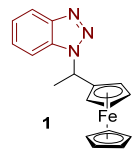
Microwave-Assisted Gold-Catalyzed Reaction of Benzylic Alcohols: Substrate Scope and Mechanistic Investigations

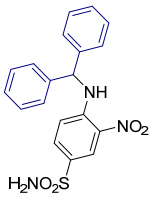
Amanda K. Melanese, Robert G. Iafe*
Department of Chemistry and Biochemistry, California State University San Marcos

Introduction

There is an increasingly high demand for the synthesis of organic compounds that possess novel mechanisms of action (nMoAs) needed to circumvent challenges in drug discovery.[1] The 1,1-diarylalkane is a common scaffold found in many active pharmaceutical agents and medicinally relevant compounds.[2] We have developed a novel synthetic strategy to afford these small molecules using gold catalysis. This highly regio- and stereoselective method was successfully applied to obtain a diverse library of compounds via a Friedel–Crafts-like reaction of benzylic alcohols under microwave irradiation. With high reproducibility involving both nucleophilic and electrophilic substrate scopes in good-to-excellent yields, the reaction mechanism was investigated through a series of control experiments to determine the pathway of the catalytic system.



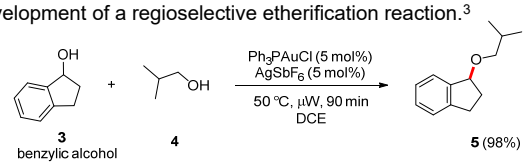
1
anticancer



2
lead compound for leukemia

Research Background

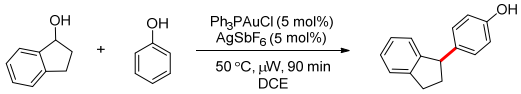
Previous Work: Initial investigations on gold catalysis resulted in the development of a regioselective etherification reaction.[3]



3 benzylic alcohol + **4** → **5** (98%)

New C–O Bond

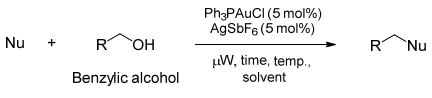
Our Work: Using similar conditions as above, the reaction of phenol as the nucleophile resulted in a Friedel–Crafts reaction pathway instead of an etherification reaction.



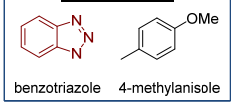
3 + **6** → **7** (88%)

New C–C Bond

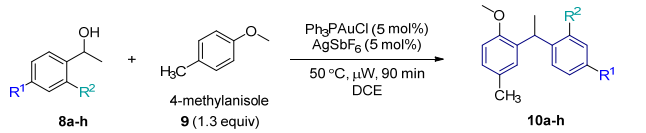
Reaction Scheme:

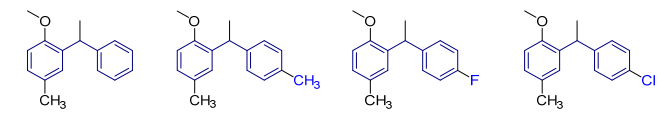


Nucleophiles



Electrophilic Substrate Scope



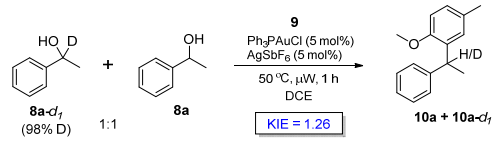


10a (99%) **10b** (94%) **10c** (97%) **10d** (90%)

10e (81%) **10f** (34%) **10g** (84%) **10h** (NR)

Mechanistic Investigations

Kinetic Isotope Effect (KIE) Study: Competition Reaction

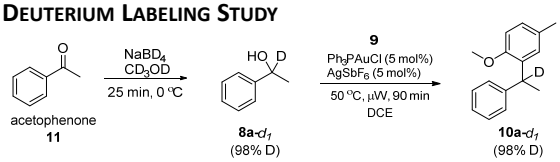


8a-d_1 (98% D) + 1:1 **8a** → **10a + 10a-d_1**

KIE = 1.26

- 2° KIE = 1.26 suggests $sp^3 \rightarrow sp^2$ hybridization involved in the rds.[4]

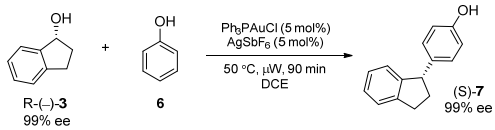
Deuterium Labeling Study



acetophenone **11** → **8a-d_1** (98% D) → **10a-d_1** (98% D)

- 100% retention of deuterium suggests that the rds does not go through a gold carbene.[5]

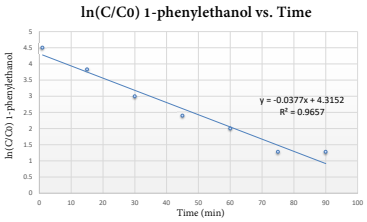
Stereochemistry Study

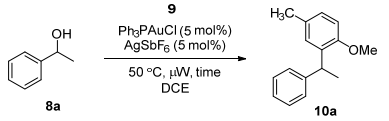


R-(–)-**3** 99% ee + **6** → (S)-**7** 99% ee

- 100% retention of stereochemistry suggests that the rds is not a carbocation.

