Product-selectivity control by the nature of the catalyst: Lewis acid-catalyzed selective formation of ring-fused tetrahydroquinolines and tetrahydroazepines *via* intramolecular redox reaction†

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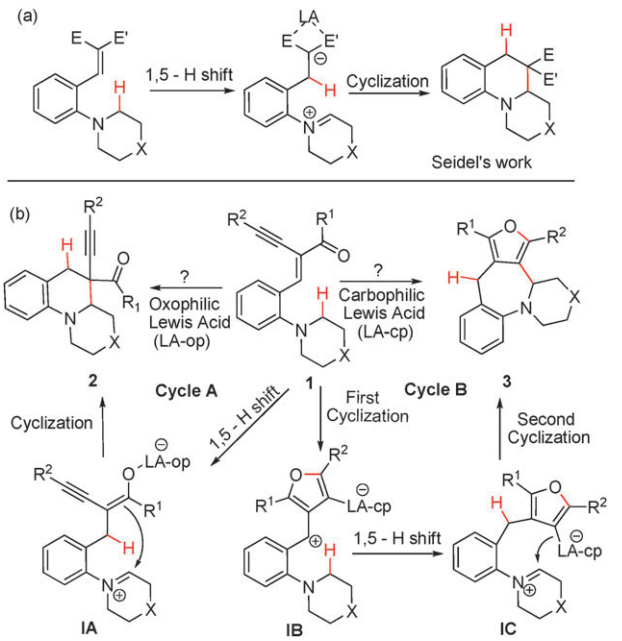
Selective synthesis of ring-fused tetrahydroquinolines and tetrahydroazepines from the same starting materials was achieved by subtle use of the oxophilic $Sc(OTf)_3$ or carbophilic IPrAuOTf as the catalyst.

The development of methodology for the direct functionalization of relatively unactive C–H bonds has now become a rapidly growing topic of research,[1] which offers an intriguing opportunity for the rapid buildup of molecular complexity. However, the functionalization of inert and sterically hindered sp^3 C–H bonds[2–4] is still a particularly difficult challenge, owing to the strength of sp^3 C–H bonds and the metal cannot reach to a C–H bond to be activated. Recently, Sames and co-workers[4a–e] have developed an alternative and efficient redox-neutral strategy to address this issue, wherein a suitable unsaturated moiety is introduced and activated by an electrophilic metal, which in turn induces a selective C–H bond cleavage *via* a 1,5-hydride shift. On the other hand, construction of distinct types of complex molecules from identical starting materials simply by subtle choice of the catalyst is an interesting but often very challenging issue in modern organic synthesis.[5] Here we report a Lewis acid-catalyzed intramolecular redox reaction for selective synthesis of fused tetrahydroquinolines and tetrahydroazepines, and show the selectivity of the product can be controlled by the nature of the catalyst.

Seidel and co-workers[4f,g] recently reported an intriguing Lewis acid-catalyzed redox domino[6] 1,5-hydride shift/cyclization reaction for an efficient synthesis of tetrahydroquinolines, in which a C–H bond α to the tertiary amine nitrogen (*tert*-amine effect[7]) is replaced by a C–C bond that becomes part of the newly formed tetrahydroquinoline ring system (Scheme 1(a)). Meanwhile, others[8] and our group[9] have showed that conjugated yne-enones undergo cyclization readily in the presence of a transition metal complex (such as a gold complex), in which a carbocationic furanyl gold intermediate[8a,9e,f,10] was involved for those gold-catalyzed reactions.[11] During these studies, we envisaged that yne-enones **1** might undergo novel intramolecular redox domino reaction in the presence of Lewis acid (Scheme 1(b)). We speculated that two distinctly different compounds (*e.g.* tetrahydroquinolines **2** and tetrahydroazepines **3**) might be produced, the selectivity of which may be controllable by subtle choice of different Lewis acids. Under the catalysis of oxophilic Lewis acid (Scheme 1(b), Cycle A), the reaction would proceed through a zwitterionic intermediate **IA** *via* a 1,5-hydride shift, which in turn would undergo cyclization to give tetrahydroquinolines **2**. In this case, the alkyne moiety plays a role as a substituent. In contrast, carbophilic Lewis acid would trigger a heterocyclization (first cyclization) by activation of the alkyne moiety to generate the furanyl intermediate **IB** with a reactive carbocation;[8a,9e,f,10] after 1,5-hydride shift to produce the intermediate **IC** and subsequent ring closure (second cyclization), polycyclic tetrahydroazepines **3** may be produced. It is obvious that cycle B is a novel and alternative strategy to generate a more active hydrogen acceptor **IB**, which is quite different from the direct activation of the acceptor by metal.



