unable to dearomatize biaryl compound **1a** using diazo compound **2a** in the presence of silver, rhodium or gold salts as catalysts, which are frequently used in reactions involving carbene (Table 1, entries 1–3). We were pleased to find that **1a** reacted with **2a** in the presence of Cu(OTf) 0.5PhH at 90 °C to give 27% of spiro product **3a** as a single isomer, along with a small amount of **4a** (entry 4). The reaction generated a spiro-structure with adjacent quaternary and tertiary carbon centers in one step. Screening of copper salts showed Cu(acac)$_2$ to perform the best in terms of yield and reaction time (entries 5–9). Lowering the reaction temperature increased the selectivity for **3a** over the Stevens rearrangement product **4a**, improving the isolated yield of **3a** to 72% (entry 10). Solvent screening identified methyl *tert*-butyl ether (MTBE) as the best (entries 11–13). The reaction proceeded smoothly with only 5 mol% of Cu(acac)$_2$, albeit with a slightly lower yield (entry 14).

Substrate scope

With the optimal conditions in hand, we tested the generality of this Cu(acac)$_2$-catalyzed Sommelet–Hauser rearrangement. Diazo compounds with different ester groups, such as methyl, *tert*-butyl and substituted benzyl esters, reacted smoothly (**3b–**

Table 1 Optimization of reaction conditions^a

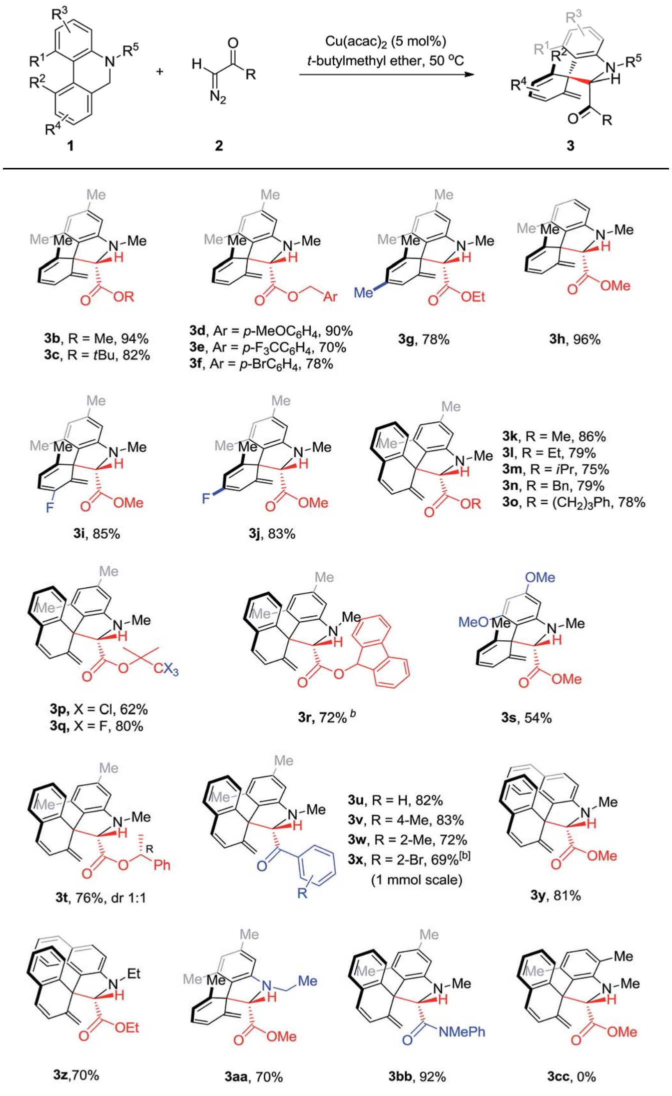


Entry	Catalyst	Solvent	T/°C	Yield of **3a**/%	Yield of **4a**/%
1	Rh$_2$(OAc)$_4$ (5 mol%)	Toluene	90	<5	—
2	(Ph$_3$P)AuCl	Toluene	90	–^{b}	—
3	AgOTf	Toluene	90	NR	—
4	Cu(OTf) 0.5PhH	Toluene	90	27	<5
5	Cu(OTf)$_2$	Toluene	90	NR	—
6	Cu(MeCN)$_4$PF$_6$	Toluene	90	32	<5
7	CuTC	Toluene	90	47	<5
8	Cu(acac)$_2$	Toluene	90	63	<5
9	Cu(hfacac)$_2$	Toluene	90	<5	—
10	Cu(acac)$_2$	Toluene	50	72	—
11	Cu(acac)$_2$	MTBE	50	83	—
12	Cu(acac)$_2$	DCE	50	53	—
13	Cu(acac)$_2$	THF	50	72	—
14	Cu(acac)$_2$ (5 mol%)	MTBE	50	79	—

