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Journal

Chemistry - A European Journal, 20(9)

ISSN

0947-6539

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Publication Date

2014-02-24

DOI

10.1002/chem.201304204

Peer reviewed

Published in final edited form as:
Chemistry. 2014 February 24; 20(9): 2445–2448. doi:10.1002/chem.201304204.

One-Pot Synthesis of Fused Pyrroles via a Key Gold Catalysis-Triggered Cascade

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Abstract

A two-step, one-pot synthesis of fused pyrroles is realized by firstly condensing *N*-alkynylhydroxammonium salt with readily enolizable ketone under mild basic condition and then subjecting the reaction mixture to a gold catalyst, which triggers a cascade reaction featured by a facile initial 3.3-sigmatropic rearrangement of the gold catalysis product, i.e., an *N*,*O*-dialkenylhydroxamine. The reaction provides a facile access to polycyclic pyrroles in moderate to good yields.

Keywords

pyrrole; rearrangement; gold; catalysis; hydroxamine

Recently we reported an efficient synthesis of 2-alkylindoles based on the 3,3-sigmatropic rearrangements of *O*-vinyl-*N*-arylhydroxyamines (e.g., **1**), which are generated via gold-catalyzed additions of *N*-arylhydroxyamines to terminal alkynes (Scheme 1).[1] The pericyclic reaction occurs readily at ambient temperature, which is attributed to the weak N-O bond. Relying on the same type of facile 3,3-sigmatropic rearrangements, a related chemistry using hydroxamic acids or *N*-hydroxycarbamates as substrates was realized via a dual Au and Zn catalysis and showed much better reaction scopes in the synthesis of *N*-protected substituted indoles (Scheme 1).[2]

In both cases, the gold catalyses were key as the requisite *O*-alkenyl-*N*-aryl hydroxamines could not be otherwise easily prepared.[3] We envisioned that related *N*,*O*-dialkenylhydroxamines, again difficult to access if in the absence of electronic assistance and/or excessive heating,[4] could also be made available via gold catalysis,[5] and their further transformations would offer valuable opportunities to develop versatile synthetic methods based on an initial gold catalysis. Herein, we report an implementation of the approach, which led to the development of a two-step, one-pot expedient synthesis of fused pyrroles.[6]

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Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201xxxxxx.

Our design is shown in Scheme 2. It is envisioned that the condensation between a ketone and an *N*-monosubstituted hydroxamine (e.g., **3**) would lead to the more stable *N*-hydroxyenamine form **4** instead of the nitrone form **4'** if the ketone has an electron-withdrawing group at its α-position. If the alkyl group of the original hydroxamine has an ideally positioned C-C triple bond, **4** could undergo gold-catalyzed cyclization to deliver an *N*-alkenyl-*O*-alkenylhydroxamine (e.g., **5**), which, like the related intermediate **1**, should undergo rapid 3,3-sigmatropic rearrangement. The thus-formed cyclic imino ketone (e.g., **6**) could tautomerize to an enamine (e.g., **7**), which might undergo transannular dehydrative cyclization to complete the gold catalysis-triggered cascade and deliver the product **8** as a 2,3-dihydro-1H-pyrrolizine product (n = 1) or as a 5,6,7,8-tetrahydroindolizine (n = 2). Such a bicyclic pyrrole skeleton can be found in bioactive indole alkaloids as part of the indole ring such as polysin[7] and flinderoles,[8] antibacterial indoloquinone 7-methoxymitosene[9] (Figure 1) as well as synthetic compounds studies in medicinal chemistry.[10]

To implement the design, we synthesized the *N*-hydroxyenamine **4a** by condensing *N*-(pent-4-yn-1-yl)hydroxylamine and 1,3-cyclohexanedione and treated it with various gold catalysts in dichloromethane (Table 1). To our delight, the desired reaction occurred readily in the presence of $Ph_3PAuNTf_2$, affording the desired tricyclic pyrrole **8a** in a moderate 50% yield (entry 1). Notably, the eight-membered ring intermediate of type **7** was not detected by ^1H NMR, suggesting that its subsequent transannular condensation was facile. This encouraging result was readily improved by using other gold catalysts (entries 2–5). In particular, both $BrettPhosAuNTf_2$[11] (entry 3) and $Mor\text{-}DalPhosAuNTf_2$[12] (entry 4) led to >80% NMR yield of the desired product. Although the latter catalyst was slightly more effective, the reaction was much slower and, moreover, the crude ^1H NMR was less clean than in the case using the former catalyst. As a result, $BrettPhosAuNTf_2$ was preferred. On the other hand, $AuCl_3$ was less effective as a catalyst (entry 6), and the reaction was most likely not promoted by a Brønsted acid as CF_3COOH, even with a large excess amount, was totally incapable of promoting the reaction (entry 7).

