DOI: 10.1002/chem.201000667

Gold-Catalyzed Domino Reactions Consisting of Regio- and Stereoselective 1,2-Alkyl Migration

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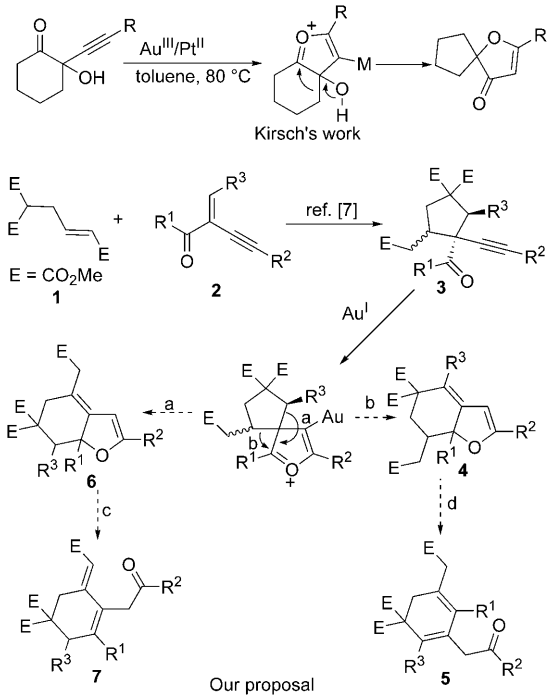
Domino or tandem reactions have shown their unrivalled power in organic synthesis due to their high capability in merging several reactions into one operation.[1] Recently, incorporation of a 1,2-alkyl migration step into the domino/tandem reactions has been found to be a powerful strategy for the rapid construction of architecturally complex molecules.[2] Meanwhile, selective synthesis of different products from the same starting material(s) by the subtle choice of the catalyst is a challenging issue and has attracted much interest by many chemists in recent years.[3–5]

Recently, Kirsch and co-workers reported an interesting Au^{III}- and Pt^{II}-catalyzed tandem heterocyclization and pinacol-type rearrangement for the efficient synthesis of substituted 3(2*H*)-furanones, in which the oxygen lone pair of the hydroxy group may provide the critical driving force (Scheme 1).[6] Very recently, we developed a *t*BuOK-catalyzed tandem Michael addition of crotonate-derived malonate **1** with 2-(1-alkynyl)-2-alken-1-ones **2** that led to the formation of highly substituted, multifunctionalized cyclopentanes **3** in good yields.[7] During this study, we envisioned that compounds **3** would form an oxonium-containing vinyl–gold intermediate in the presence of cationic gold complex, which might in turn undergo a 1,2-alkyl migration through pathway a or b (Scheme 1) and subsequent transformations through pathway c or d. For this hypothesis, two challenging selectivity issues need to be addressed: 1) the regioselective 1,2-alkyl migration (pathway a or b), especially when R^3 is an alkyl group; 2) how to selectively get one product if several products can be formed. We report herein a cationic gold(I)-catalyzed domino reactions consisting of highly regioselective and stereospecific 1,2-alkyl migration and heterocyclization or oxygen transfer.[2k,8]



Scheme 1. Previous work and proposed working hypothesis.

We tested this hypothesis by examining the tandem reaction of ketone **3a** under the catalysis of cationic gold(I) complex. After several attempts, pleasingly, the reaction succeeded under conditions A (Scheme 2): IPrAuCl/AgOMs (5 mol%), 1,2-dichloroethane (DCE), 80°C gave the fused 5,6-bicyclic **6a** containing a quaternary carbon stereocenter in 94% isolated yield as a single diastereomer. The bicyclic compound **6a** was produced by a tandem regioselective 1,2-

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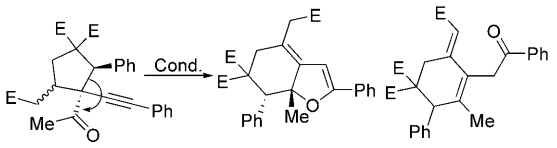
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201000667.