^{a} Unless stated otherwise, the reaction was conducted with **1a** (0.10 mmol), **2a** (0.20 mmol), and a metal catalyst (10 mol%). ^{b} An unidentified product was formed.

f). A diazo substrate with an electron-withdrawing group (CF_3) led to a slightly lower yield (**3e**). The reaction tolerated additional methyl groups, a fluorine atom and methoxyl groups in the biaryl aniline skeleton (**3g–3j**, **3t**). Naphthalene-based substrates and a binaphthalene derivative reacted uneventfully to give the spiro compounds in decent to excellent yields (**3k–3r**, **3t–3z** and **3bb**). Stereoinduction did not occur with the (*R*)-1-phenylethanol-derived diazo compound, such that a pair of diastereoisomers was isolated in a 1 : 1 ratio (**3t**). This rearrangement was compatible with ketones and amides, which afforded the desired products in decent to good yields (**3u–3x**). Introducing a methyl group adjacent to the C–N bond completely inhibited this transformation (**3cc**). The reaction tolerated an aryl-Br bond. Scale-up also proved possible, with compound **3x** isolated in 69% yield on the 1.0 mmol scale.

Table 2 Substrate scope[a]



3b, R = Me, 94%
3c, R = *t*Bu, 82%

3d, Ar = *p*-MeOC$_6$H$_4$, 90%
3e, Ar = *p*-F$_3$CC$_6$H$_4$, 70%
3f, Ar = *p*-BrC$_6$H$_4$, 78%

3g, 78%

3h, 96%

3i, 85%

3j, 83%

3k, R = Me, 86%
3l, R = Et, 79%
3m, R = *i*Pr, 75%
3n, R = Bn, 79%
3o, R = (CH$_2$)$_3$Ph, 78%

3p, X = Cl, 62%
3q, X = F, 80%

3r, 72% [b]

3s, 54%

3t, 76%, dr 1:1

3u, R = H, 82%
3v, R = 4-Me, 83%
3w, R = 2-Me, 72%
3x, R = 2-Br, 69%[b]
(1 mmol scale)

3y, 81%

3z,70%

3aa, 70%

3bb, 92%

3cc, 0%

[a] The reaction was conducted with **1** (0.10 mmol), diazo compound **2** (0.20 mmol), and Cu(acac)$_2$ (0.005 mmol, 5 mol%) in MTBE at 50 °C. [b] The reactions were performed in toluene.

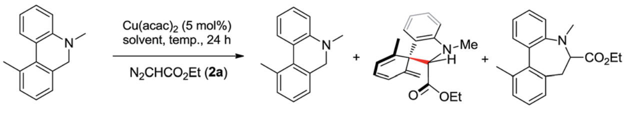
The two *ortho*-substituents (R^1 and R^2 in Table 2) strongly influenced the efficiency of the Sommelet–Hauser reaction and selectivity for this type of rearrangement over Stevens rearrangement (Scheme 2). For example, under the standard conditions at 50–90 °C, the conversions of **5** were less than 55%, while isolated yields of **6** were no more than 35%. Product **6** was much less stable during purification than products **3a–3bb**. Performing the reaction at higher temperature in toluene gave Stevens rearrangement product **7** as the major product, with **5** recovered at 55% yield.

Synthetic applications

Preliminary synthetic studies were performed to demonstrate the utility of this rearrangement. Under 1 atm H_2, the diene compound **3k** underwent chemoselective 1,4-hydrogenation in the presence of Pd/C to give **8k** in 83% yield, whose structure was unambiguously confirmed by single-crystal X-ray diffraction analysis. The *N*-methyl group could be further modified *via* rhodium-catalyzed C–H functionalization to afford **9k**. Finally, the ester functionality could be reduced to the corresponding alcohol using DIBAL-H at −78 °C without eliminating the diene moiety. The diene was further cyclized in the presence of the MeNHOH·HCl catalyst to yield polycyclic compound **10k** in 57% yield (Scheme 3).