Kinetic Analyses

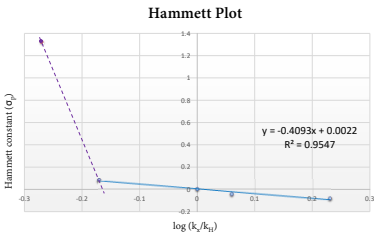


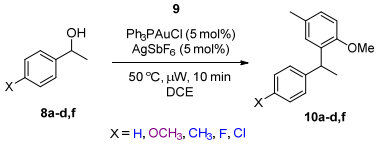


8a → **10a**

- Straight line shows first order reactivity
- No induction period suggests the catalytic gold is not behaving as gold nanoparticles

Hammett Plot



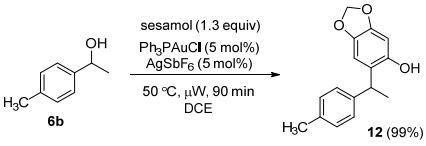


8a-d,f → **10a-d,f**

X = H, OCH_3, CH_3, F, Cl

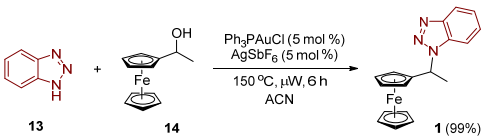
- Negative slope reveals a slight buildup of positive charge in the transition state
- The methoxy substituent is possibly going through a different mechanism

Biological Applications



6b → **12** (99%)

- Compounds similar to **12** have shown activity against P388 murine lymphocytic leukemia.[6]



13 + **14** → **1** (99%)

- Compound **1** exhibits anticancer properties effective against lung and esophageal cancer.[7]

Conclusion

With low catalyst loading and near 1:1 equivalence ratio, our gold-catalyzed microwave protocol exhibits high efficiency in obtaining a class of 1,1-diarylalkanes and heterocyclic compounds in good-to-excellent yields. Our findings from the mechanistic investigations suggest that the rate determining step involves $sp^3 \rightarrow sp^2$ hybridization. The stereochemical arylation experiment reveals a novel gold mechanistic pathway currently unprecedented in the literature. Future work includes expanding the scope of the stereoselectivity of the reaction with other enantiopure reagents and chiral gold ligands.

Acknowledgements

Special thank you to:

- ACS DOC SURF Program and Pfizer
- Dr. Robert G. Iafe
- Araceli A. Alvarez
- Lab Mates: Emily Aguilar, Brysa Alvarado, Emily Lyon, Daniel Ruiz, Kaylee Shoemaker

References

1. (a) Gerry, C. J.; Schreiber, S. L. *Nat. Rev. Drug Discov.* **2018**, 17, 333–352. (b) Spellberg, B.; Bartlett, J. G.; N. *Engl. J. Med.* **2013**, 368, 299–302. (c) Mondal, S.; Roy, D.; Panda, G.; *ChemCatChem.* **2018**, 10, 1941-1967. 2. (a) Ren, Y.; Zhang, L.; Cheng-He, Z.; Rong-Xia, G. *Med. Chem.* **2014**, 640. (b) Kharb, R.; Sharma, P. C.; Yar, M. S. *J. Enzyme Inhib. Med. Chem.* **2011**, *26*, 1–21. 3. Vinson, A. R. S.; Davis, V. K.; Arunasalam, A.; Jesse, K. A.; Hamilton, R. E.; Shattuck, M. A.; Hu, A. C.; Iafe, R. G.; Wenzel, A. G. Synlett 2015, 26, 765–770. 4. Gómez-Gallego, M.; Sierra, M. A. *Chem. Rev.* **2011**, 111, 4857–4963. 5. Wang, D.; Cai, R.; Sharma, S.; Jirak, J.; Thummanapelli, S. K.; Akhmedov, N. G.; Zhang, H.; Liu, X. Petersen, J. L.; Shi, X. *J. Am. Chem. Soc.* **2012**, *134*, 9012–9019. 6. Jurd, V. L.; Narayanan, K. D. Paull, *J. Med. Chem.* **1987**, 30, 1752–1756. 7. Snegur, L. V.; et. all. *Appl. Organomet. Chem.* **2008,** 22, 139-147.