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Stereoselective One-Pot Synthesis of 1-Aminoindanes and 5,6-Fused Azacycles Using a Gold-Catalyzed Redox-Pinacol-Mannich-Michael Cascade**

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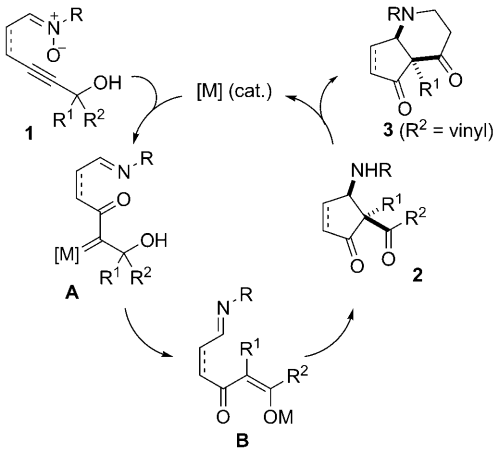
Dedicated to Professor T. V. RajanBabu on the occasion of his 60th birthday

One way to improve the synthetic efficiency of the redox reaction is to couple the reduction/oxidation steps with the desired skeletal bond formations.[1] This strategy removes the need for extra steps for the generation or protection of reactive functional groups, or for oxidation state adjustment. However, this requires that the redox precursors are more readily available than, and able to be catalytically transformed in situ into, their functional group counterparts that undergo the desired transformation.[2] Recently, a number of gold-catalyzed redox-exchange procedures via oxygen transfer have been reported. For example, Toste and co-workers and Zhang and co-workers reported sulfoxide-mediated or amine-*N*-oxide-mediated redox reactions to generate carbene equivalents for sp^2 or sp^3 C–H functionalization or 1,2-pinacol shifts.[3–5] Furthermore, we have reported the waste-free generation of azomethine ylide from an intramolecular redox reaction between a nitrone and an alkyne.[6] The unique advantage of using nitrones as oxidants is that they are derived from readily available hydroxylamines and therefore do not require stoichiometric oxidants such as *m*CPBA (*meta*-chloroperbenzoicacid) or H_2O_2 for the substrate preparation.[4] Furthermore, two highly versatile intermediates, namely an imine or a metal carbenoid, could be generated in situ, which can be advantageously utilized in the rapid assembly of pharmaceutically important N heterocycles through cascade reactions.

We focused on the 1-aminoindane framework, which is a common core of medicinal agents with various activities, such as CB2 agonists, NMDA receptor agonists, and inhibition of neuronal monoamine re-uptake.[7] The 5,6-fused piperidine rings motif with a quaternary center is often also found in natural products or pharmaceutical agents, such as NSC 344505, meloscine, and scandine.[8] The synthetic challenge of these target compounds continues to inspire creative reaction design that allows for their efficient synthesis through a rapid increase in molecular complexity.

We envisioned that metal carbenoid **A**,[6,9] generated from the redox reaction of a readily available 3°-alcohol precursor (**1**), could be transformed into metal enolate **B** through a 1,2-alkyl (pinacol) shift (Scheme 1).[10–11] With the selective



Scheme 1. The proposed redox-pinacol-Mannich-Michael cascade reaction.

migration between the two alkyl group (R^1 and R^2) secured, it should be possible to incorporate a variety of alkyl groups (R^1) at the quaternary position of β-amino cyclopentanone **2** using Mannich addition. Notably, if the nonmigrating group (R^2) is a vinyl group, the initially formed α,β-unsaturated carbonyl compound would undergo a spontaneous Michael reaction to afford synthetically useful 5,6-fused azabicycles in a single operation. Herein, we report our preliminary results on the assembly of these skeletons using a gold-catalyzed redox cascade process.

