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Gold Meets Rhodium: Tandem One-Pot Synthesis of β-Disubstituted Ketones via Meyer–Schuster Rearrangement and Asymmetric 1,4-Addition

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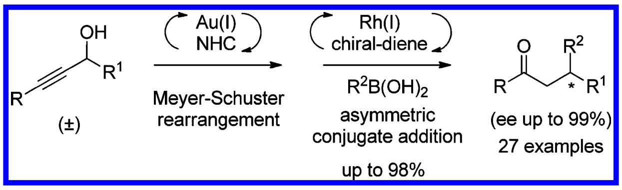
ABSTRACT



An asymmetric one-pot tandem Au/Rh-catalyzed synthesis of highly enantioenriched β-disubstituted ketones starting from racemic propargyl alcohols is disclosed. The compatibility of the two metal complexes (Au/Rh) and their orthogonal ligand systems (NHC/diene) in this bimetallic catalytic system is investigated.

Recently, the combination of several transition-metal-catalyzed transformations in one single reaction vessel (one-pot) has gained increasing interest as molecular complexity is rapidly generated without the need for isolation or purification of intermediates, therefore enhancing efficiency and sustainability by reducing costs and waste production.[1] On the other hand, the combination of several metal complexes in one reaction flask dramatically increases the system's complexity enabling redox-processes or ligand-exchange reactions between the metal centers leading to undesired side reactions or catalyst deactivation.

As part of our interest in tandem one-pot transformations,[2] we envisioned combining gold and rhodium catalysis in a new one-pot transformation. While there are numerous reports of one-pot transformations in particular involving palladium catalysis,[3] much less is known about other bimetallic systems utilizing homogeneous gold catalysts. The one-pot combination of gold and palladium recently gained increasing attention and is by far the best studied system,[4] while the combination of gold and other

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(3) For a review, see: (a) Lee, J. M.; Na, Y.; Han, H.; Chang, Y. *Chem. Soc. Rev.* **2004**, *33*, 302. (b) van den Beuken, E. K.; Feringa, B. L. *Tetrahedron* **1998**, *54*, 12985.

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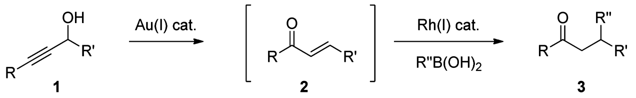
transition metals is far less explored.[5] To the best of our knowledge there is only one report on a one-pot Rh/Au dual-catalytic system in which the gold-catalyst is a simple Au(III) halide precursor without any ligand system on gold.[6]

In order to study the metal−ligand interactions of the first one-pot Au(I)/Rh(I) system, we envisioned to use a Au(I)-catalyzed Meyer−Schuster rearrangement of a propargyl alcohol **1** leading, with complete atom-economy,[7] to the corresponding enone **2** followed by a Rh-catalyzed boronic acid 1,4-addition to access β-disubstituted ketones **3** in a very rapid fashion from easily accessible starting materials (Scheme 1).

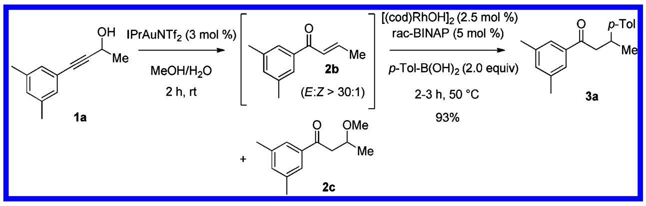
Scheme 1. One-Pot Au(I)/Rh(I) Dual Catalysis



While the classical Meyer−Schuster rearrangement[8] requires harsh reaction conditions (strong acids and elevated temperatures), there have been several reports on much milder conditions employing Au catalysis starting from propargyl acetates[9] or more conveniently directly from the corresponding propargyl alcohol.[10]