To improve the overall operational efficiency, we probed whether the synthesis of the *N*-hydroxyenamine precursor **4** and the subsequent gold catalysis could be integrated into a one-pot process. First, we examined the synthesis of **4a** via the condensation between *N*-(pent-4-yn-1-yl)hydroxammonium trifluoroacetates and 1,3-cyclohexanedione in the presence of a base, at ambient temperature and under N_2 atmosphere. The protonated hydroxamine was used as its free form is prone to oxidation. Mindful of the potential inhibition of gold catalysis by base, we limited the choices of bases to those of mild nature. As shown in Table 2, while K_2CO_3 (entry 1) worked poorly, the other bases including 8-methylquinoline (entry 2), sodium tosylate (entry 3), NaOAc (entry 4) and $NaHCO_3$ (entry 5) were all effective, with the last one affording the highest NMR yield of **4a**.

With the mild conditions (Table 2, entry 5) established for the preparation of **4a**, a subsequent Au catalysis using the optimized conditions in Table 1 in a one-pot manner was then performed. To our delight, the reaction proceeded smoothly although expectedly slower, and the one-pot overall isolated yield was good (Entry 1, Table 3).

With the one-pot, two-step reaction realized, we then probed the reaction scope. A series of readily available substituted 1,3-cyclohexanediones were first examined. To our delight, many of them underwent the reaction smoothly, affording substituted tricyclic pyrroles in mostly good yields (Table 3, entries 2–6). Interestingly, when the two carbonyl groups are sterically differentiated as in the case of **2c** or **2f**, the more hindered one remained unchanged while the α-unsubstituted one was incorporated into the pyrrole ring of the isolated product (entries 3 and 6), indicating a high level of steric preference. In addition to cyclohexane-1,3-diones, cyclopentane-1,3-diones also participated in the reaction without accident, affording **8g** with an exquisite linear azatriquinane skeleton. While the overall yields in most cases are moderate, these one-pot reactions are serviceable considering the enhanced operational efficiency and, moreover, the average yield for each step is >70%.

To further expand the reaction scope, we turned to acyclic 1,3-diketone compounds. Instead of the anticipated product, an acyl-substituted 1,2-fused pyrrole (i.e., **9**, Scheme 3), the isoxazonium intermediate **10** was detected. This heteroarene is likely formed during the first condensation step in the absence of the gold catalysis and, moreover, $NaHCO_3$ might not be involved in the reaction, either, as shown in the proposed mechanism (Scheme 3). Indeed, when the substrates were mixed in DCE, **10** were formed in 60% NMR yield within the same time frame.

To circumvent the formation of 10 or its congeners, we reasoned that an electron-withdrawing R1 or R2 group in 10 might hinder its formation due to the destabilization of the positively charged isoxazole ring. Indeed, when 1,1,1-trifluoropentane-2,4- dione was employed, the expected bicyclic pyrrole was obtained in 42% yield (Table 4, entry 1). Though with a low efficiency, the reaction was highly selective toward the less electrophilic carbonyl group. An alternative approach to avoid the formation of isoxazonium intermediates is to replace one of the carbonyl group with other electron-withdrawing groups. For example, when a 4-nitrophenyl group was employed, a low yet serviceable yield of the substituted bicyclic pyrrole **8i** was realized (entry 2). We also varied the *N*-alkynylhydroxamine. A benzene-fused variant (i.e., **11**) reacted without incident to afford the tetracyclic pyrrole **8j** in a good overall yield for the two step sequence (entry 3), and a homolog with a one-carbon longer linker also participated in the reaction smoothly, thus leading to the formation of a piperidine-fused tricyclic pyrrole (i.e., **8k**) in a good overall yield (entry 4).