We first inspected the viability of the redox-pinacol-Mannich cascade reaction on 3°-alcohol substrates that were derived from cycloalkanones. After a brief examination of the reaction conditions, we found that treating **1b** with $AuCl_3$

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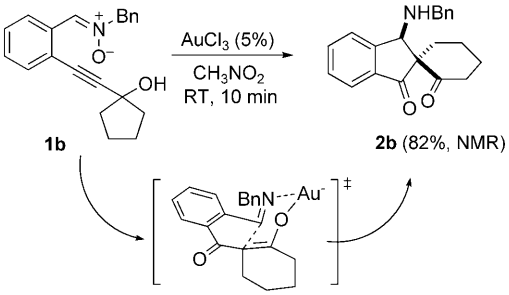
(5 mol%) in nitromethane gave the desired spirocyclic β-amino diketone **2b** in 82% yield (determined by ^{1}H NMR spectroscopy) after only 10 minutes at room temperature [Eq. (1)]. Gold(I) salts containing various ligands typically took a longer reaction time and afforded diminished yields of the product. However, $PtCl_2$, Cu(OTf), $Cu(OTf)_2$, and TfOH (each at 5% loading), turned out to be inactive.[12] Notably, we only observed a single diastereomer of **2b** in the ^{1}H NMR spectrum of the crude mixture (d.r. > 20:1). The relative stereochemistry of the related **2e** was unambiguously confirmed by X-ray crystallography (see the Supporting Information, Figure S1),[13] and the preference for the observed diastereomer could be rationalized by the gold-chelated cyclic transition state [Eq. (1)].

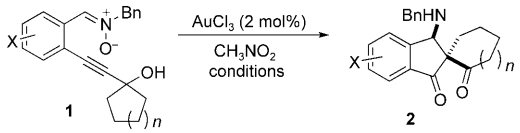


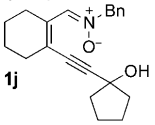
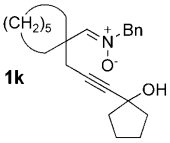
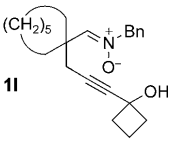
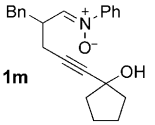
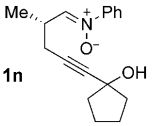
(1)

Encouraged by this, we extended the procedure to synthesize 5–8 membered spirocycles; Table 1, entries 1–4). Using only 2 mol% of $AuCl_3$, almost all spirocycles formed efficiently at room temperature in less than 2 hours with exceptional selectivity, although harsher conditions were required for the larger rings, which formed with lower diastereoselectivities, presumably owing to transannular ring strain (Table 1, entries 3 and 4). Electronic effects on the aromatic core did not make a marked difference to the efficiency of this redox cascade (Table 1, entries 5–7) nor did the electronic demands of the N substituent (Table 1, entries 8 and 9). Alkyl/alkenyl-bridged substrates **1j–l** also reacted successfully under these condition (Table 1, entries 10–12). Gratifyingly, this cascade reaction was successfully extended to nitrone substrates that have an enolizable α center, such as **1m** and **1n**. Substrates **1m–n** reacted smoothly with *N*-Ph nitrone, although the diastereoselectivity relative to the existing center was modest (Table 1, entries 13 and 14).

In principle, the selective migration of R^1 or R^2 groups in **1** would allow for the incorporation of various moieties at the quaternary position, which would lead to the aforementioned product diversity (Scheme 1). Therefore, we examined the selective 1,2-pinacol shift of various groups from tertiary alcohol substrates with different R^1 and R^2 functionalities (Table 2). The reaction of acyclic *gem*-dimethyl substrate **1o** with 2 mol% of $AuCl_3$ indicated that the diastereomeric ratio of the product is highly dependent on the reaction medium (3:1 in CH_3NO_2 versus 14:1 in CH_2Cl_2); therefore, we chose dichloromethane as the preferred solvent for acyclic substrates in our investigation (Table 2).[14] The relative migration tendency of the 1,2-shift also depends on the steric bulk