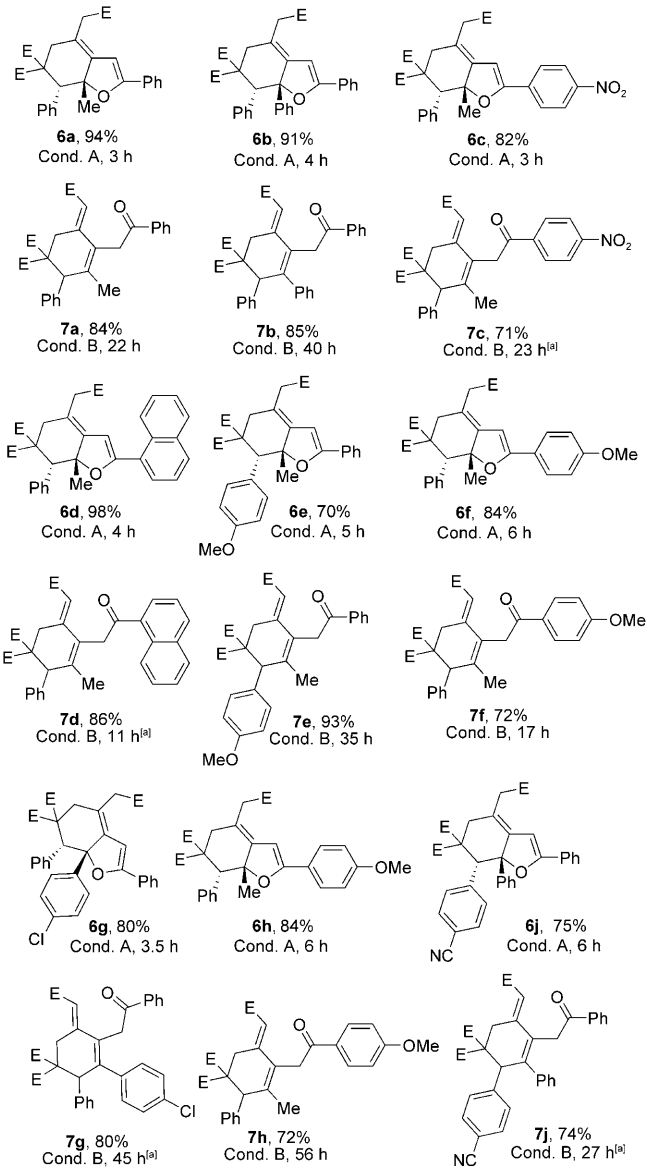
Scheme 2. Reaction conditions tested for the tandem reaction of **3a** catalyzed by a cationic gold(I) complex. DCE = dichloroethane, Ms = mesyl.

alkyl migration of the phenyl-substituted ketone and heterocyclization. Interestingly, 84% yield of moncyclic compound **7a** was achieved in a stereospecific fashion under conditions B (Scheme 2). Compound **7a** was formed by the tandem selective 1,2-alkyl migration and oxygen-transfer transformation. Under the catalysis of IPrAuCl/AgOMs (5 mol%), compound **7a** can be indeed afforded but in a lower yield (77%) with some unidentified products after longer reaction time (38 h).

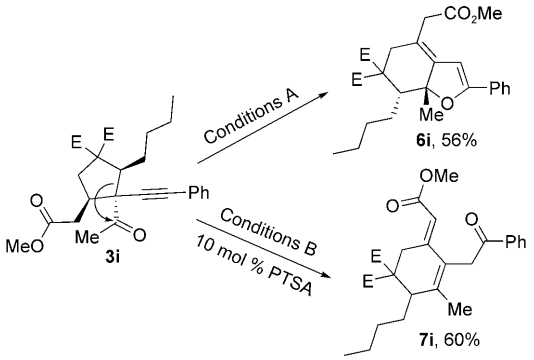
With the optimal reaction conditions in hand, we next turn to examine the scope of this product-selectivity controlled tandem reaction (Scheme 3). Gratifyingly, under conditions A and B, the 1,2-alkyl migration steps are highly regioselective, that is, only the R^3-substituted alkyl groups would undergo the 1,2-migration. Under conditions A, the reactions underwent a tandem heterocyclization and selective 1,2-alkyl migration leading to the fused 5,6-bicyclic compounds in high to excellent yields. In contrast, monocyclic compounds **7** could be obtained in good to excellent yields by a tandem 1,2-alkyl migration and oxygen-transfer reaction in a stereospecific fashion under conditions B. Electron-donating and -withdrawing groups on the benzene ring of R^3 are compatible and the reactions give compounds **6** or compounds **7** in good yields (Scheme 3, **6e**, **7e**, **6j**, and **7j**). In some cases, 10 mol% of PTSA was added to accelerate the reaction (Scheme 3, **7c**, **7d**, **7g**, and **7j**). The stereochemistry and structures of representative compounds **6b** and **7a** were further established by X-ray crystallography analysis.[9]

When the R^3 group is aliphatic, the difference between the two alkyl groups (the difference starts from the γ carbon) is very tiny. To our surprise, the 1,2-alkyl migrations are still unbelievably highly selective; for example, the reaction of compound **3i** with $R^3 = n\text{-}C_4H_9$ gave **6i** (conditions A) in 56% yield or **7i** (conditions B) in 60% yield, respectively (Scheme 4).