In summary, we have developed a facile two-step, one-pot methods for the synthesis of a range of fused pyrroles from *N*-alkynylhydroxamines and readily enolizable ketones. By varying the substrates, fused pyrroles of different bicyclic, tricyclic and tetracyclic skeletons can be readily access in moderate to good yields. This reaction employs a key gold catalysis to trigger a cascade process featuring an initial facile 3.3-sigmatropic rearrangement of the gold catalysis product, i.e., an *N*,*O*-dialkenylhydroxamine. Our further work on combining gold catalysis with facile downstream transformations will be reported in due course.

Experimental Section

One-pot synthesis of fused pyrroles (8a–k) with the gold catalysis-triggered cascade: To vial with magnetic stirring bar was added *N*-alkylhydroxylammonium trifluoroacetate (0.1 mmol), ketones **2a–i** (1.2 equiv.), $NaHCO_3$ (1.2 equiv.) and 1,2-dichloroethane (2 mL). The system was degassed with N_2 and the mixture was stirred at room temperature. The reaction was monitored by TLC. Upon finished, the cap was opened and the BrettPhosAuNTf$_2$ (5 mol%) was added. The reaction was allowed to stir at room ptemperature until completion (monitored by TLC), and was concentrated under reduced pressure. The residue was purified by flash column chromatography to afford the product **8a–k**.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The authors thank NIGMS (R01 GM084254) for generous financial support.

References

1. Wang Y, Ye L, Zhang L. Chem. Commun. 2011; 47:7815–7817.
2. Wang Y, Liu L, Zhang L. Chem. Sci. 2013; 4:739–746.
3. For a review, see: Joule JA. Sci. Synth. 2000; 10:380–383.
4. For selected examples, see: Sheradsky T. Tetrahedron Lett. 1970; 11:25–26. Trofimov BA, Korostova SE, Belabanova LN, Mikhaleva AI. Zh. Org. Khim. 1978; 14:2182–2184. Ngwerume S, Camp JE. J. Org. Chem. 2010; 75:6271–6274. [PubMed: 20718448] Ngwerume S, Lewis W, Camp JE. J. Org. Chem. 2012; 78:920–934. [PubMed: 23270303]
5. For selected reviews, see: Hashmi ASK. Chem. Rev. 2007; 107:3180–3211. [PubMed: 17580975] Fürstner A, Davies PW. Angew. Chem., Int. Ed. 2007; 46:3410–3449. Patil NT, Yamamoto Y. Chem. Rev. 2008; 108:3395–3442. [PubMed: 18611054] Jiménez-Núñez E, Echavarren AM. Chem. Rev. 2008; 108:3326–3350. [PubMed: 18636778] Gorin DJ, Sherry BD, Toste FD. Chem. Rev. 2008; 108:3351–3378. [PubMed: 18652511] Arcadi A. Chem. Rev. 2008; 108:3266–3325. [PubMed: 18651778] Abu Sohel SM, Liu R-S. Chem. Soc. Rev. 2009; 38:2269–2281. [PubMed: 19623349] Wang S, Zhang G, Zhang L. Synlett. 2010:692–706. Rudolph M, Hashmi ASK. Chem. Commun. 2011; 47:6536–6544.
6. For selected examples of Au/Pt-catalyzed pyrrole or fused pyrrole formation, see: Arcadi A, Giuseppe SD, Marinelli F, Rossi E. Adv. Synth. Catal. 2001; 343:443–446. Li G, Huang X, Zhang L. Angew. Chem., Int. Ed. 2008; 47:346–349. Yan Z-Y, Xiao Y, Zhang L. Angew. Chem., Int. Ed. 2012; 51:8624–8627. Kern N, Hoffmann M, Blanc A, Weibel J-M, Pale P. Org. Lett. 2013; 15:836–839. [PubMed: 23350973]
7. Ngantchou I, Nyasse B, Denier C, Blonski C, Hannaert V, Schneider B. Bioorg. Med. Chem. Lett. 2010; 20:3495–3498. [PubMed: 20529682]
8. Fernandez LS, Buchanan MS, Carroll AR, Feng YJ, Quinn RJ, Avery VM. Org. Lett. 2008; 11:329–332. [PubMed: 19090698]
9. Allen GR, Poletto JF, Weiss MJ. J. Am. Chem. Soc. 1964; 86:3877–3878.
10. Saida, M.; Inoue, T.; Beppu, K.; Tagami, Y.; Shinohara, I.; Fujimoto, N.; Tsuji, M.; Noda, K. Jpn. Kokai Tokkyo Koho. Japan: Hisamitsu Pharmaceutical Co., Inc.; 1990. p. 8
11. (a) Fors BP, Watson DA, Biscoe MR, Buchwald SL. J. Am. Chem. Soc. 2008; 130:13552–13554. [PubMed: 18798626] (b) Ye L, He W, Zhang L. Angew. Chem., Int. Ed. 2011; 50:3236–3239.
12. (a) Hesp KD, Stradiotto M. J. Am. Chem. Soc. 2010; 132:18026–18029. [PubMed: 21133383] (b) Luo Y, Ji K, Li Y, Zhang L. J. Am. Chem. Soc. 2012; 134:17412–17415. [PubMed: 23039251]