Scheme 1 (a) Seidel's work and (b) proposed working hypothesis in this work.

This hypothesis was initially tested with yne-enone **1a** under the catalysis of a series of Lewis acids.[12] After numerous attempts, we were pleased to find that the reaction gave ring-fused tetrahydroquinoline **2a** with high diastereoselectivity (15 : 1) in 86% combined isolated yield in refluxing 1,2-dichloroethane (DCE) under the catalysis of oxophilic

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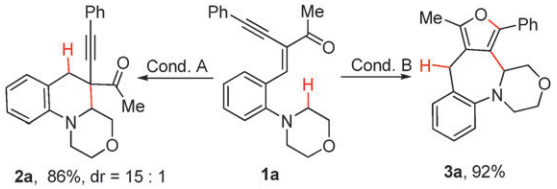
Lewis acid, 10 mol% of $Sc(OTf)_3$ (eqn (1): Conditions A).[13] In contrast, 92% yield of fused tetracyclic **3a** can be isolated under the catalysis of carbophilic IPrAuOTf (5 mol%, generated *in situ* from 1 : 1 ratio of IPrAuCl and AgOTf) in CH_3CN (eqn (1): Conditions B) at room temperature.

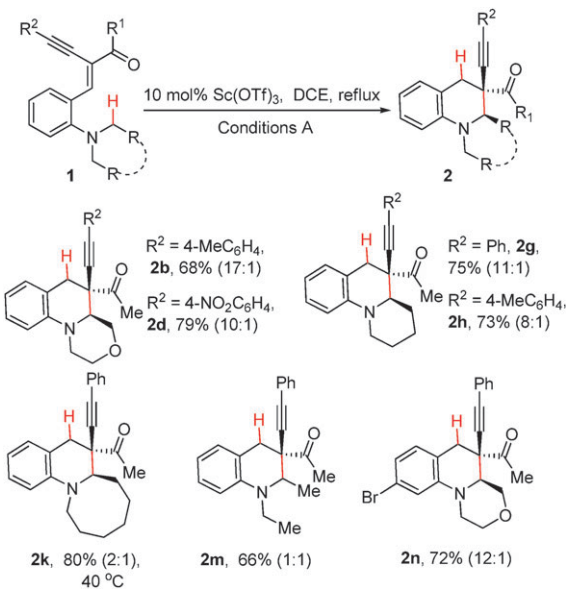


(1)

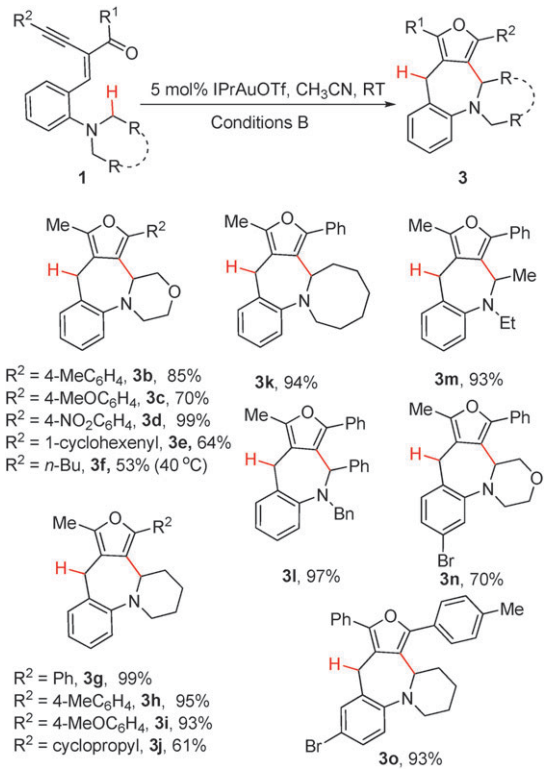
Conditions A: $Sc(OTf)_3$(10 mol%), DCE, reflux, 35 h
Conditions B: IPrAuOTf(5 mol%), CH_3CN, RT, 3 h.

