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A Modular, Efficient, and Stereoselective Synthesis of Substituted Piperidin-4-ols

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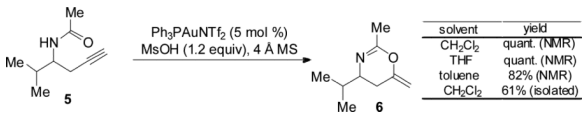
Keywords

piperidine; cyclization; gold; stereoselectivity; reduction

Piperidine is a key structural motif in various alkaloids and a variety of compounds studied in medicinal chemistry. Though many methods have been developed for their construction, there is still a need for noval approaches, especially those with high efficiency, good modularity and excellent stereoselectivity.

Recent intense research in gold catalysis[1] has provided several novel methods of piperidine synthesis.[2,3] For example, we reported earlier that piperidin-4-ones could be prepared in a two-step, [4+2] manner;[2a] however, the products are limited to those with ring nitrogen substituted with hard-to-remove aliphatic groups or benzyl groups suffering from low regioselectivities. To address this deficiency and develop a generally effective and modular synthesis of *N*-unsubstituted piperidines, we envisioned, as shown in Scheme 1, that a gold-catalyzed cyclization of *N*-homopropargyl amide **2** would offer cyclic imidate **3**, which could be chemoselectively reduced to afford α-amino ether **A**. We anticipated that **A** would undergo spontaneous Ferrier rearrangement to furnish piperidin-4-one **B**, which might be further reduced in situ to the corresponding alcohol (i.e. **4**). Several aspects of this design are noteworthy: 1) the sequence is highly modular and flexible; it is an overall {[2+3]+1} annulation from readily available imines, propargyl Grignard, and carboxylic acids or their derivatives; 2) enantiomeric synthesis is readily achievable as chiral amine **1** would be easily prepared from chiral sulfinyl imines;[4] 3) it constitutes an alternative to an aza-Petasis-Ferrier rearrangement, which has not been realized.[5,6] This is a surprising void as the Petasis-Ferrier rearrangement[7] has been applied with much success in total synthesis of complex natural products.[8] 4) the piperidine nitrogen is free and could be readily derivatized; 5) the gold catalysis is not the key transformation but instead employed to deliver requisite intermediates for subsequent processes. This sequential combination of gold catalysis and other distinctively different transformations in a one-pot process offer new opportunities to develop versatile synthetic methods with high efficiency.



solvent	yield
CH_2Cl_2	quant. (NMR)
THF	quant. (NMR)
toluene	82% (NMR)
CH_2Cl_2	61% (isolated)

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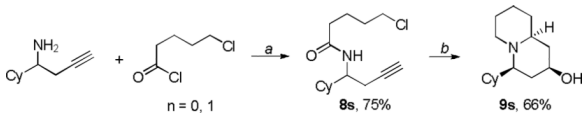
(1)

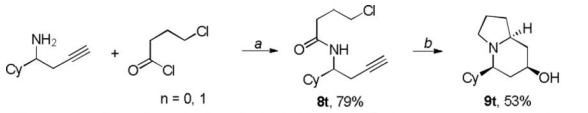
We began the implementation of the design by examining the feasibility of the gold catalysis[9] using amide **5** as the substrate. To our delight, the gold-catalyzed cyclization proceeded quantitatively in either CH_2Cl_2 or THF at ambient temperature (Eq 1). The keys to this reaction were the addition of MsOH (1.2 equiv) to prevent the nitrogen of imidate **6** from coordinating to and thus deactivating the gold catalyst[10] and the use of molecular sieves to minimize hydrolysis.

Due to the sensitivity of imidate **6** to hydrolysis, we decided to study its reduction in a one-pot process. Hence, upon the complete consumption of amide **3** in the gold catalysis, various reductants were added. To our delight, with borane the all *cis*-isomer (i.e., **7**) was indeed formed. Screening other reductants especially boron-based ones revealed that catecholborane (5 equiv) worked the best (entries 5-9), and an 80% isolated yield was achieved in CH_2Cl_2 and at -78 °C. Notable is that **7** was formed with excellent diastereoselectivity, and other potential diastereomers were formed in negligible amounts. The relative stereochemistry of **7** was initially established via NMR studies and later corroborated by the structure of **9p** (vide infra) established by X-ray crystallography (see SI).