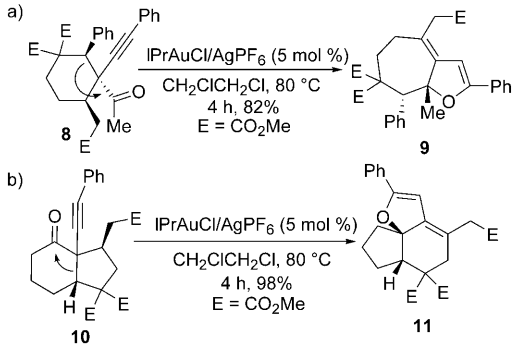
The reaction of compound **8** with a 6-membered ring could give the 5,7-fused bicyclic compound **9** under both conditions (82% yield under the catalysis of IPrAuCl/$AgPF_6$; Scheme 5a). Moreover, fused 5,6,5-tricyclic compound **11** could be obtained from the reaction of bicyclic **10** in excellent yield, which provided a rapid and efficient route to this kind of tricyclic compound (Scheme 5b).



Scheme 3. Selective transformations under two standard conditions. [a] After consumption of the starting material, 10 mol% of 4-methylbenzenesulfonic acid (PTSA) was added, E = CO_2Me.

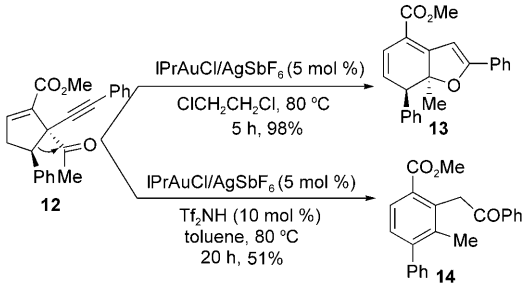


Scheme 4.



Scheme 5.

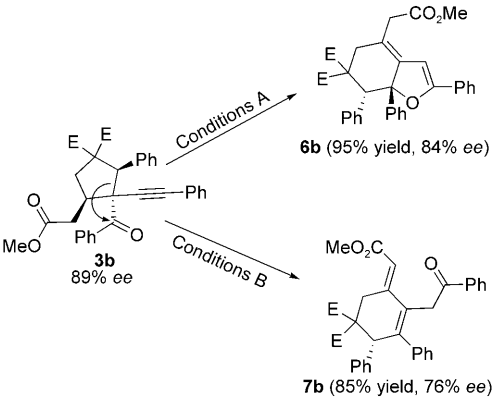
Next, we examined substrate **12** with a cyclopentene ring. Gratifyingly, 1,2-alkyl migration could also take place by a chemoselective cleavage of the $sp^3C–sp^3C$ bond rather than the $sp^2C–sp^2C$ bond. The reaction afforded a fused bicyclic compound **13** under catalysis by IPrAuCl/$AgSbF_6$ in DCE, while 51% yield of substituted phenyl carboxylate was obtained with Tf_2NH (10 mol%; Tf = trifluoromethanesulfonyl) as an additive (Scheme 6).



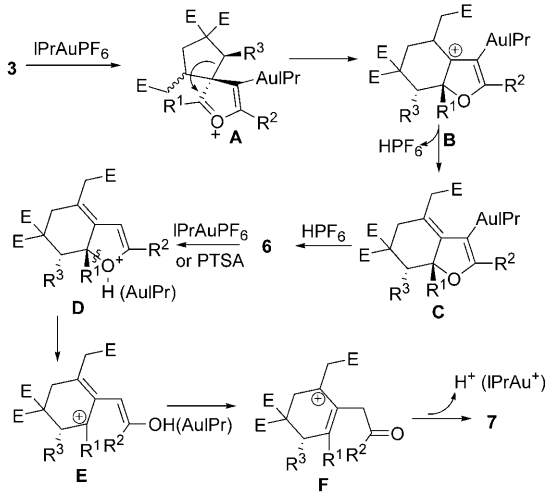
Scheme 6.

