Catalytic Intermolecular Hetero-Dehydro-Diels-Alder Cycloadditions: Regio- and Diasteroselective Synthesis of 5,6-Dihydropyridin-2-ones†

Jesús Manuel Fernández-García,[a] Manuel Á. Fernández-Rodríguez,[b] and Enrique Aguilar[a],*

[a] *Instituto Universitario de Química Organometálica “Enrique Moles”, Universidad de Oviedo, C/Julián Clavería, 8, 33006, Oviedo, Asturias (Spain).*

[b] *Departamento de Química, Área de Química Orgánica, Facultad de Ciencias, Universidad de Burgos, Pza. Misael Bañuelos, s/n, 09001, Burgos, Spain.*

eah@uniovi.es

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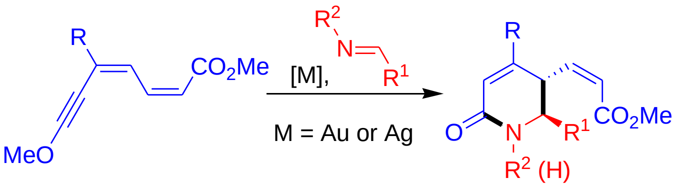
ABSTRACT



A novel catalyzed intermolecular hetero-dehydro-Diels-Alder reaction between *push-pull* 1,3-dien-5-ynes and aldimines or silylaldimines is reported. The sequence is promoted both by gold(I) or silver(I) catalysts and leads to the diastereo- and regioselective formation of 5,6-dihydropyridin-2-ones.

The field of metal-catalysis (together with bio-, and organo-catalysis, one of the three feet of the vital catalytic tripod in the current scenario of organic synthesis) has achieved considerable improvement over the last decade.[1]

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† Dedicated to Professor Rafael Suau, in memoriam.

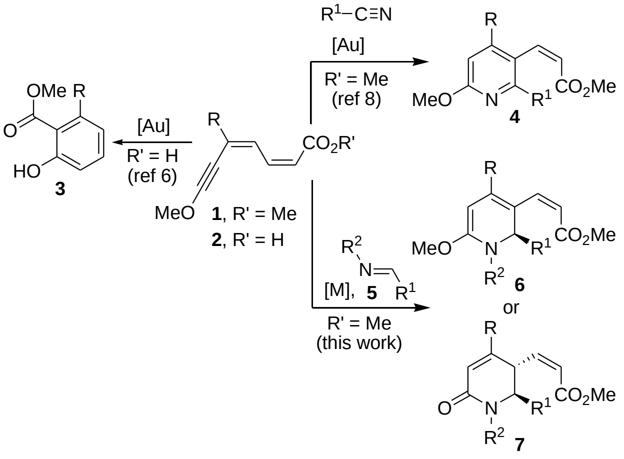
(1) For selected recent reviews on catalysis: (a) Grondal, C.; Jeanty, M.; Enders, D. *Nature Chem.* **2010**, *2*, 167-178. (b) Díez-González, S.; Marion, N.; Nolan, S. P. *Chem. Rev.* **2009**, *109*, 3612-3676. c) Hargaden, G. C.; Guiry, P. J. *Chem. Rev.* **2009,** *109,* 2505-2550. (d) Fürstner, A. *Chem. Soc. Rev.* **2009**, *38*, 3208-3221. (e) Gorin, D. J.; Sherry, B. D.; Toste, F. D. *Chem. Rev.* **2008**, *108*, 3351-3378. (f) Dondoni, A.; Massi, A. *Angew. Chem. Int. Ed.* **2008**, *47*, 4638-4660. (g)

In this regard, the well-recognized ability of coinage metals (especially gold derivatives) and platinum to activate triple bonds for the attack of different nucleophiles has resulted in the development of an impressive array of organic transformations, mainly cyclizations;[2] moreover, some of them represent efficient routes to substituted heterocyclic compounds.[3] However, relatively few gold-catalyzed intermolecular cycloadditions have been reported.[4]