Table 1: Spirocycle synthesis by a ring-expansion/Mannich reaction sequence.[a]



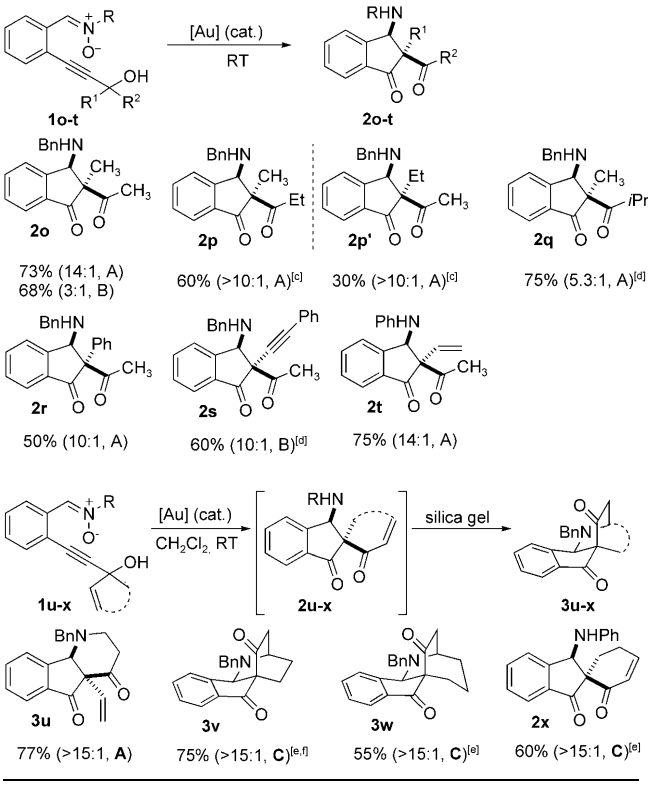
Entry	Substrate	Conditions	Yield of **2** [%] (d.r.)[b]
1	**1a**, X = H, *n* = 0	RT, 1 h	69
2	**1b**, X = H, *n* = 1	RT, 1 h	78
3	**1c**, X = H, *n* = 2	50 °C, 0.5 h[c]	58 (10:1)
4	**1d**, X = H, *n* = 3	70 °C, 0.5 h[c]	76 (2:1)
5	**1e**, X = 4-Me, *n* = 1	RT, 0.5 h	83
6	**1f**, X = 5-MeO, *n* = 1	RT, 1.5 h	87
7	**1g**, X = 5-F, *n* = 1	RT, 1 h	84
8	**1h**, X = H, *n* = 1, *N*-Ph	RT, 1.5 h	74
9	**1i**, X = H, *n* = 1, *N*-Ar (Ar = *p*-$CO_2MeC_6H_4$)	RT, 1.5 h	68
10	 **1j**	RT, 1 h	67
11	 **1k**	RT, 1.5 h	69 (3:1)
12	 **1l**	50 °C, 0.5 h	78
13	 **1m**	RT, 0.5 h	70 (1.7:1)[d]
14	 **1n**	RT, 0.5 h	70 (1.6:1)[d]

[a] [**1**] = 0.1 M in CH_3NO_2. [b] Yield of isolated product (diastereomeric ratio in parentheses; isolated as a single diastereomer unless otherwise noted). [c] 5 mol% catalyst. [d] Diastereoselectivity relative to the center α to the nitrone. Bn = benzyl.

of the migrating alkyl group, in the order Me > Et > *i*Pr (as shown by the formation of **2p**/**2p′**, and **2q**), which indicates that it is a concerted 1,2-shift that goes through a sterically congested transition state. Notably, aryl,[15c] alkynyl,[15d] and alkenyl[15c] groups migrated preferentially over methyl group in acyclic substrates **1r–t** in a highly diastereoselective manner, as shown in the preferential formation of **2r**, **2s**, and **2t**.[16,17]

