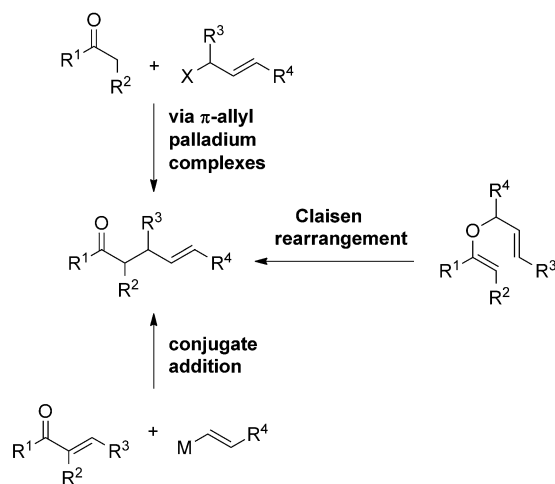# Towards the Ideal Synthesis of Homoallylic Ketones

Sofía Ferrer,[a] Michael E. Muratore,[a] and Antonio M. Echavarren*[a, b]

Homoallylic ketones combine arguably two of the most synthetically useful functional groups in organic chemistry and are, therefore, very valuable synthetic intermediates. General methods for the synthesis of these intermediates include the allylation of carbonyl compounds via π-allyl palladium(II) complexes,[1] the 1,4-addition of vinylmetal nucleophiles onto α,β-unsaturated compounds,[2] and the Claisen rearrangement of allyl vinyl ethers (Scheme 1).[3] The control of the regioselectivity in the latter procedure can be achieved by a domino process consisting of a copper-catalyzed C—O bond coupling of alkenyl iodides with allylic alcohols, followed by sigmatropic rearrangement.[4]

The synthetic equivalence of acetylenes with carbonyl compounds was first recognized in this context by the group of Trost who found that homoallylic ketones could be obtained by the Ru^{II}-catalyzed addition of allyl alcohols to terminal alkynes, in a process that probably took place by means of the cycloaddition of both unsaturated substrates to form a ruthenacyclopentene intermediate.[5]

In the last decade, cationic gold(I) complexes have emerged as the most reactive catalysts for the activation of alkynes towards the nucleophilic addition of a wide range of hetero- and carbonucleophiles.[6] Although the first synthetically useful applications of homogeneous gold catalysis in organic synthesis involved the attack of alcohols onto alkynes,[7] it was not until 2013 that a method for the preparation of allyl vinyl ethers based on this process was developed. This process was achieved by the group of Aponick, who developed a tandem intermolecular hydroalkoxylation/Claisen rearrangement (Scheme 2).[8] This new cascade reaction led to the direct formation of γ,δ-unsaturated ketones from simple starting materials in a single step and with excellent stereoselectivity in most cases. This transformation was performed by using 5 mol% of both neutral gold(I) complex [Au(Cl)(IPr)] (IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene) and AgBF$_4$, which was required to generate the gold(I) cationic species in situ.

In a step towards the development of a highly efficient synthesis of homoallylic ketones, the group of Nolan has pushed this method towards its limits by reducing the amount of gold(I) catalyst by an order of magnitude and by conducting the reaction in the absence of solvent, using a 1:3 alkyne to allyl alcohol ratio.[9] Importantly, by using [Au(NTf$_2$)(IPr^{Cl})] (Tf = triflate; IPr^{Cl} = 4,5-dichloro-1,3-bis(2,6-diisopropylphenyl)-1H-imidazol-2-ylidene) as the catalyst, which proved to be robust