We have recently described an efficient and simple procedure for the synthesis of push-pull dienynes **1** and **2**,[5] which have proved to be appropriate substrates for metal-catalyzed transformations. For instance, the carboxylic acid substrates **2** undergo an unusual cycloaromatization reaction[6,7] to afford 2,3-disubstituted phenols **3** (Scheme 1); moreover, non-activated nitriles regioselectively attack the metal-complexed triple bond of esters **1** leading, after cyclization, to tetrasubstituted pyridines **4**,[8] this being the first example of an intermolecular catalyzed hetero-dehydro-Diels-Alder (HDDA) reaction.[9]

Continuing with our interest to explore the reactivity of dienynes **1**, we have considered testing their behaviour against aldimines **5** which, through an HDDA reaction, should lead to 1,2-dihydropyridines **6** or, more probably, to 5,6-dihydropyriridones **7** after hydrolysis; the methoxy substituted triple bond carbon would behave this way as a masked carbonyl surrogate. Interestingly, the 5,6-dihydropyridin-2-one skeleton is found in compounds presenting antibacterial, or antiviral activities, as well as in herbicides, plant growth regulators[10] or in free radical scavengers; moreover, properly substituted 5,6-dihydropyridin-2-ones have been regarded as useful intermediates for the preparation of spatially defined non-peptidic scaffolds, constrained counterparts of natural amino acids.[11]

Scheme 1. Metal-catalyzed transformations involving push-pull dienynes **1** and **2**.



Taking into account our previous results in the reaction with nitriles,[8] the initial essays were carried out with dienyne **1a** ($c = 0.1$ M) and aldimine **5a** (5 equiv). 1,2-Dichloroethane (DCE) was used as solvent, the temperature was settled at 85 ºC, and several transition metal complexes were tested as catalysts for the desired transformation. No reaction was observed with transition metals such as Pd, Fe, Ni;[12] however, the reaction proceeded with coinage metals (Table 1, entries 1-5, 8-10) as well as with Pt and Zn (entries 6, 7). After work-up, dihydropyridone **7a** was isolated, albeit in low yield, for Zn (entry 7), or observed by NMR for Pt (entry 6) and for several cationic Au(I) catalysts bearing aromatic phosphines (entries 2-4), independently of the electronic nature of the phosphine ligand. Moderate yields were reached for Cu(II) (entry 8), Au(III) (entry 1), Ag (entries

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For an insight comprised of a series of commentaries and reviews, see: *Small Molecule Catalysis* (Eds.: Mitchinson, A.; Finkelstein, J.) in *Nature* **2008**, *455*, 303-349. For recent reviews on bio-catalysis, see: (h) Reed, M. T. *Angew. Chem. Int. Ed.* **2011**, *50*, 138-174. (i) Yu, H.-L.; Ou, L.; Xu, J.-H. *Curr. Org. Chem.* **2010**, *14*, 1424-1432. For a recent special issue on *Organocatalysis*, see: j) (Eds.: Jacobsen, E. N.; MacMillan, D. W. C.) in *Proc. Nat. Acad. Sci.* **2010**, *107*, 20648-20677. k) For a highlight on gold and organocatalysis combined see: Hashmi, A. S. K.; Hubbert, C. *Angew. Chem. Int. Ed.* **2010**, *49*, 1010-1012.

(2) Selected recent reviews: (a) Hummel, S.; Kirsch, S. F. *Beilstein J. Org. Chem.* **2011**, *7*, 847-859. (b) Garayalde, D.; Nevado, C. *Beilstein J. Org. Chem.* **2011**, *7*, 767-780. (c) Sengupta, S.; Shi, X. *ChemCatChem* **2010**, *2*, 609-619. (d) Shapiro, N. D.; Toste, F. D. *Synlett* **2010**, 675-691. (e) Wang, S.; Zhang, G.; Zhang, L. *Synlett* **2010**, 692-706. (f) Gorin, D. J.; Toste, F. D. *Nature* **2007**, *446*, 395-403. (g) Nolan, S. P. *Nature* **2007**, *445*, 496-497. (h) Hashmi, A. S. K. *Chem. Rev.* **2007**, *107*, 3180-3211. (i) Patil, N. T.; Yamamoto, Y. *Arkivoc* **2007**, *v*, 6-19. (j) Yamamoto, Y. *J. Org. Chem.* **2007**, *72*, 7817-7831; erratum *J. Org. Chem.* **2008**, *73*, 5210.