Interestingly, when the nonmigrating group (R^2) is a vinyl group, the initially formed products (**2**) spontaneously cyclized via a tandem Michael addition. For example, treatment of divinyl substrate **1u** with $AuCl_3$ (2 mol%) in dichloromethane at room temperature for 20 mininutes gave the corresponding Michael adduct **3u**, that has a vinyl

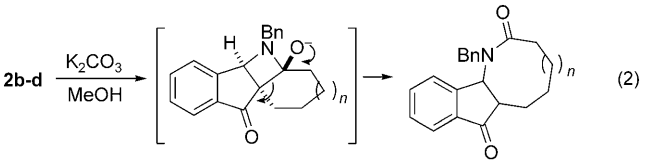
Table 2: Selective 1,2-shift and tandem Michael addition.[a,b]

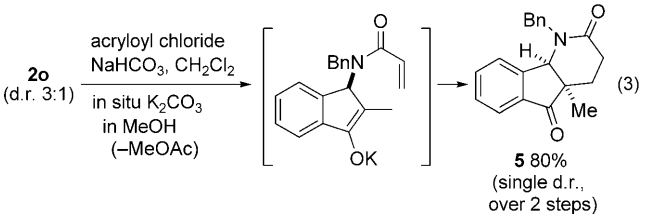


[a] Conditions A: $AuCl_3$ (2 mol%) in CH_2Cl_2; Conditions B: $AuCl_3$ (2 mol%) in CH_3NO_2; Conditions C: $[\{tBu_2(o\text{-Ph-}C_6H_4)P\}Au]NTf_2$ (5 mol%) in CH_2Cl_2 unless otherwise noted. [b] Yield of isolated product(s) after chromatography (diastereomeric ratio from the ^1H NMR spectrum of the crude mixture). [c] **2p** and **2p′** were obtained as an inseparable mixture. [d] 5 mol% catalyst. [e] A minor amount (21% of **2v′**, 27% of **2w′**, or 25% of **2x′**) of alkene migration was also obtained. [f] The crude mixture was treated with silica gel (RT, 10 h) before chromatography. Tf = trifluoromethanesulfonyl.

substituted quaternary center, in 77% yield as a single diastereomer. When **1v**, derived from 2-cyclopentenone, was treated with 5 mol% of $[\{tBu_2(o\text{-Ph-}C_6H_4)P\}Au]NTf_2$ in dichloromethane, the ^1H NMR spectrum of the crude mixture indicated the preferential formation of alkyl shifted product **2v** along with a small amount of alkene shifted by-product **2v′** in a ratio of approximately 3:1.[18] Upon treating this mixture with silica gel in CH_2Cl_2, **2v** was cleanly converted into its Michael adduct (**3v**; isolated in 75% yield for the overall cascade transformation). Alternatively, when the crude reaction mixture was purified by chromatography on silica gel (with 5% of triethylamine in the eluent), **2v** was obtained in 65% yield. Similarly, 2-cyclohexenone-derived **1w** gave the intramolecular Michael adduct **3w**, whilst *N*-Ph nitrone **2x** was isolated without any Michael addition. The structures of **3v** and **3w** were confirmed by single-crystal X-ray analysis (Figure S1).[13] We also examined various secondary alcohol substrates with $R^1 = H$ and R^2 = methyl, aryl, allyl, and vinyl groups. However, unlike the reported propensity for hydrogen migration,[15] these reactions afforded only messy mixtures even after extensive trials.

The diverse heterocyclic structures obtained using our cascade protocol could then be successfully transformed into various other useful compounds [Eq. (2) and Eq. (3)]. For example, when 6–8 membered spirocyclic 1-aminoindanes **2b–d** were treated with K_2CO_3 in methanol, 8–10 membered medium-sized lactams **4b–d** were obtained in 77–80% yield through a *trans*-acylation process [Eq. (2)]. When a diastereomeric mixture of **2o** (d.r. 3:1) was initially acylated with acryloyl chloride, then treated in situ with K_2CO_3 in MeOH solution, 5,6-fused azacycle **5** (80% yield) was obtained as a single diastereomer through the deacetylation-Michael addition pathway [Eq. (3)]. The isomeric mixture at the quaternary position of **2o** is stereochemically inconsequential, owing to the formation of the enol intermediate.





