Nitrogen Heterocycles

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

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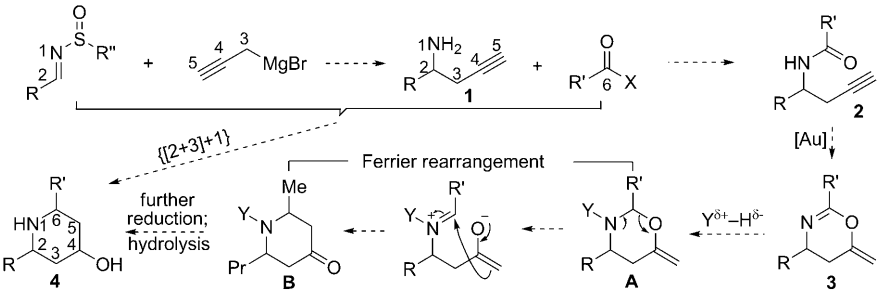
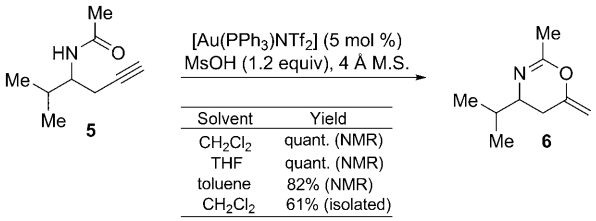
Piperidine is a key structural motif in various alkaloids and a variety of compounds studied in medicinal chemistry. Though many methods have been developed for their construction, there is still a need for novel approaches, especially those with high efficiency, good modularity, and excellent stereoselectivity.

Recent intense research in gold catalysis[1] has provided several novel methods for the synthesis of piperidines.[2,3] For example, we have previously reported that piperidin-4-ones could be prepared in a two-step, [4+2] manner;[2a] however, the products were limited to those in which the ring nitrogen atoms contained hard-to-remove aliphatic substituents or benzyl groups which afforded low regioselectivities. To address this deficiency and develop a general and modular synthesis of N-unsubstituted piperidines, we envisioned 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** (Scheme 1). 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 (**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, a propargyl Grignard, and carboxylic acids or their derivatives. 2) The enantiomeric synthesis is readily achievable as chiral amine **1** would be easily prepared from chiral sulfinyl imines.[4] 3) This sequence constitutes an alternative to an aza-Petasis–Ferrier rearrangement, which has not yet been realized.[5,6] The lack of reported aza-Petasis–Ferrier rearrangement is surprising as the Petasis–Ferrier rearrangement[7] has been applied with much success in total syntheses of complex natural products.[8] 4) The piperidine nitrogen atom is free and could be readily derivatized. 5) The gold catalysis is not the key transformation step but is instead employed to deliver the requisite intermediate (i.e., **3**) 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.



Scheme 1. Our design for a modular synthesis of N-unsubstituted piperidines.

We began our investigation 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 dichloromethane or tetrahydrofuran at ambient temperature [Eq. (1); M.S. = molecular sieves]. The keys to this reaction were the addition of MsOH (1.2 equiv) in order to prevent the nitrogen atom of imidate **6** from coordinating to, and thus deactivating, the gold catalyst[10] and the use of molecular sieves to minimize hydrolysis.



Solvent	Yield
CH_2Cl_2	quant. (NMR)
THF	quant. (NMR)
toluene	82% (NMR)
CH_2Cl_2	61% (isolated)

(1)

Owing 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 **5** from the gold-catalysis step, various reductants were added. To our delight, the all-*cis*-isomer **7** was formed selectively when borane was used as the reductant (Table 1, entry 1). Screening other reductants, especially boron-based ones, revealed that catecholborane (5 equiv) worked the best (Table 1, entries 5–9), and the product was isolated in 80% yield by running the reaction in dichloromethane at −78 °C. Notably, **7** was formed with excellent diastereoselectivity, and other potential dia-

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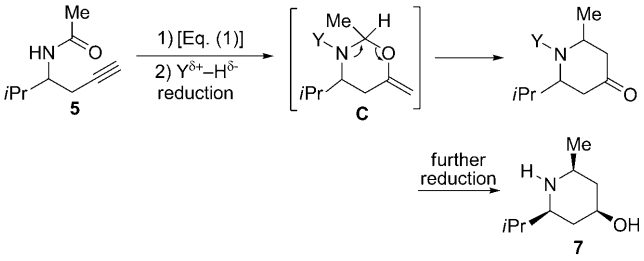
Table 1: One-pot, sequential gold catalysis and reduction: Optimization of the reduction reaction conditions.[a]