After initial screening experiments, we found reaction conditions compatible with a sequential Au/Rh tandem transformation (Scheme 2). Propargyl alcohol **1a** was transferred into product **3a** by employing an NHC ligand on the gold catalyst (3 mol % $IPrAuNTf_2$) and a bidentate phosphine ligand (5 mol % *rac*-BINAP) as a ligand on the Rh-precursor. $[(cod)RhOH]_2$ (2.5 mol %) was sufficient to undergo the conjugate addition reaction to give **3a** in a remarkably high yield of 93% in a sequential one-pot transformation. A solvent mixture of $MeOH/H_2O$ afforded a fast (ca. 1−2 h) and mild (room temperature) Au-catalyzed Meyer−Schuster reaction, while the same conditions were suitable for a very fast Rh-catalyzed conjugate addition. These conditions turned out to be very general and allowed the synthesis of a large library of racemic β-disubstituted ketones.

Scheme 2. Racemic Au/Rh Sequential Tandem Sequence

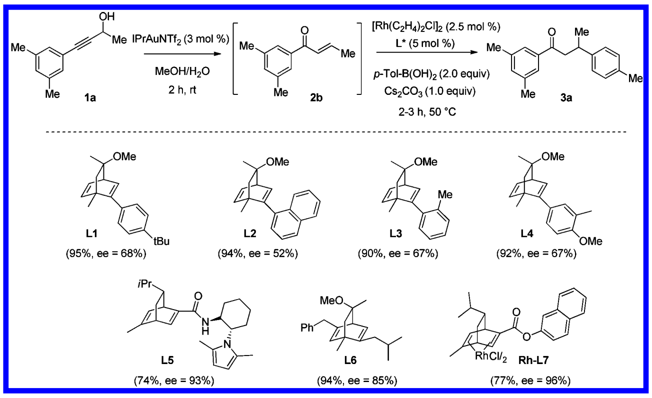


Control experiments combining the two transition metals from the start of the reaction demonstrated that free phosphine ligand employed in the first step slows down the Meyer−Schuster rearrangement significantly, presumably caused by the formation of the catalytic inactive species $[NHCAuL]^+$ (L = BINAP) (see the Supporting Information).

At this stage, we invisioned using an orthogonal ligand system on gold and rhodium while at the same time developing an asymmetric tandem transformation by utilizing a chiral diene ligand. Diene ligands are known to efficiently bind to Rh(I),[11] yet be very poor ligands for Au(I),[12] making them ideal for an orthogonal-ligand system in this bimetallic tandem tranformation and also unique in comparison to the well studied tandem-phosphine ligand−Au/M transformations.

A ligand screening of several chiral diene ligands demonstrated that there is no ligand−ligand exchange between the two metal centers and that Hayashi's diene ligand **L7** is a very effcient ligand in inducing high enantioselectivies (96% ee) in the 1,4-addition with this fairly challenging substrate[13] to yield **3a** in moderate yields (Scheme 3). It is noteworthy that there are not many dual-metal-catalyzed tandem transformations involving an asymmetric reaction step; in particular, there are no asymmetric dual-metal-catalyzed transformations with one metal being gold.[14]