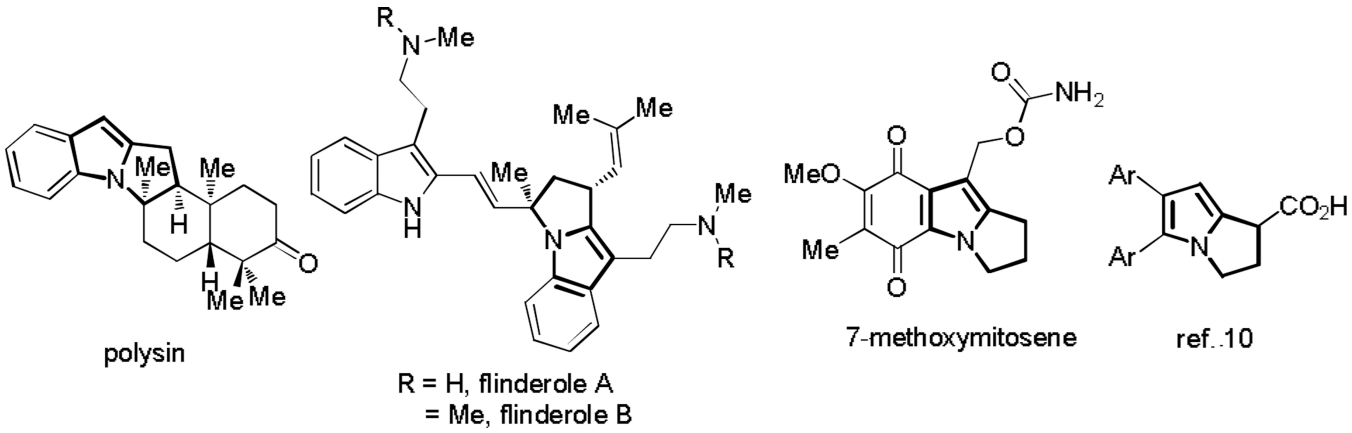
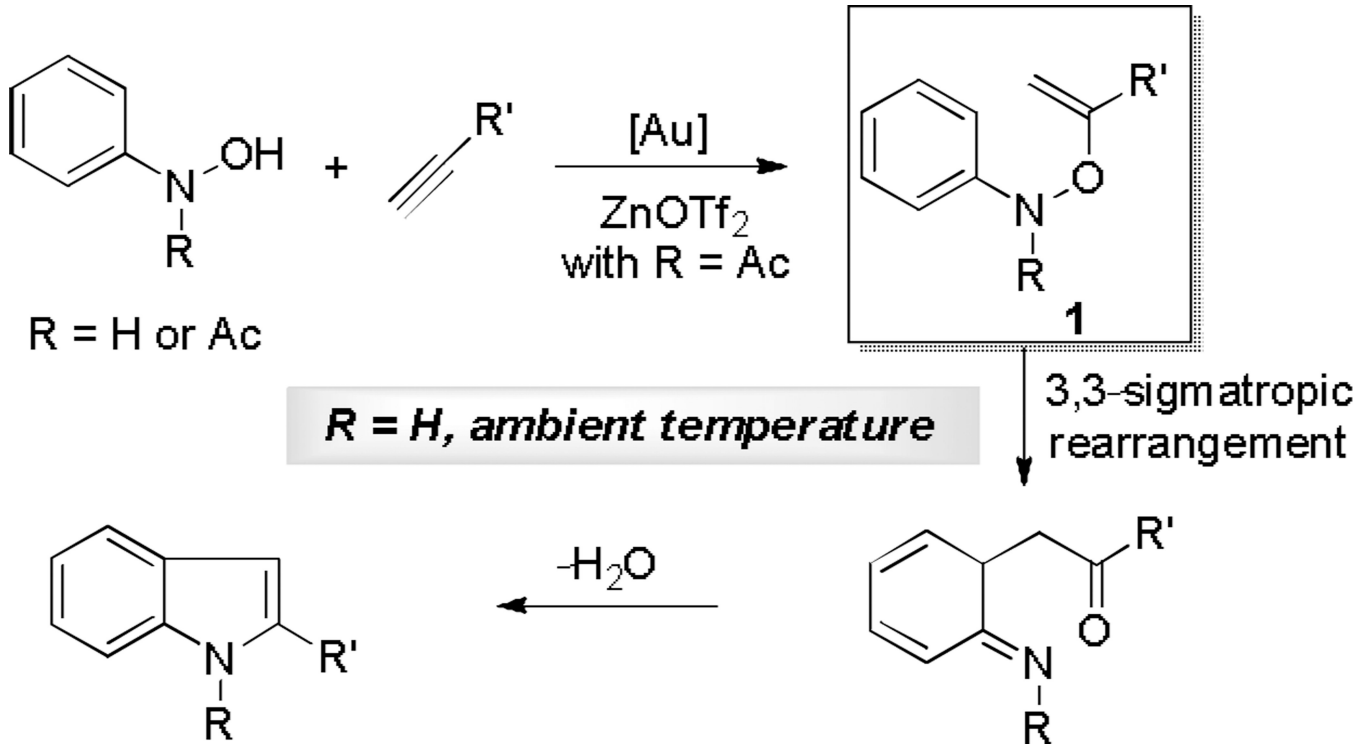