(3) For reviews on gold-catalyzed synthesis of heterocyclic motifs, see: (a) Rudolph, M.; Hashmi, A. S. K. *Chem. Commun.* **2011**, 47, 6536-6544. (b) Hashmi, A. S. K.; Buhrle, M. *Aldrichimica Acta* **2010**, *43*, 27-33. (c) Hashmi, A. S. K. *Pure Appl. Chem.* **2010**, *82*, 657-668. (d) Cossy, J. *Pure Appl. Chem.* **2010**, *82*, 1365-1373. (e) Das, A.; Abu Sohel, S. M..; Liu, R.-S. *Org. Biomol. Chem.* **2010**, *8*, 960–979. (f) Shen, C. *Tetrahedron* **2008**, *64*, 7847–7870. (g) Shen, C. *Tetrahedron* **2008**, *64*, 3885–3903. (h) Krause, N.; Belting, V.; Deutsch, C.; Erdsack, J.; Fan, H.-T.; Gockel, B.; Hoffmann-Roder, A.; Morita, N.; Volz, F. *Pure Appl. Chem.* **2008**, *80*, 1063–1069.

(4) Recent examples: (a) Davies, P. W.; Cremonesi, A.; Dumitrescu L. Intermolecular and Selective Synthesis of 2,4,5-Trisubstituted Oxazoles by a Gold-Catalyzed Formal [3+2] Cycloaddition *Angew. Chem. Int. Ed.* DOI : 10.1002/anie.201103563, Published Online: July, 26, 2011. URL (accessed July 27, 2011). (b) Melhado, A. D.; Amarante, G. W.; Wang, Z. J.; Luparia, M.; Toste, F. D. *J. Am. Chem. Soc.* **2011**, *133*, 3517-3527. (c) Melhado, A. D.; Luparia, M.; Toste, F. D. *J. Am. Chem. Soc.* **2007**, *129*, 12638-12639. (d) Asao, N.; Nogami, T.; Lee, S.; Yamamoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 10921-10925.

(5) Barluenga, J.; García-García, P.; de Sáa, D.; Fernández-Rodríguez, M. A.; Bernardo de la Rúa, R.; Ballesteros, A.; Aguilar, E.; Tomás, M. *Angew. Chem. Int. Ed.* **2007**, *46*, 2610-2612.

(6) García-García, P.; Fernández-Rodríguez, M. A.; Aguilar, E. *Angew. Chem. Int. Ed.* **2009**, *48*, 5534-5537.

(7) For a gold-catalyzed cyclization involving other 1,3-dien-5-yne systems, such as *o*-(alkynyl)styrenes, see: Martínez, A.; García-García, P.; Fernández-Rodríguez, M. A.; Rodríguez, F.; Sanz, R. *Angew. Chem. Int. Ed.* **2010**, *49*, 4633-4637, and references cited therein.

(8) Barluenga, J.; Fernández-Rodríguez, M. A.; García-García, P.; Aguilar, E. *J. Am. Chem. Soc.* **2008**, *130*, 2764-2765.

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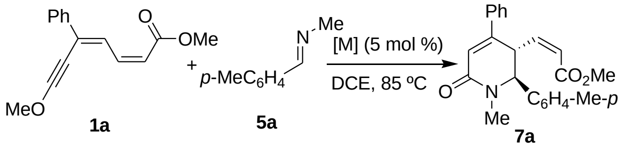
(10) Fisyuk, A. S.; Bundel, Y. *Chem. Heterocycl. Compd.* **1999**, *35,* 125-145.

(11) (a) Cardillo, G.; Fabbroni, S.; Gentilucci, L.; Perciaccante, R.; Piccinelli, F.; Tolomelli, A. *Tetrahedron*, **2004**, *60*, 5031-5040, and references cited therein. (b) Hanessian, S.; Seid, M.; Nilsson, I. *Tetrahedron Lett.,* **2002**, *43*, 1991-1994.

(12) See Supporting Information.