Scheme 3. Ligand Optimization



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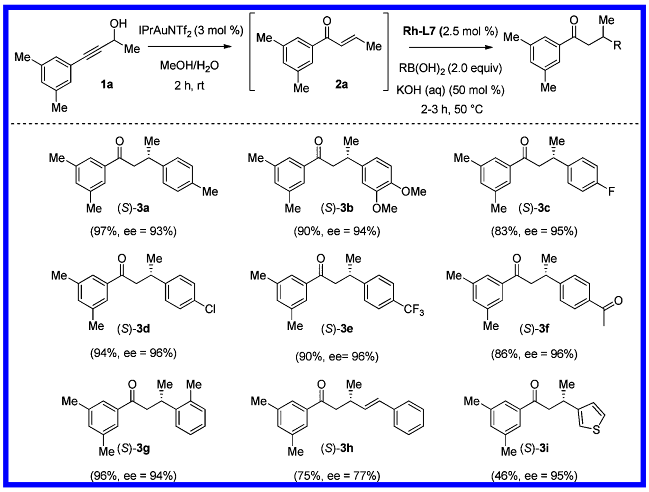
(10) (a) Ramón, R. S.; Gaillard, S.; Slawin, A. M. Z.; Porta, A.; D'Alfonso, A.; Zanoni, G.; Nolan, S. P. *Organometallics* **2010**, *29*, 3665. (b) Ramón, R. S.; Marion, N.; Nolan, S. P. *Tetrahedron* **2009**, *65*, 1767. (c) Engel, D. A.; Lopez, S. S.; Dudley, G. B. *Tetrahedron* **2008**, *64*, 6988. (d) Lee, S. I.; Baek, J. Y.; Sim, S. H.; Chung, Y. K. *Synthesis* **2007**, 2107. (e) Engel, D. A.; Dudley, G. B. *Org. Lett.* **2006**, *8*, 4027.

The lowered yields with ligands **L5** and **L7** were caused by the formation of **2c** as a side product which is generated by methanol addition to the corresponding enone **2b**.[15] The formation of this side product is fast upon addition of base to the Au-catalysis system. The addition of external base in the ligand screening experiments (1 equiv Cs_2CO_3) was necessary in order to promote the Rh-catalyzed 1,4-addition when starting with the $[RhCl(C_2H_4)_2]_2$ precursor. In contrast, starting with $[(cod)RhOH]_2$ did not require addition of external base, as the rhodium hydroxide is assumed to be the catalytic active species.[16] As Hayashi's ligand **L7** showed excellent enantioselectivities, we performed some solvent screening experiments on the initial Meyer−Schuster rearrangement in order to avoid the use of methanol as solvent in the tandem transformation (see the Supporting Information). Interestingly, the solvent has a large impact on the *E*/*Z*-selectivity of **2b**, and only $MeOH/H_2O$ gave high *E*-selectivities. Performing, for example, the catalysis in dioxane/H_2O (5:1) led to a 4:1 mixture of *E*/*Z*-isomers, while interestingly, employing this mixture in the dual-metal catalysis still yielded the final product in 86% yield and 86% ee, making a matched−mismatched combination of the chiral-diene complex with the two *E*/*Z*-isomers likely to rationalize the still high enantioselectivity.

A base screening experiment led to the optimized reaction conditions for the asymmetric tandem transformation. Changing the base to KOH and reducing the amount to 50 mol % generates, in the presence of boronic acid, a buffered solution in which methanol addition is slow relative to the Rh-catalyzed addition and **3a** could be isolated in 97% yield and 93% ee.

With these optimized conditions in hand the scope of boronic acids was investigated (Scheme 4).

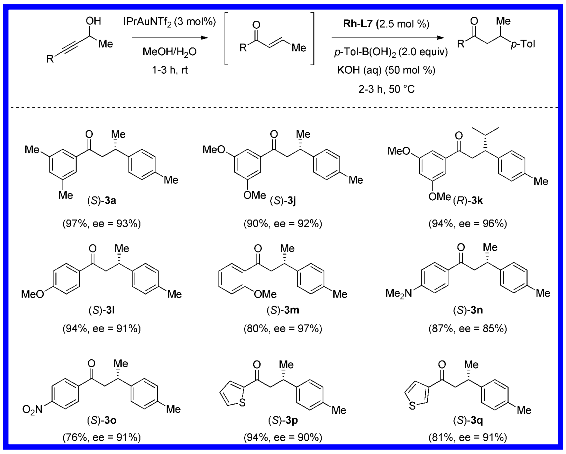
Scheme 4. Scope with Regard to the Boronic Acid



The addition of electron-rich (**3a**,**b**), electron-poor (**3c**−**e**), base-sensitive (**3f**), sterically hindered ortho-substituted (**3g**) boronic acids was possible in excellent yields with very high enantioselectivities (93−96% ee).