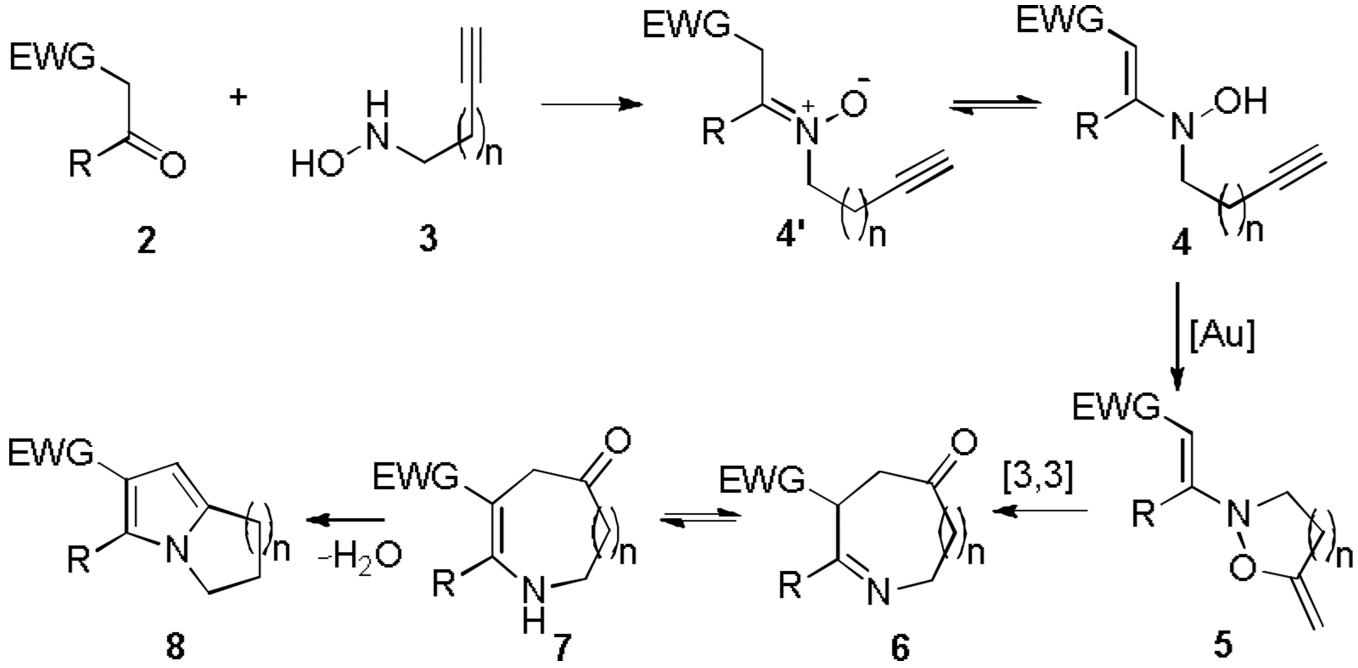