In summary, we have described a novel pinacol-Mannich-Michael cascade, utilizing a metal carbenoid and an imine generated from a gold-catalyzed redox reaction. The remarkable versatility of these intermediates for cascade reactions was demonstrated in highly diastereoselective, one-pot syntheses of various synthetically important skeletons, such as spirocycles, 1-aminoindanes, and 5,6-fused azacycles at ambient temperature. Using the current protocol, we were able to introduce various alkyl, alkenyl, alkynyl, and aryl groups at the quaternary center. Furthermore, the mechanistic uncertainty regarding the nature of the gold-catalyzed redox chemistry of the nitrone became clear from the unambiguous involvement of the carbenoid and the imine.[6b,19] Further efforts in our laboratory are aimed at the target-oriented synthesis of biologically active natural products utilizing this atom-efficient, step-, and redox-economical approach.[1d]

Experimental Section

Representative procedure for the gold-catalyzed formation of **2v** and **3v**: $[\{tBu_2(o\text{-Ph-}C_6H_4)P\}Au]Cl$ (2.8 mg, 9.5 μmol, 5 mol%) and $AgNTf_2$ (3.6 mg, 9.5 μmol) were dissolved in dichloromethane (3 mL) and substrate **1v** (60.0 mg, 0.189 mmol) was added to the mixture at room temperature. After 20 min, the reaction was judged to be complete (TLC), and was quenched by addition of 3 drops of Et_3N. After removal of the solvent under vacuum, the residue was purified using chromatography on silica gel (EtOAc/hexanes = 1:4 containing 5% Et_3N) to afford **2v** (65% yield). Alternatively, upon completion of the reaction, the crude mixture was treated with silica gel (approx. 50 mg) and was stirred overnight at room temperature.

After evaporation of solvent and chromatography on silica gel (EtOAc/hexanes = 1:4), **3v** was obtained in 75% yield.

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[12] See the Supporting Information for details of catalyst screening (Table S1).

[13] CCDC 753771 (**2e**), 753772 (**3v**), and 753773 (**3w**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[14] For the cyclic substrates in Table 1, the diastereoselectivity remained the same in CH_2Cl_2 or CH_3NO_2 solvent (Table S1).

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[16] In the case of **1r–t**, methyl shift products (**2r′–2t′**) could not be observed.

[17] The reaction of **1t**-Bn with *N*-Bn in the place of *N*-Ph gave a lower ratio of vinyl versus alkyl migration (2:1, 55% total yield) under Conditions A.

[18] The reaction of cyclic substrates with $AuCl_3$ typically resulted in a poorer ratio of alkyl and alkenyl shift products (approx. 1:1). For details of catalyst optimization for the reaction of **1v**, see the Supporting Information (Table S2). Intriguingly, the selective alkyl migration in cyclic substrates **1v–x** is in sharp contrast to vinyl migration in acyclic substrate **1t**. The reason for this switch of migratory aptitude is not clear and further mechanistic studies are underway.

[19] Possible alternative mechanisms for the redox chemistry of the nitrone: 1) [3+2] cycloaddition followed by a rearrangement into acyl aziridines, 2) a 1,3-sigmatropic shift, or 3) via a diradical intermediate. See: a) J. P. Freeman, *Chem. Rev.* **1983**, *83*, 241–261; b) J. A. Berson, *Acc. Chem. Res.* **1972**, *5*, 406–414; c) K. Knobloch, K. W. Eberbach, *Org. Lett.* **2000**, *2*, 1117–1120.