9 and 10) and a cationic Au(I) (generated in situ by mixing 5 mol % of $AuClPEt_3$ and 5 mol % of $AgSbF_6$, entry 5) complexes. After these results, an extensive screening of other reaction condition parameters (temperature, solvent, concentration, number of equivalents of imine, catalyst loading) was performed, either employing $AgSbF_6$ by itself or the system $AuClPEt_3/AgSbF_6$, as catalysts.[13] Thus, the best conditions found were $AuClPEt_3$ (5 mol %)/$AgSbF_6$ (5 mol %) [entry 5, *Method A*], or $AgSbF_6$ (5-10 mol %), [entry 10, *Method B*], in DCE at 85 ºC, which led only to moderate yields of adduct **7a**.

Table 1. Catalyst Screening for the Intermolecular HDDA Cycloaddition of **1a** with Aldimine **5a**.[12]

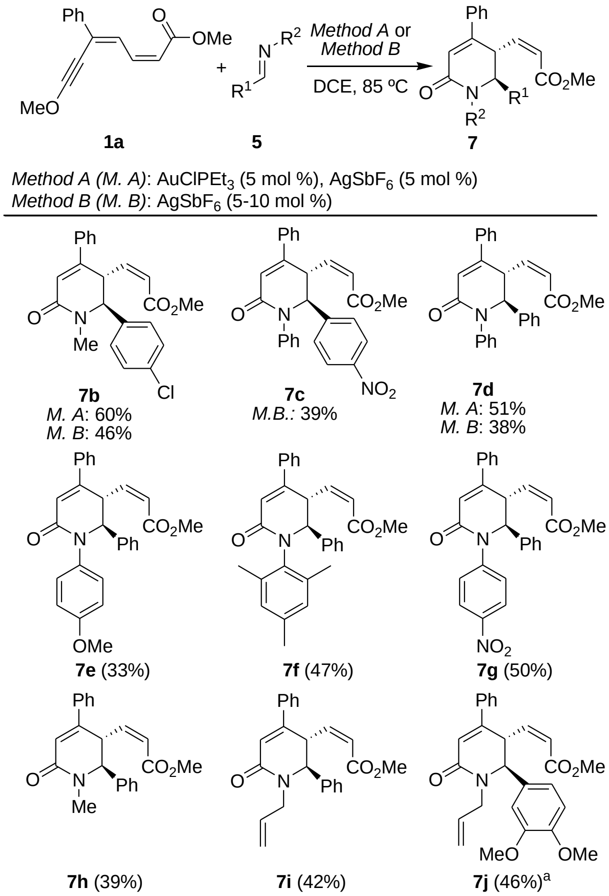


entry	[M]	**7a**[a]
1	$AuCl_3$	39
2	AuClP(*p*-CF_3-C_6H_4)$_3$/$AgSbF_6$	(14)
3	$AuClPPh_3/AgSbF_6$	(12)
4	AuClP(*p*-MeO-C_6H_4)$_3$/$AgSbF_6$	(14)
5	$AuClPEt_3/AgSbF_6$	43
6	$PtCl_4$	(15)
7	$ZnCl_2$	22
8	$Cu(OTf)_2$	35
9	$AgBF_4$	39
10	$AgSbF_6$	47

[a] Isolated yield based on the starting dienyne **1a**; in brackets, NMR estimated yield (**7a** not isolated) employing 1,3,5-trimethoxybenzene as internal standard.

Once *Method A* or *Method B* conditions were established as the best ones found for the desired transformation, a wide variety of aldimines **2** were tested to analyze the scope and limitations of this novel HDDA cycloaddition (Scheme 2). Usually, the reactions were completed overnight (12-14 h) under both conditions. Interestingly, except for compound **7a**, whenever both methods were employed to prepare the same adducts (**7b**,**d**), *Method B* provided lower yields than *Method A*; therefore, the latter one was chosen to perform most of the scope screening reactions. Indeed, the process works nicely for aldimines with phenyl (**7d-i**), or either electron-withdrawing (**7b**,**c**) or electron-donating (**7j**) aryl substituents. Apparently, *ortho*-substitution does not lead to a decrease in the reaction yield (**7f**). The substitution pattern at the nitrogen atom is of a wider scope as it tolerates methyl, phenyl and both electron-withdrawing and electron-donating substituted phenyl rings. Of particular relevance are the cases of the *p*-methoxyphenyl (**7e**) and allyl (**7i**,**j**) groups, which are prone to undergo removal leading to NH-dihydropyridones. In all cases, *complete diastereo- and regioselectivity were observed in the cycloaddition*.