Figure 1.
Natural products and/or bioactive compounds containing a 2,3-dihydro-1H-pyrrolizine moiety.

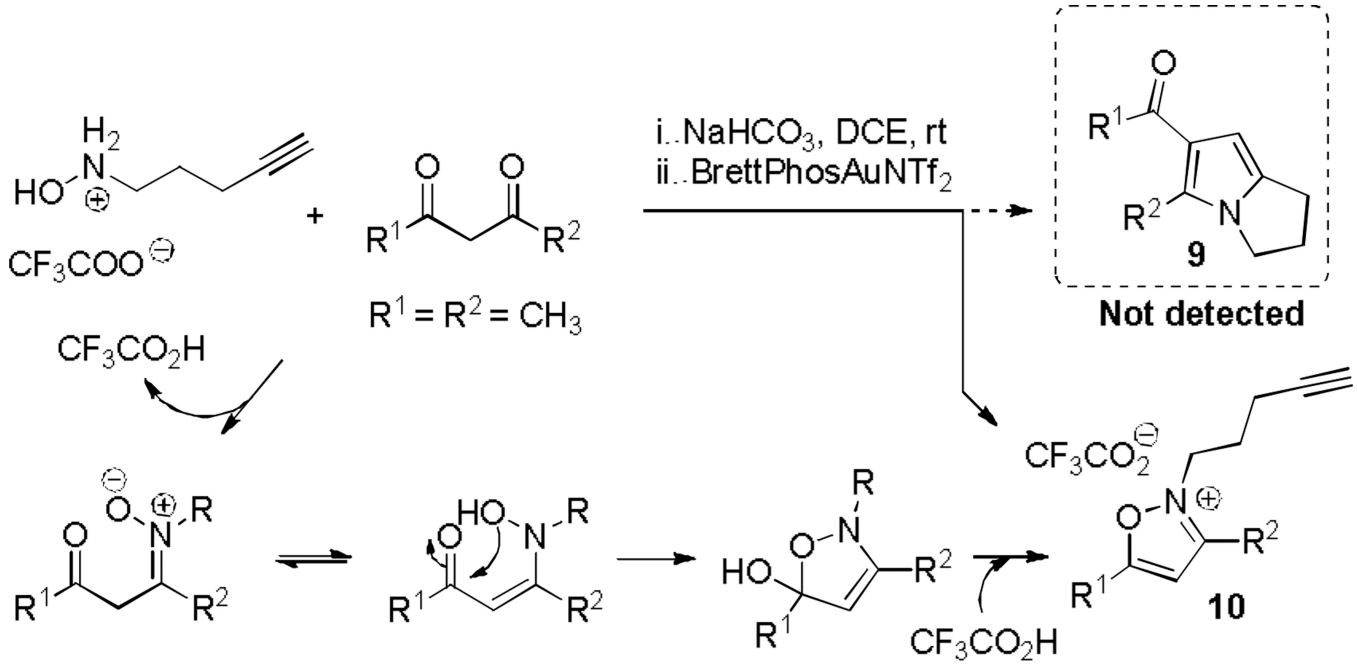


Scheme 1.

Indole synthesis triggered by initial gold-catalyzed generations of *O*-alkenyl-*N*-arylhydroxamines[1] or their *N*-acyl variants.[2]



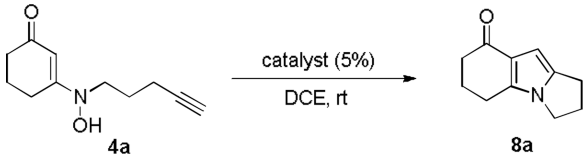
Scheme 2.
Reaction design.