Scheme 1. General methods for the synthesis of homoallylic ketones. NPhth = Phthalimide.
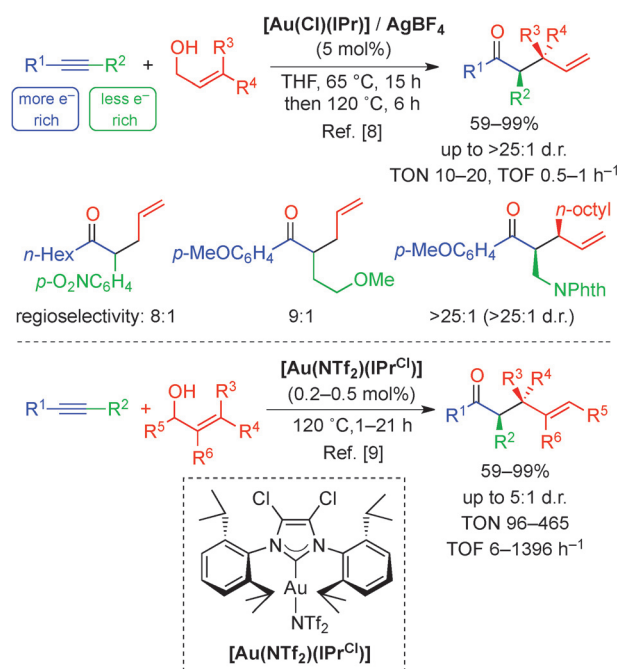
[a] S. Ferrer, Dr. M. E. Muratore, Prof. A. M. Echavarren
    Institute of Chemical Research of Catalonia (ICIQ)
    Av. Països Catalans 16, 43007 Tarragona (Spain)
    E-mail: aechavarren@iciq.es

[b] Prof. A. M. Echavarren
    Departament de Química Analítica i Química Orgànica
    Universitat Rovira i Virgili
   C/Marcel·li Domingo s/n, 43007 Tarragona (Spain)

Scheme 2. Gold(I)-catalyzed synthesis of homoallylic ketones by hydroalkoxylation/Claisen rearrangement.

enough to withstand the relatively harsh reaction conditions, the addition of a hygroscopic and light-sensitive silver salt was no longer necessary. By reducing the catalyst loading to 0.2–0.5 mol%, the new process took place with turnover numbers (TON) from 96 to 465 and turnover frequencies (TOF) from 6 to 1396 h^{-1}.

The regioselectivity of this process was largely controlled by the electronic nature of the alkyne substituents (Scheme 2).[8] Thus, the most electron-rich alkyne substituent (Scheme 2, blue) ended up at the ketone terminus, whereas the least electron-rich group (Scheme 2, green) became the α-substituent of the final ketone product. This result can be explained by the initial attack of the alcohol onto the alkyne gold(I) complex in a Markovnikov manner, hence by attack at the carbon bearing the most electron-rich group.

The overall mechanistic scenario is reasonably well-understood and follows well-known principles in homogeneous gold(I) catalysis (Scheme 3).[8,10] However, even with the assis-
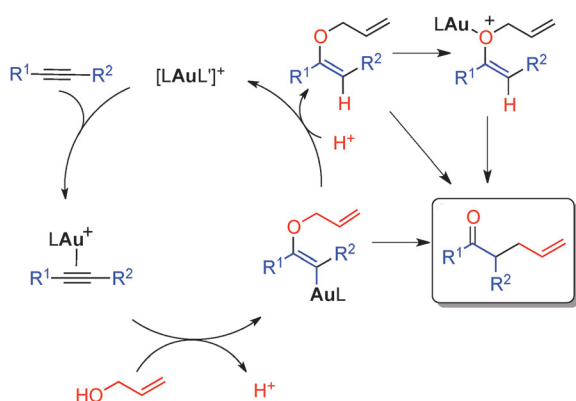
Scheme 3. Catalytic cycle for the gold(I)-catalyzed synthesis of homoallylic ketones by hydroalkoxylation/Claisen rearrangement.

tance of high-level computations, no unambiguous conclusion could be drawn on whether the final step proceeded by simple thermal [3,3]-sigmatropic rearrangement, or if it was promoted by gold(I) through lowering of the activation energy by coordination to the enol ether oxygen. A direct [3,3]-sigmatropic rearrangement could also take place from the allyloxy vinylgold(I) intermediate to form a C–gold(I) ketone enolate, which would undergo protonolysis to give the final compounds. Regarding the observed diastereoselectivity, the major products resulted from a Claisen rearrangement proceeding through chair transition states.[8]

One may legitimately wonder whether this process constitutes a significant improvement and if it is the most efficient synthesis of homoallylic ketones. From the point of view of catalytic efficiency and simplicity, the reaction discovered by Aponick is the best method for the synthesis of a wide variety of homoallylic ketones from inexpensive and commercially available materials. The further refinement by the group of Nolan is also an excellent example of green chemistry in chemical synthesis.[10] In particular, the demonstration that this process can be carried out efficiently under solvent-free conditions should encourage other groups to develop even more challenging processes, including cascade transformations, in the

absence of solvent and with lower catalyst loadings than those usually employed in most gold(I)-catalyzed transformations.