Scheme 2. Scope of the intermolecular HDDA cycloaddition.



All yields are isolated yields based on the starting dienyne **1**. Numbers in bracketts correspond to reactions performed under Method A conditions. [a)] Reaction carried out with $AuClPEt_3$ (10 mol %), $AgSbF_6$ (10 mo l%).

The identity of compounds **7** was ascertained by NMR spectroscopic experiments (including COSY, HSQC, HMBC and NOESY).[12] Even though the relative configuration of the new stereogenic centers could be assigned trans on the basis of the coupling constant values,[14] and a di-axial conformation could be deduced from NOESY experiments, an X-Ray structure elucidation of **7c** was also obtained, which allowed confirmation the proposed trans stereochemistry.[12]

To analyze the substrate electronic requirements, the intermolecular HDDA reaction conditions were tested in simpler substrates. However, dihydropyridone formation was not observed either for (*E*)-1-phenyloct-1-en-3-yne **8**

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(13) For silver or gold catalyzed reactions see: Hashmi, A. S. K. In *Silver in Organic Chemistry*, Harmata, M., Ed.; John Wiley & Sons, Inc.: Hoboken, NJ, 2010; pp 357-379.

(14) (a) Cabrera, J.; Hellmuth, T.; Peters, R. *J. Org. Chem.*, **2010**, *75*, 4326-4329. (b) Bennett, D. M.; Okamoto, I.; Danheiser, R. L. *Org. Lett.*, **1999**, *1*, 641-644.

(a neutral enyne; Figure 1) nor (*Z*)-methyl nona-2-en-4-ynoate **9** (an electron-deficient enyne), while just traces were GC/MS-detected for (*E*)-4-ethoxy-1-phenylbut-1-en-3-yne **10** (electron-rich enyne). Therefore, as it happened for the reaction with nitriles, the electronic nature of the conjugated system is crucial for the intermolecular HDDA reaction to occur: a push-pull system is needed. On the other hand, that is not the only requisite; interestingly, methyl (*E*)-5-ethoxy-pent-1-en-3-ynoate **11** led only to GC/MS-traces of the desired adduct, thus indicating that remaining double bond of dienynes **1** may also play some role in the reaction.

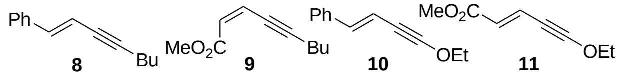


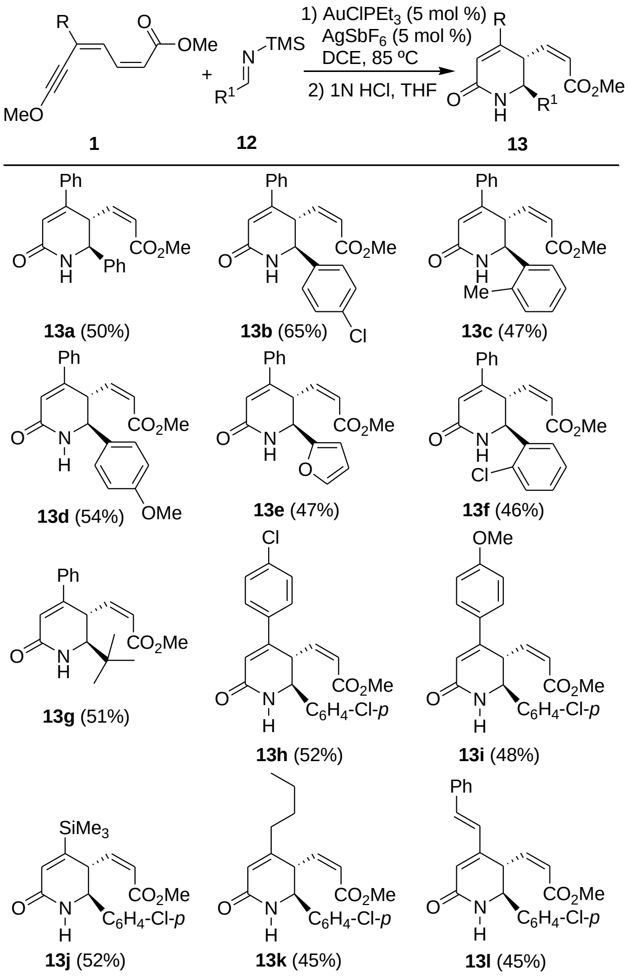
Figure 1. Other enyne systems tested under the reaction conditions