We then tested a range of secondary amides as substrates following the optimized one-pot sequence with some fine tunings of reaction temperatures and the amount of the borane. As shown in Table 2, different acyl groups including aliphatic (entries 1-7) and aromatic ones (entries 8-11) were readily allowed. Steric bulk was well tolerated although the reduction was slower (entry 4). Different functional groups including a non-conjugated C-C double bond (entry 6), fluoro groups (entries 7 and 9), a carboxylate (entry 11) and a naphthyl group (entry 10) were tolerated. However,



(2)



[a] Et_3N, CH_2Cl_2; [b] i) $Ph_3PAuNTf_2$ (5 mol %), MsOH (1.2 eq.), 4 Å MS, 1 h; ii) catecholborane (6 eq.), -40 °C, 24 h; iii) MeOH, K_2CO_3, reflux, 8 h.

(3)

trifluoroacetamide **8** (R = CF_3, R = Cy) was not a suitable substrate as its weakly nucleophilic carbonyl group failed to undergo gold-catalyzed cyclization. Notably, high to excellent diastereoselectivities were observed in the cases of aliphatic amides. However, the catecholborane reduction in the cases of aromatic amides (entries 8-11) was very slow at -40 °C, and the reactions were run at ambient temperature in order to achieve completion in 24 h; low diastereoselectivities were observed in most of these cases. To our delight, while the major isomers were the expected all-*cis* ones, the minor component in each case appeared to be the 4-OH epimer, which was confirmed via oxidation of the separated isomers of **9j** to a common piperidin-4-one.[11] These results indicated that the piperidine ring-forming step was highly diastereoselective even at room temperature. In contrast to entry 6, the vinyl group in acrylamide **8l** (entry 11) was reduced during the reaction, and piperidine **9l** with an ethyl group instead was isolated in 47% yield. Substrates with an aryl group at the

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homopropargylic position worked equally well in this one-pot process (entries 13-18), and at -40 °C the diastereoselectivities were mostly excellent. Again, steric bulk (entries 15 and 17) were readily tolerated.

A key feature in these piperidin-4-ol products is that the ring nitrogen is free and could be readily derivatized. For example, subsequent one-pot intramolecular alkylations (Eq. 2 and 3) provided quick access to quinolizidine and indolizidine skeletons, respectively, which can be found in the structures of a range of alkaloids.[12]

As a demonstration of the synthetic utility of this chemistry, an enantioselective synthesis of (+)-subcosine II[13,14] was achieved in 6 steps in an overall 22% yield (Scheme 2). Notably, homopropargyl amine **10** was easily prepared in >94% *ee* using Ellman's sulfinyl imine chemistry,[4a] and neither the gold catalysis nor the reduction/Ferrier rearrangement compromised the stereochemistry integrity of the original chiral carbon center.

In conclusion, we have developed a one-pot synthesis of piperidin-4-ols v i a sequential gold-catalyzed cyclization, chemoselective reduction and spontaneous Ferrier rearrangement. This reaction has a broad substrate scope and shows excellent diastereoselectivities in the ring formation step; in combination with a routine amide formation, it constitutes a highly flexible and diastereoselective [5+1] cycloaddition approach to piperidines. Since homopropargylic amines could be readily prepared with excellent *e.e.* from chiral sulfinyl imines and propargylmagnesium bromide, this overall {[2+3]+1} modular approach offers an ideal solution to enantioselective synthesis of various substituted piperidine. Importantly, the piperidine nitrogen is free and can be readily derivatized. By coupling with one-pot intramolecular alkylations, this chemistry provides a rapid access to quinolizidines and indolizidines and allows a succinct enantioselective synthesis of (+)-subcosine II.