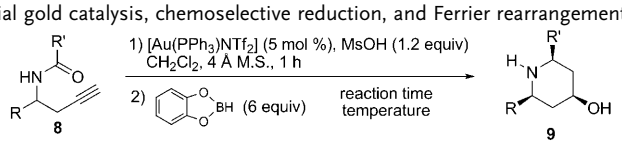
Entry	Solvent	Reductant (equiv)	Conditions		Yield [%][b]	
			T [°C]	t [h]	**7**	isomer
1	CH_2Cl_2	$BH_3{\cdot}Et_2O$ (5)	−40	2	41	–
2	CH_2Cl_2	$NaBH_3CN$ (5) $AlCl_3$ (2)	0 to RT		–[c]	–
3	CH_2Cl_2	DIBAL-H (5)	−78 to RT		–	–
4	CH_2Cl_2	9-BBN	−40	8	5	–
5	CH_2Cl_2	catecholborane (5)	−40	2	76	5
6	THF	catecholborane (5)	−40	2	72	4
7	toluene	catecholborane (5)	−40	2	60	10
8	CH_2Cl_2	catecholborane (5)	0	2	77	7
9	CH_2Cl_2	catecholborane (5)	−78	4	86[d]	3

[a] [**5**] = 0.05 M. [b] Estimated by ^{1}H NMR spectroscopy, using diethyl phthalate as an internal reference. [c] 50% of **6** leftover. [d] 80% yield of isolated product. DIBAL-H diisobutylaluminum hydride; 9-BBN = 9-borabicyclo[3.3.1]nonane; THF = tetrahydrofuran.

stereomers were formed in negligible amounts. The relative stereochemistry of **7** was initially established by NMR spectroscopy studies and later confirmed by X-ray crystallographic analysis of **9p** (see the Supporting Information).[11]

We then tested a range of secondary amides as substrates following the optimized one-pot sequence with some fine-tuning of reaction temperatures and the amount of the borane. Different acyl groups, including aliphatic (Table 2, entries 1–7) and aromatic substituents (Table 2, entries 8–11) were well-tolerated. Sterically bulky substituents (Table 2, entry 4) also successfully afforded the cyclized product, although it required a more-prolonged reaction time. Different functional groups, including a nonconjugated C–C double bond (Table 2, entry 6), fluoro groups (Table 2, entries 7 and 9), a carboxylate (Table 2, entry 11), and a naphthyl group (Table 2, entry 10) were also tolerated. However, 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 reductions of aromatic amides (Table 2, entries 8–11) were very slow at −40 °C, and the reactions were run at ambient temperature in order to achieve completion in 24 hours; as a result, low diastereoselectivities were observed in most of these cases. To our delight, whilst the major isomers were the expected all-*cis* isomers, the minor component in each case appeared to be the 4-OH epimer, which was confirmed by oxidation of the separated isomers of **9j** to afford a common piperidin-4-one.[12] These results indicated that the piperidine-ring-forming step was highly diastereoselective, even at room temperature. In contrast to Table 2, entry 6, the vinyl group in acrylamide **8l** (Table 2, entry 12) was reduced during the reaction, and piperidine **9l** with an ethyl group instead was isolated in 47% yield.

Table 2: Scope of the one-pot sequential gold catalysis, chemoselective reduction, and Ferrier rearrangement.[a]



Entry	**8** R, R′	t [h]	T [°C]		Yield of **9** [%][b] (d.r.)	Entry	**8** R, R′	t [h]	T [°C]		Yield of **9** [%][b] (d.r.)
1	*n*Hept, Me	4	−78	**9a**	72 (>25:1)	10[c]	Cy, 1-naphthyl	24	RT	**9j**	67 (4:1)
2	Cy, *n*Pr	6	−40	**9b**	71 (10:1)	11[c]	Cy, 4-$MeO_2CC_6H_4$	24	RT	**9k**	78 (2:1)
3	Cy, Cy	6	−40	**9c**	73 (10:1)	12[c]	Cy, vinyl	24	−40 to RT	**9 l**[d]	47 (4:1)
4	Cy, *t*Bu	12	−40	**9d**	68 (13:1)	13	Ph, Me	8	−78	**9m**	77 (>25:1)
5	Cy, Bn	6	−40	**9e**	79 (15:1)	14	Ph, *i*Pr	12	−40	**9n**	77 (>25:1)
6	Cy, 	24	−40	**9f**	72 (17:1)	15	Ph, *t*Bu	12	−40	**9o**	83 (11:1)
7[c]	Cy, FCH_2	24	−40	**9g**	52 (>25:1)	16	4-$MeOC_6H_4$, Me	12	−40	**9p**	80 (>25:1)
8[c]	Cy, Ph	24	RT	**9h**	70 (13:1)	17	*o*-tolyl Me	16	−40	**9q**	74 (>25:1)
9[c]	Cy, 3-FC_6H_4	24	RT	**9i**	61 (1.5:1)	18	4-$CF_3C_6H_4$, Me	12	−40	**9r**	81 (>25:1)

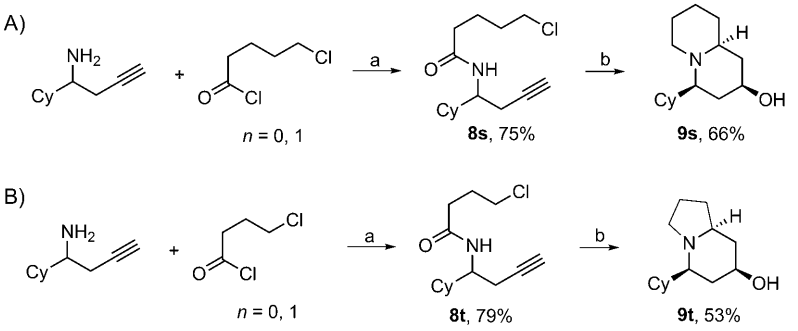
[a] [**8**] = 0.1 M. [b] Yield of isolated product. [c] 8 equiv of catecholborane. [d] R′ = Et. Bn = benzyl; Cy = cyclohexyl.