Scheme 3.
Applying acyclic 1,3-diketone compounds to the reaction condition

Table 1

Reaction discovery and optimization



4a 8a

Entry	Catalyst	Time	Yield[a]
1	$Ph_3PAuNTf_2$	4.5 h	50%
2	$IPrAuNTf_2$	7 h	72%
3	**$BrettPhosAuNTf_2$**	**0.5 h**	**82%**
4	$MorDalPhosAuNTf_2$	6 h	85%
5	$PhosphiteAuNTf_2$	2 h	57%
6	$AuCl_3$	overnight	42%[c]
7	CF_3COOH[c]	overnight	<1%[c]

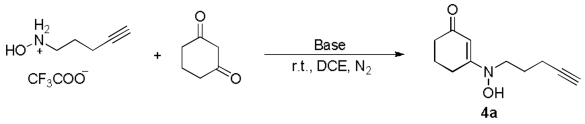
[a] NMR yield, determined by using diethyl phthalate as the internal reference.

[b] Not finished when stopped.

[c] 10 equivalents used.

Table 2

Optimizing the conditions of the condensation step

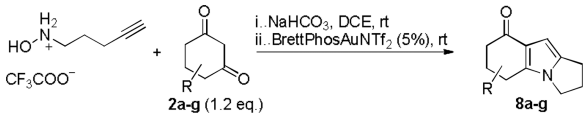


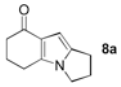
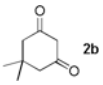
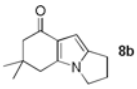
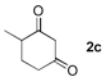
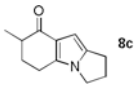
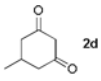
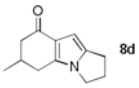
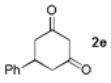
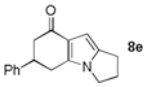
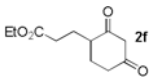
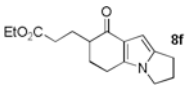
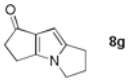
Entry	Base	Time	Yield[a] (%)
1	K_2CO_3 (1.5 eq.)	4 h	37
2	8-Methylquinoline (1.2 eq.)	3 h	88
3	TsONa (1.0 eq.)	2 h	80
4	NaOAc (1.2 eq.)	2.5 h	83
5	$NaHCO_3$ (1.2 eq.)	1.5 h	93

[a]NMR yield, determined by using diethyl phthalate as the internal reference.

Table 3

One-pot synthesis of tricyclic pyrroles from different 1,3-cyclodiketones



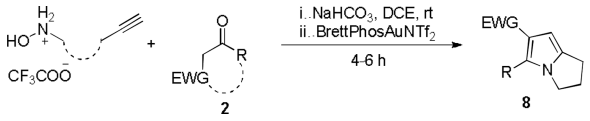
Entry	Substrate	Product	Yield[a]
1			75%, 4 h
2			55%, 4 h
3			62%[b], 4.5 h
4			52%, 4 h
5			57%, 3.5 h
6			63%[b], 8 h
7			50%, 7.5 h

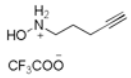
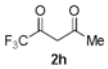
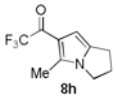
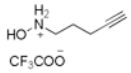
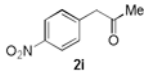
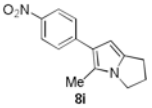
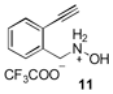
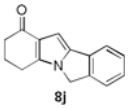
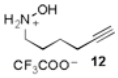
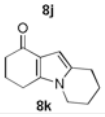
[a] One-pot overall isolated yield. Reaction time referring to the both steps.

[b] Regiochemistry established by nOe experiments.

Table 4

Expanded reaction scope[a]



Entry	Hydroxylamine	Ketone 2	Product	Yield[b]
1		 2h	 8h	42%[c]
2		 2i	 8i	37%
3	 11	 2a	 8j	61%
4	 12	 2a	8j  8k	56%

[a]Reactions were run with the same condition as in Table 3.

[b]Isolated yield.

[c]Structure as shown, determined by nOe experiment.