Experimental Section

General procedure for the preparation of piperidin-4-ols

4 Å MS (100 mg) was added to an oven-dried Schlenk tube. The tube was flamed dried under vacuum and filled with N_2 three times. Under N_2, an amide (0.1 mmol), PPh_3AuNTf_2 (5 mol%), freshly distilled CH_2Cl_2 (1.6 mL), and a freshly prepared solution of $MeSO_3H$ in CH_2Cl_2 (0.4 mL, 0.03 M) were sequentially added to the reaction tube. The reaction mixture was stirred at room temperature for 1 h before the reduction at the indicated reaction temperature. Catecholborane (0.6 mmol) was added to the reaction vessel and the progress of the reduction was monitored by TLC. Upon completion, the reaction was quenched with MeOH and then stirred at room temperature for 15 min. A saturated disodium tartrate aqueous solution was added to the reaction, and the reaction mixture was stirred for another 15 min. The resulting mixture was treated with 10% NaOH (saturated with NaCl) and extracted with CH_2Cl_2 three times. The combined organic layers were dried with anhydrous $MgSO_4$, filtered and concentrated under *vacuum*. The residue was purified through silica gel flash chromatography.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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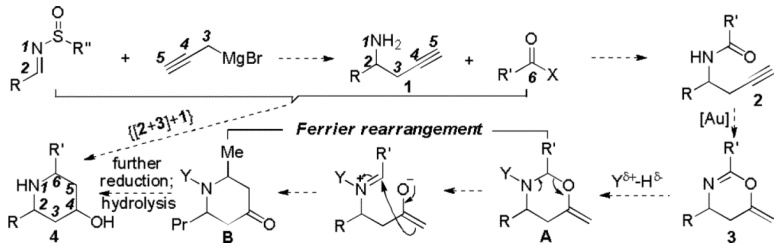

Scheme 1.
Modular synthesis of *N*-unsubstituted piperidines: design

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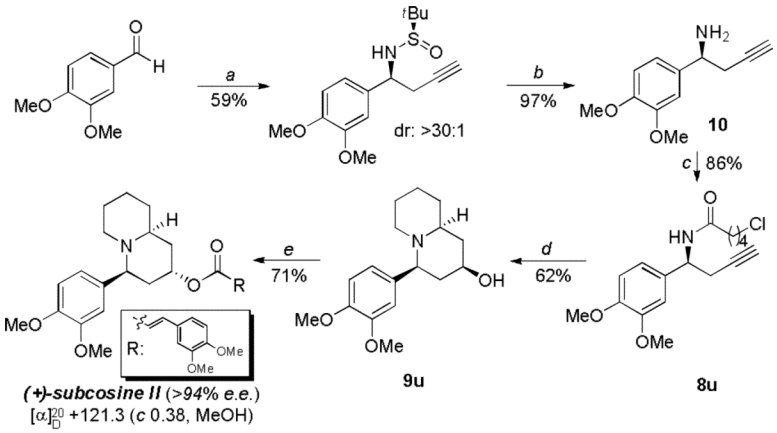

[a] ^{t}BuSONH$_2$, CuSO$_4$, CH$_2$Cl$_2$; propargylmagnesium bromide; [b] conc. HCl, MeOH; [c] Cl(CH$_2$)$_4$COCl, CH$_2$Cl$_2$, Et$_3$N; [d] i) Ph$_3$PAuNTf$_2$ (5 mol %), MsOH (1.2 eq.), 4 Å MS, 1 h; ii) Catecholborane (8 eq.) -40 °C, 24 h; iii) MeOH, K$_2$CO$_3$, reflux, 4 h. [e] Ph$_3$P (2.5 eq.), DEAD (2.5 eq.), *trans*-3,4-(MeO)$_2$PhCH=CHCO$_2$H (2 eq.), toluene, 12 h.

Scheme 2.
Six-step, enantioselective total synthesis of (+)-subcosine II.