Substrates containing an aryl group at the homopropargylic position worked equally well in this one-pot process (Table 2, entries 13–18), and at −40 °C the diastereoselectivities were mostly excellent. Again, steric bulk (Table 2, entries 15 and 17) in the substituents was readily tolerated.

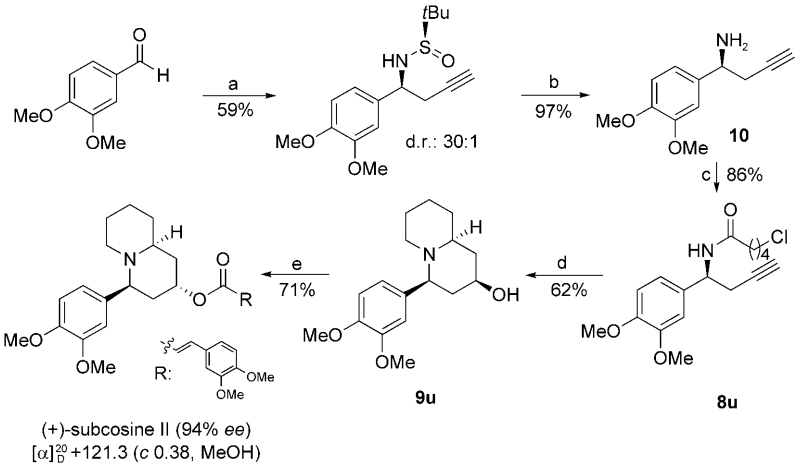
A key feature in these piperidin-4-ol products was that the nitrogen atom in the ring was free and could be readily derivatized. For example, subsequent one-pot intramolecular alkylation (Scheme 2) provided quick access to the quinolizidine and indolizidine skeletons, which can be found in the structures of a range of alkaloids.[13]

As a demonstration of the synthetic utility of this procedure, an enantioselective synthesis of (+)-subcosine II[14,15] was achieved in six steps in a 22% overall yield (Scheme 3). Notably, homopropargyl amine **10** was easily prepared in greater than 94% *ee* using the sulfinyl imine chemistry reported by Ellman et al.,[4a] and neither the gold catalysis nor the reduction/Ferrier rearrangement compromised the stereochemical integrity of the original chiral carbon center.

In conclusion, we have developed a one-pot synthesis of piperidin-4-ols by 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. As homopropargylic amines can be readily prepared with excellent *ee* values from chiral sulfinyl imines and propargylmagnesium bromide, this overall {[2+3]+1} modular approach offers an ideal solution to the enantioselective synthesis of various substituted piperidines. Importantly, the piperidine nitrogen atom is unsubstituted and can be readily derivatized. By coupling with one-pot intramolecular alkylation reactions, this chemistry provides a rapid access to quinolizidines and indolizidines, and allowed us to complete a succinct enantioselective synthesis of (+)-subcosine II.



Scheme 2. a) Et_3N, CH_2Cl_2; b) 1. $[Au(PPh_3)NTf_2]$ (5 mol%), MsOH (1.2 equiv), 4 Å M.S., 1 h; 2. catecholborane (6 equiv), −40 °C, 24 h; 3. MeOH, K_2CO_3, reflux, 8 h. Ms = methanesulfonyl; Tf = trifluoromethanesulfonyl.



Scheme 3. Six-step, enantioselective total synthesis of (+)-subcosine II. a) (*R*)-*t*Bu-$SONH_2$, $CuSO_4$, CH_2Cl_2; propargylmagnesium bromide; b) conc. HCl, MeOH; c) $Cl(CH_2)_4COCl$, CH_2Cl_2, Et_3N; d) 1. $[Au(PPh_3)NTf_2]$ (5 mol%), MsOH (1.2 equiv), 4 Å M.S., 1 h; 2. catecholborane (8 equiv), −40 °C, 24 h; 3. MeOH, K_2CO_3, reflux, 4 h; e) Ph_3P (2.5 equiv), DEAD (2.5 equiv), *trans*-3,4-$(MeO)_2C_6H_3CH{=}CHCO_2H$ (2 equiv), toluene, 12 h. DEAD = diethyl azodicarboxylate.

Experimental Section

General procedure for the preparation of piperidin-4-ols: 4 Å M.S. (100 mg) were added to an oven-dried Schlenk tube. The tube was flamed dried under vacuum and flushed with N_2 three times. Under a N_2 atmosphere, an amide (0.1 mmol), $[Au(PPh_3)NTf_2]$ (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 three times with CH_2Cl_2. The combined organic layers were dried with anhydrous $MgSO_4$, filtered, and concentrated under vacuum. The residue was purified by flash chromatography on silica gel.

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