We envisioned that silyl aldimines **12** could be appropriate substrates to extend the reaction to the synthesis of *N*-unsubstituted dihydropyridones, which are in principle more appealing, interesting and versatile substrates. The reactions were carried out employing the previously developed *Method A* conditions; in this case, a further hydrolysis step was required[15] and led to *N*-unprotected *trans*-5,6-dihydropyridin-2-ones **13** in moderate yields (Scheme 3).

The scope of the reaction was explored regarding the substitution both at the dienyne and the silyl aldimine counterparts. Thus, several aryl groups with different electronic properties [phenyl (**13a**), bearing electron-donating groups (**13c**,**d**) or electron-withdrawing groups (**13b**,**f**)] and substitution patterns [*ortho* (**13c**,**f**), *para* (**13b**,**d**,**h-l**)], heteroaryl (**13e**), and *tert*-butyl (**13g**) substituents are tolerated at the silyl aldimine moiety while the R group at the dienyne displays a wide scope as it may be a phenyl (**13a-g**), an electron-withdrawing substituted aryl group (**13h**), an electron-donating substituted aryl (**13i**), a silyl (**13j**), an alkyl (**13k**) or an alkenyl (**13l**) substituent.

The formation of dihydropyridones **5** (or **13**) can be explained according to a mechanism similar to the one proposed for the reaction with nitriles.[8] The selective formation of the *anti* diastereoisomer can be understood assuming that the cyclization step should take place through preferred transition state **IB**, which is less hindered than **IA** (Figure 2).

Scheme 3. Scope of the intermolecular HDDA cycloaddition employing silyl aldimines.



All yields are isolated yields based on the starting dienyne **1**.

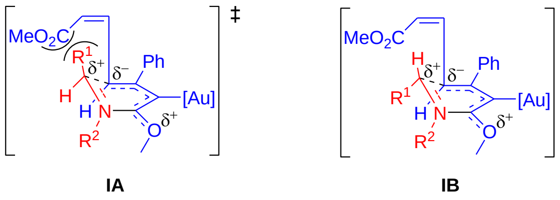


Figure 2. Proposed origin of the diastereoselectivity

In summary, we have reported a novel catalyzed intermolecular hetero-dehydro-Diels-Alder reaction that occurs between *push-pull* 1,3-dien-5-ynes **1** and aldimines or silylaldimines. The sequence is promoted both by gold(I) or silver(I) catalysts and leads to the

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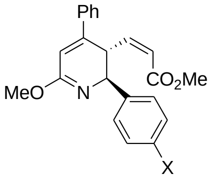
[15] Dihydropyridines **14a,b** were isolated in just 29% and 13% yield in preliminary reactions carried out between dienyne **1a** and *N*-trimethylsilyl benzaldimines **12a,b**. The low yield of **14**, probably due to product decomposition during chromatographic purification, prompted us to perform an *in situ* additional hydrolysis step.



14a (X = H), 29%
14b (X = Cl), 13%

diastereo- and regioselective formation of 5,6-dihydropyridin-2-ones. Labeling, designed NMR experiments and theoretical calculations directed to gain some insight into the reaction mechanism and work to expand this new method to other unsaturated nucleophiles are currently underway in our lab and will be reported in due course.

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Supporting Information Available. Tables with a more extensive list of catalyst and reaction conditions screening, a discussion regarding the preferred conformation of dihydropyridones **7** (based on NOE experiments performed on compound **7b**), experimental procedures and characterization data of all new compounds, compund **7c** cif. This material is available free of charge via the Internet at http://pubs.acs.org.http://pubs.acs.org