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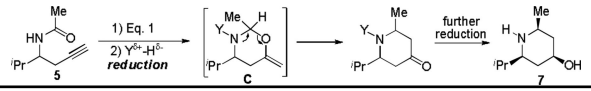
Table 1

One-pot, sequential gold catalysis and reduction: reduction condition optimization.[a]



entry	solvent	reductant	conditions	Yield[b]	
				7	isomer
1	CH_2Cl_2	BH_3•Et_2O (5 equiv)	-40 °C, 2 h	41%	-
2	CH_2Cl_2	$NaBH_3CN$ (5 equiv) $AlCl_3$ (2 equiv)	0 °C to rt	-[c]	-
3	CH_2Cl_2	DIBAL-H (5 equiv)	-78 °C to rt	-	-
4	CH_2Cl_2	9-BBN	-40 °C, 8 h	5%	-
5	CH_2Cl_2	Catecholborane (5 equiv)	-40 °C, 2 h	76%	5%
6	THF	Catecholborane (5 equiv)	-40 °C, 2 h	72%	4%
7	toluene	Catecholborane (5 equiv)	-40 °C, 2 h	60%	10%
8	CH_2Cl_2	Catecholborane (5 equiv)	0 °C, 2 h	77%	7%
9	CH_2Cl_2	Catecholborane (5 equiv)	-78 °C, 4 h	86%[d]	3%

[a] [**5**] = 0.05 M.

[b] Estimated by ^{1}H NMR using diethyl phthalate as internal reference.

[c] 50% of **6** left.

[d] 80% isolated yield.

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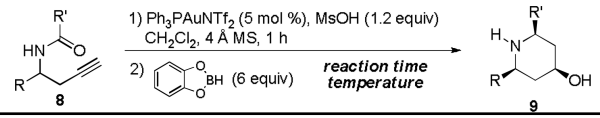
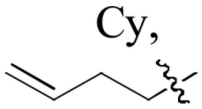
Table 2

One-pot sequential gold catalysis, chemoselective reduction, and Ferrier rearrangement: scope study.[a]



entry	8 R, R'	Time, Temp.	9, yield[b] dr	entry	8 R, R'	Time, Temp.	9/yield[b]
1	^{n}Hept, Me	4h -78 °C	**9a**, 72% >25:1	10[c]	Cy, 1-naphthyl	24 h, rt	**9j**, 67% 4:1
2	Cy, *n*-Pr	6 h, -40 °C	**9b**, 71% 10:1	11[c]	Cy, 4-MeO$_2$CPh	24 h, rt	**9k**, 78% 2:1
3	Cy, Cy	6 h, -40 °C	**9c**,73 % 10:1	12[c]	Cy, vinyl	24 h, -40°C→rt	**9l**[d], 47% 4:1
4	Cy, *t*-Bu	12 h, -40 °C	**9d**, 68% 13:1	13	Ph, Me	8 h, -78 °C	**9m**, 77% >25:1
5	Cy, Bn	6 h, -40 °C	**9e**, 79% 15:1	14	Ph, *i*-Pr	12 h, -40 °C	**9n**, 77% >25:1
6		24 h, -40 °C	**9f**, 72% 17:1	15	Ph, *t*-Bu	12 h, -40 °C	**9o**, 83% 11:1
7[c]	Cy, FCH$_2$	24 h, -40 °C	**9g**, 52% >25:1	16	4-MeOPh, Me	12 h, -40 °C	**9p**, 80% >25:1
8[c]	Cy, Ph	24 h, rt	**9h**, 70% 13:1	17	*o*-tolyl Me	16 h, -40 °C	**9q**, 74% >25:1
9[c]	Cy, 3-FPh	24 h, rt	**9i**, 61% 1.5:1	18	4-CF$_3$Ph, Me	12 h, -40 °C	**9r**, 81% >25:1

[a] [**8**] = 0.1 M.

[b] isolated yields.

[c] 8 equiv. of catecholborane.

[d] R' = Et.

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