Finally, to probe the stereoselectivity of the 1,2-alkyl migration step, optically active **3b** (89% enantiomeric excess (*ee*)) was prepared and subjected to conditions A and B. It was found that the chiral information could be transferred into the products to give **6b** in 95% yield with 84% *ee* under conditions A or **7b** in 85% yield with 76% *ee* under conditions B (Scheme 7). These results indicated that the 1,2-alkyl migration is a stereospecific step.

One plausible mechanism that accounts for the product selectivity is depicted in Scheme 8. Spiro-bicyclic, oxonium-containing vinyl–gold intermediate **A**, generated from the intramolecular attack of the carbonyl group to the gold-activated alkyne,[2] would trigger a selective 1,2-alkyl migration from the same face of the heterocyclic ring to give allylic cation-containing vinyl–gold intermediate **B**. Deprotonation would form the bicyclic vinyl–gold intermediate **C**. Upon subsequent protonation, intermediate **C** would give the bicyclic product **6**. Compound **6** would undergo further rearrangement by the protonation and C–O cleavage to give the intermediates **D**, **E**, and **F** under catalysis by $IPrAuPF_6$ or



Scheme 7.



Scheme 8. Plausible mechanism for product selectivity.

additional PTSA.[10] The final product **7** was formed by loss of the acidic proton alpha to the ester group of intermediate **F**.

In summary, we have developed a cationic gold(I)-catalyzed tandem reaction containing highly regioselective and stereospecific 1,2-alkyl migration and heterocyclization or oxygen transfer. The starting materials are easily prepared from the tandem cyclization of 2-(1-alkynyl)-2-alken-1-ones and crotonate-derived malonate, which would make these reactions useful in target-oriented synthesis. Further studies to expand the scope of the reaction, such as using substrates with heterocyclic rings, and synthetic applications are ongoing in our laboratory.

Experimental Section

Typical procedure for the synthesis of 6a under conditions A: IPrAuCl (9.3 mg, 5 mol%), AgOMs (3.0 mg, 5 mol%) and dry DCE (2.5 mL) were added to a dry Schlenk tube and the mixture was stirred at room temperature for 0.5 h in the dark. Compound **3a** (142.5 mg, 0.3 mmol) was added and the resulting mixture was stirred at 80°C for 3 h. After the reaction was complete, which was determined by TLC analysis, the

reaction mixture was concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel (hexanes/acetate = 4: 1) to give **6a** as a colorless oil (134.2 mg, 94%).

Typical procedure for the synthesis of 7a under conditions B: IPrAuCl (9.3 mg, 5 mol%), $AgPF_6$ (3.8 mg, 5 mol%) and dry DCE (2.5 mL) were added to a dry Schlenk tube and the mixture was stirred at room temperature for 0.5 h in the dark. Compound **3a** (142.5 mg, 0.3 mmol) was added and the resulting mixture was stirred at 80 °C for 22 h. After the reaction was complete, which was determined by TLC analysis, the reaction mixture was concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel (hexane/acetate = 4: 1) to give **7a** as a white solid (119.9 mg, 84%).

Acknowledgements

We are grateful to the NSFC (20702015) and Science and Technology Commission of Shanghai Municipality for financial support. This work was also sponsored by the 973 program (2009CB825300).

Keywords: alkyl migration · asymmetric synthesis · chirality · domino reactions · regioselectivity

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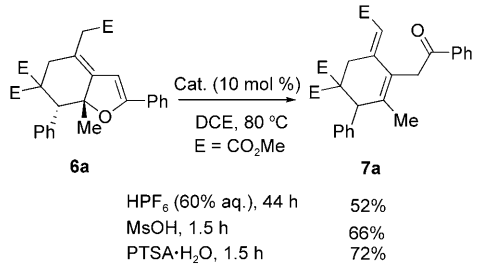
[9] CCDC-755498 (**6b**) and 755499 (**7a**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[10] The reaction of **6a** can give **7a** in moderate yields under the catalysis of 10 mol% of Brønsted acid at 80 °C in DCE, which are relatively lower than the yield (84%) from the direct isomerization of



3a (Scheme 2), indicating that the gold(I) catalyst may still play some role for this transformation.

Received: March 16, 2010
Published online: April 30, 2010