In addition to arylboronic acids, also (*E*)-styryl boronic acid led to the corresponding allyl compound **3h** in good yields with reduced enantioselectivities. A heteroaromatic boronic acid such as 3-thienylboronic acid was equally suitable, affording **3i** with high enantioselectivities, but a low conversion for the second step was observed.

Scheme 5. Scope of Propargyl Alcohols



As the next step, several propargyl alcohols with diverse aromatic substitution were analyzed (Scheme 5). In general, electron-rich systems (**3a**, **3j**, **3m**,**n**) led in high yields (> 80%) and in high enantioselectivities to the corresponding products. Changing the alkyl group from methyl to isopropyl (**3k**) as well as sterically demanding groups (**3m**) increased the enantioselectivities. Electron-deficient (**3o**) as well as heteroaromatic backbones such as **3p** and **3q** led to the products in high yields and enantioselectivities.

This tandem transformation also works with the readily available diarylpropargyl alcohols when heated slightly to 50 °C, and then the Meyer−Schuster rearrangement is as fast as with substrates from Scheme 5. Various 3,3-diaryl ketones, important substructures of many pharmaceuticals containing a diarylmethine stereocenters,[17] can be

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(11) (a) Gendrineau, T.; Chuzel, O.; Eijsberg, H.; Genet, J. P.; Darses, S. *Angew. Chem., Int. Ed.* **2008**, *47*, 7669. (b) Paquin, J. F.; Defieber, C.; Stephenson, C. R. J.; Carreira, E. M. *J. Am. Chem. Soc.* **2005**, *127*, 10850. (c) Fischer, C.; Defieber, C.; Suzuki, T.; Carreira, E. M. *J. Am. Chem. Soc.* **2004**, *126*, 1628. (d) Hayashi, T.; Ueyama, K.; Tokunaga, N.; Yoshida, K. *J. Am. Chem. Soc.* **2003**, *125*, 11508. For a review on Rh-catalyzed asymmetric 1,4-addition, see: (e) Edwards, H. J.; Hargrave, J. D.; Penrose, S. D.; Frost, C. G. *Chem. Soc. Rev.* **2010**, *39*, 2093. (f) Hayashi, T.; Yamasaki, K. *Chem. Rev.* **2003**, *103*, 2829. (g) Fagnou, K.; Lautens, M. *Chem. Rev.* **2003**, *103*, 169.

(12) Cinellu, M. A. In *Modern Gold Catalyzed Synthesis, Chapter 7, Gold−Alkene Complexes*; Hashmi, A. S. K., Toste, F. D., Eds.; Wiley-VCH: Weinheim, 2012.

(13) In most reports, Rh-catalyzed 1,4-additions are performed with cyclic enones while this particular acyclic substrate contains only a small methyl group as stereodifferentiating group.

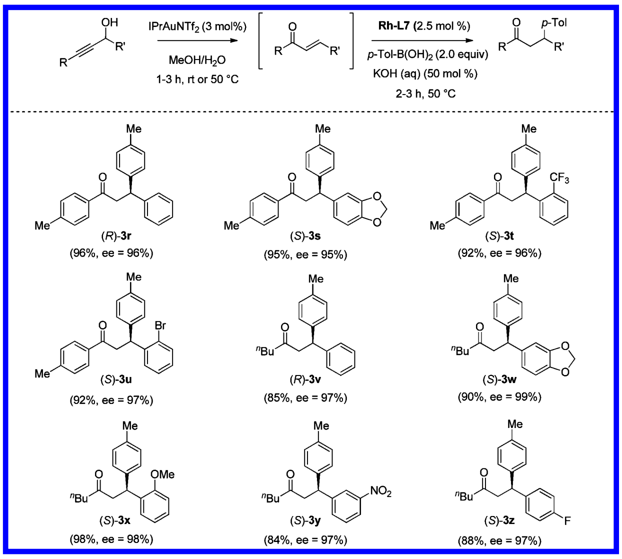
(14) For a review on asymmetric tandem transformations, see: Clavier, H.; Pellissier, H. *Adv. Synth. Catal.* **2012**, *354*, 3347.