Using the optimized conditions, the scope of the $Sc(OTf)_3$-catalyzed domino 1,5-hydride shift/cyclization reaction was explored (Scheme 2). Polycyclic **2b** and **2d** containing a morpholine ring can be obtained with high diastereoselectivity in 68% and 79% yields, respectively. The piperidine derived compounds **1g–h** also give reasonable yields of the desired products **2g–h** with good diastereoselectivities. Gratifyingly, the corresponding eight-membered amine and acyclic diethyl amine starting materials (**1k** and **1m**) can readily rearrange to produce the corresponding products **2k** and **2m**, respectively, in good to high yields, albeit the diastereoselectivities are not high. Substrate **1n** with a convertible group (Br) worked well under conditions A to give the expected product **2n** in 72% yield with high diastereoselectivity (12 : 1); the structure of the major isomer was further confirmed by X-ray diffraction analysis.[14]

Next, we focused on the carbophilic Au(I)-catalyzed domino cyclization/1,5-hydride shift/cyclization reaction for synthesis of ring-fused tetrahydroazepines, and the results are summarized in Scheme 3. The Au(I)-catalyzed domino reactions of the morpholine derived compounds **1b–f** afford the corresponding products **3b–f** in moderate to excellent yields. The substituent (R^2) on the alkyne moiety also plays a significant role in yields.



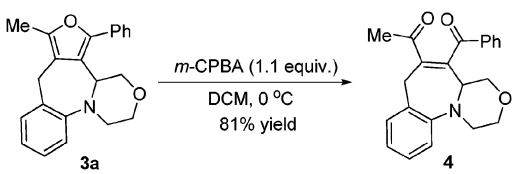
Scheme 2 Oxophilic $Sc(OTf)_3$-catalyzed domino 1,5-hydride shift/cyclization reaction.



Scheme 3 Carbophilic Au(I)-catalyzed domino cyclization/1,5-hydride shift/cyclization reaction.

For example, the reactions of aryl substituted substrates **1b–d** gave higher yield (70–99%) than alkyl or alkenyl substituted ones (53–64%), since the aryl substituted alkyne is more active to undergo heterocyclization and in turn give the cationic furanyl gold intermediate. Similar results were obtained for piperidine derived ones (**3g–j**) and the structure of **3g** was further determined by X-ray diffraction analysis.[14] The cyclic eight-membered amine starting material **1k** can readily undergo the domino process to yield the corresponding product **3k** in 94% yield. Starting materials derived from noncyclic amines such as dibenzyl or diethyl amine can give rise to the expected products upon rearrangement (**1l–m**). The reactions of **1n–o** with a convertible group (Br) on the phenyl ring can also proceed smoothly to afford the desired products **3n–o** in high yields.

The synthetic utility of ring-fused benzazepines was then showcased by the selective additional transformation of the representative product **3a** (eqn (2)).[15] The furan moiety of compound **3a** can readily undergo oxidative ring opening by 3-chlorobenzoperoxoic acid (*m*-CPBA) in dichloromethane (DCM) at 0 °C to produce tricyclic benzazepine **4** with convertible functional groups.[16]



(2)

In summary, we have developed a novel Lewis acid-catalyzed intramolecular redox domino reaction, in which the product

selectivity could be efficiently tuned by the nature of the Lewis acid. In the presence of oxophilic scandium(III) triflate, the reaction undergoes domino 1,5-hydride shift/cyclization to afford highly substituted multifunctionalized ring-fused tetrahydroquinolines in moderate to excellent yields with high diastereoselectivity, whereas ring-fused tetrahydroazepines could be obtained in moderate to excellent yields *via* the carbophilic gold(I)-catalyzed domino reaction under the mild conditions; this is a new alternative strategy to generate active hydrogen acceptor by a metal-mediated cyclization instead of the direct activation of the acceptor. Further studies including mechanism, scope and asymmetric catalysis are ongoing in our laboratories and will be reported in due course.

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