However, there are still some challenges to be met. Firstly, although in a number of examples the diastereoselectivity was good, lower diastereoselectivities were achieved with lower catalyst loadings. In addition, terminal alkynes were relatively poor substrates in this reaction, requiring 0.5 mol% catalyst and furnishing lower yields (48–77%, five examples) even under optimized conditions.[9] Moreover, and assuming gold(I) catalyzes the final sigmatropic rearrangement, the development of an enantioselective synthesis of homoallylic ketones employing this method would present a formidable challenge. In this scenario, the gold(I) catalyst should act as a chiral Lewis acid in the enantio-discriminating Claisen rearrangement, and this would require overcoming the intrinsic limitation posed by the linear dicoordination of gold(I) complexes, which tends to place the chiral ligand far away from the reactive center.

[1] a) X.-X. Yan, C.-G. Liang, Y. Zhang, W. Hong, B.-X. Cao, L.-X. Dai, X.-L. Hou, *Angew. Chem. Int. Ed.* **2005**, *44*, 6544–6546; *Angew. Chem.* **2005**, *117*, 6702–6704; b) B. M. Trost, J. Xu, T. Schmidt, *J. Am. Chem. Soc.* **2009**, *131*, 18343–18357; c) X. Huo, G. Yang, D. Liu, Y. Liu, I. D. Gridnev, W. Zhang, *Angew. Chem. Int. Ed.* **2014**, *53*, 6776–6780; *Angew. Chem.* **2014**, *126*, 6894–6898.

[2] a) P. Jacob III., H. C. Brown, *J. Am. Chem. Soc.* **1976**, *98*, 7832–7833; b) S. Hara, S. Ishimura, A. Suzuki, *Synlett* **1996**, 993–994; c) W. X. Zheng, X. Huang, *Synthesis* **2002**, 2497–2502; d) K. A. Hansford, J. E. Dettwiler, W. D. Lubell, *Org. Lett.* **2003**, *5*, 4887–4890; e) A. A. Dörr, W. D. Lubell, *Can. J. Chem.* **2007**, *85*, 1006–1017.

[3] T. Higashino, S. Sakaguchi, Y. Ishii, *Org. Lett.* **2000**, *2*, 4193–4195.

[4] G. Nordmann, S. L. Buchwald, *J. Am. Chem. Soc.* **2003**, *125*, 4978–4979.

[5] B. M. Trost, J. A. Martinez, R. J. Kulawiec, A. F. Indolese, *J. Am. Chem. Soc.* **1993**, *115*, 10402–10403.

[6] a) A. Fürstner, P. W. Davies, *Angew. Chem. Int. Ed.* **2007**, *46*, 3410–3449; *Angew. Chem.* **2007**, *119*, 3478–3519; b) E. Jiménez-Núñez, A. M. Echavarren, *Chem. Rev.* **2008**, *108*, 3326–3350; c) C. Obradors, A. M. Echavarren, *Acc. Chem. Res.* **2014**, *47*, 902–912; d) L. Fensterbank, M. Malacria, *Acc. Chem. Res.* **2014**, *47*, 953–965.

[7] a) R. O. C. Nomran, W. J. E. Parr, C. B. Thomas, *J. Chem. Soc. Perkin Trans. 1* **1976**, 1983–1987; b) J. H. Teles, S. Brode, M. Chabanas, *Angew. Chem. Int. Ed.* **1998**, *37*, 1415–1418; *Angew. Chem.* **1998**, *110*, 1475–1478.

[8] J. M. Ketcham, B. Biannic, A. Aponick, *Chem. Commun.* **2013**, *49*, 4157–4159.

[9] A. Gómez-Suárez, D. Gasperini, S. V. C. Vummaleti, A. Poater, L. Cavallo, S. P. Nolan, *ACS Catal.* **2014**, *4*, 2701–2705.

[10] C.-J. Li, B. M. Trost, *Proc. Natl. Acad. Sci. USA* **2008**, *105*, 13197–13202.