(15) The addition of methanol has been observed in the case of Au-catalyzed Meyer−Schuster rearrangements when non-substituted highly reactive enones were formed; see: Pennell, M. N.; Turner, P. G.; Sheppard, T. D. *Chem.—Eur. J.* **2012**, *18*, 4748and ref 10b.

(16) Hayashi, T.; Takahashi, M.; Takaya, Y.; Ogasawara, M. *J. Am. Chem. Soc.* **2002**, *124*, 5052.

(17) Chen, G.; Xing, J.; Cao, P.; Liao, J. *Tetrahedron* **2012**, *68*, 5908.

Scheme 6. Au/Rh-Tandem Synthesis of β-Diaryl Ketones



synthesized in one step in excellent yields and enantioselectivities (Scheme 6).

The absolute configuration of the final products was assigned by the X-ray crystal structure analysis of (*S*)-**3n** and (*S*)-**3u** (Figure 1) and by synthesis of (*S*)-1,3-diphenylbutan-1-one and comparison with the literature data (see the Supporting Information).

Attempts to add all components from the start did not result in full conversion. Instead, $[Rh(cod)Cl]_2$ and $[Rh(cod)OH]_2$ turned out to be inhibitors for the Meyer–Schuster reaction (see the Supporting Information), which can be rationalized through the formation of the inactive IPrAuX species.[18] Changing the counterion on rhodium to a weakly coordinating ion such as $Rh(cod)_2OTf$ resulted in the formation of the Rh-catalyzed arylation product **4**, which is generated in the absence of gold (Scheme 7).[19]

While the ligand systems on both metals are orthogonal, the counterions on the two metals seem crucial in tuning the desired reactivity. It is likely that under the reaction conditions the gold catalyst abstracts the counterion on rhodium, generating a highly active cationic Rh–diene catalyst explaining the mild reaction conditions. If the IPrAuCl generated can also further accelerate the reaction by acting as a transmetalation cocatalyst[20] is currently under investigation.

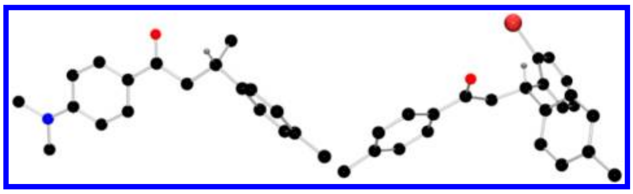
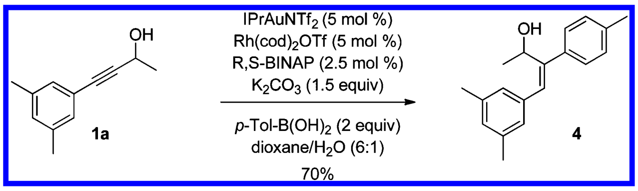


Figure 1. Solid-state molecular structures of (*S*)-**3n** and (*S*)-**3u**.

Scheme 7. Rh-Catalyzed Arylation in the Presence of Gold



In conclusion, this novel and general Au/Rh tandem transformation provides β-disubstituted ketones as valuable compounds for synthesis in high yields and enantioselectivities from easily accessible racemic propargyl alcohols by mimicking the concept of dynamic kinetic resolution. This is achieved by transformation into achiral intermediates by the gold catalyst and a subsequent enantioselective conversion by the chiral rhodium catalyst. This process is only possible as the ligand systems (NHC vs diene) are orthogonal in their binding affinities toward the two metals.

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Supporting Information Available. Experimental procedures, X-ray data (CIF), and full characterization for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) IPrAuOH is a poor catalyst in the Meyer–Schuster rearrangement, see: Gómez-Suárez, A.; Oonishi, Y.; Meiries, S.; Nolan, S. P. *Organometallics* **2013**, *32*, 1106 and ref 10a.

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The authors declare no competing financial interest.