Mechanistic studies

In a plausible catalytic cycle (Scheme 4), the reaction begins when copper salt interacts with the diazo compound to give copper–carbene complex **D**, releasing one molecule of nitrogen gas. The subsequent reaction of the copper–carbene complex with amine **1** affords the ylide **E**. Intramolecular nucleophilic attack in **E** delivers the spiro product **3** either before or after dissociation of the copper catalyst. To obtain structural information about ammonium salt **E** and explain the different reactivity between **1** and **5**, two ammonium compounds **F** and **G** were synthesized and analyzed by single-crystal X-ray diffraction. The torsional angle (C5–C6/C7–C13) was around 41° in **F** and 29° in **G**.[19] Steric repulsion between the two *ortho*-substituents increased the distortion in the biaryl structure. We reasoned that the two *ortho*-substituents in **E** should distort its structure to a similar extent as in **F**. As a result, the relatively high-energy intermediate **E** undergoes a rapid intramolecular nucleophilic reaction to deliver spiro compounds. Alternatively,

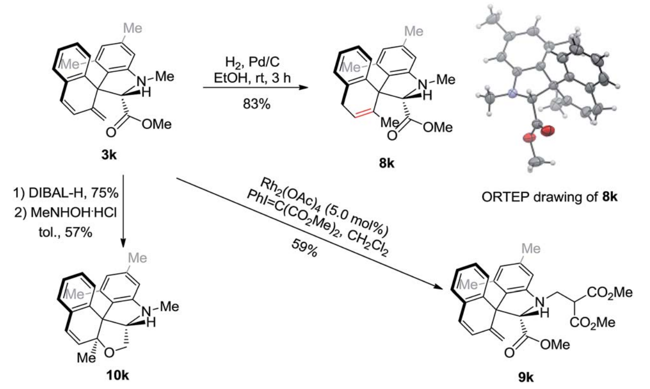


5 **5** **6** **7**

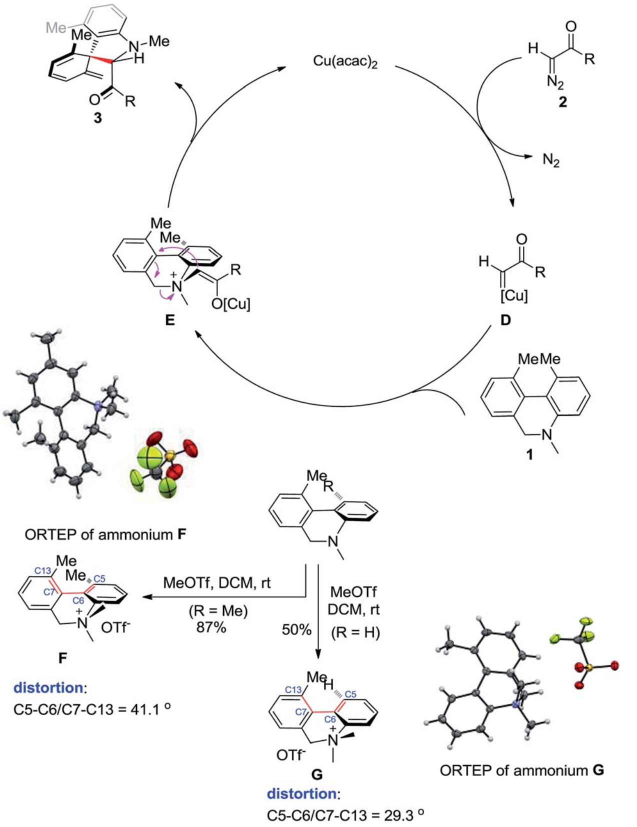
solvent	temp./°C	5	6	7
MTBE	50	64%	35%	-
MTBE	90	53%	34%	< 5%
toluene	90	43%	25%	< 5%
toluene	110	55%[a]	< 5%	33%

[a] It was contaminated with unidentified products.

Scheme 2 Substituent effects.



Scheme 3 Control experiment and synthetic applications.



Scheme 4 Plausible mechanism.

the increased torsion reduces the delocalization of the aniline lone-pair, which increases the basicity and accelerates the ammonium formation. Substituents on the substrates strongly influence the ratio of the [2,3]-rearrangement product to the Stevens rearrangement product;[13] the latter rearrangement usually proceeds *via* a bi-radical pathway under thermal conditions.[20] These considerations imply that less distorted substrates such as **5** generate lower-energy ylide intermediates, which therefore must overcome a higher activation barrier to give spiro products. Consistent with this, compound **5** was associated with lower conversion rates under the similar conditions.

Conclusions

We have reported a copper-catalyzed Sommelet–Hauser rearrangement to construct spiroindoline compounds bearing adjacent quaternary and tertiary carbon centers. Increasing the torsional strain in the biaryl substrate increases its reactivity in this transformation. This is, to our knowledge, the first report in which Sommelet–Hauser rearrangement was used to generate spiro compounds bearing five-membered N-heterocycles.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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