

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

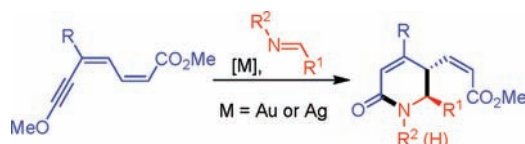
Jesús Manuel Fernández-García,[‡] Manuel Á. Fernández-Rodríguez,[§] and Enrique Aguilar^{*†}

Instituto Universitario de Química Organometálica “Enrique Moles”, Universidad de Oviedo, C/Julián Clavería, 8, 33006 Oviedo, Asturias, Spain, and 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 heterodehydro-Diels–Alder reaction between push–pull 1,3-dien-5-yne 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 organocatalysis, one of the three feet of the vital catalytic tripod in the current scenario of organic synthesis) has achieved considerable improvement over the past decade.¹ 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

[†]Dedicated to Professor Rafael Suau, in memoriam.

[‡]Universidad de Oviedo.

[§]Universidad de Burgos.

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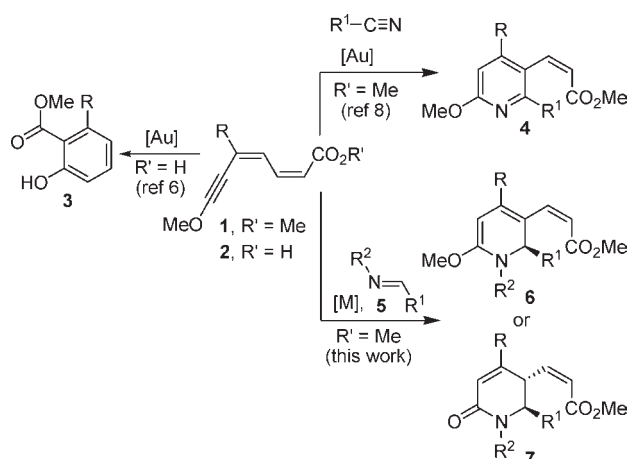
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compounds.³ However, relatively few gold-catalyzed intermolecular cycloadditions have been reported.⁴

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, nonactivated 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

Scheme 1. Metal-Catalyzed Transformations Involving Push–Pull Dienynes **1** and **2**



Continuing with our interest to explore the reactivity of dienynes **1**, we have considered testing their behavior against aldimines **5**, which through a HDDA reaction should lead to 1,2-dihydropyridines **6** or, more probably, to 5,6-dihydropyridinones **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 free radical scavengers. Moreover, properly substituted 5,6-dihydropyridin-2-ones have been regarded as useful intermediates for the preparation of spatially defined nonpeptidic scaffolds, constrained counterparts of natural amino acids.¹¹

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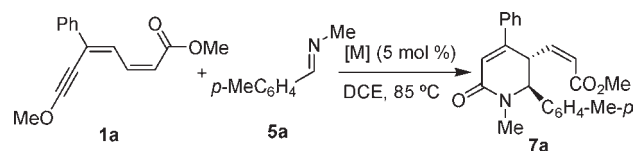
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Table 1. Catalyst Screening for the Intermolecular HDDA Cycloaddition of **1a** with Aldimine **5a**¹²



entry	[M]	7a ^a
1	AuCl ₃	39
2	AuCIP(<i>p</i> -CF ₃ -C ₆ H ₄) ₃ /AgSbF ₆	(14)
3	AuCIPPh ₃ /AgSbF ₆	(12)
4	AuCIP(<i>p</i> -MeO-C ₆ H ₄) ₃ /AgSbF ₆	(14)
5	AuCIPeT 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 diene **1a**; in brackets, NMR estimated yield (**7a** not isolated) employing 1,3,5-trimethoxybenzene as internal standard.

Taking into account our previous results in the reaction with nitriles,⁸ the initial essays were carried out with diene **1a** (*c* = 0.1 M) and aldimine **5a** (5 equiv). 1,2-Dichloroethane (DCE) was used as the solvent, the temperature was settled at 85 °C, 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 workup, 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), independent of the electronic nature of the phosphine ligand. Moderate yields were reached for Cu(II) (entry 8), Au(III) (entry 1), Ag (entries 9 and 10), and a cationic Au(I) (generated in situ by mixing 5 mol % of AuCIPeT₃ and 5 mol % of AgSbF₆, 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, employing either AgSbF₆ by itself or the AuCIPeT₃/AgSbF₆ system as catalysts.¹³ Thus, the best conditions found were AuCIPeT₃ (5 mol %)/AgSbF₆ (5 mol %) [entry 5, Method A] or AgSbF₆ (5–10 mol %) [entry 10, Method B] in DCE at 85 °C, which led only to moderate yields of adduct **7a**.

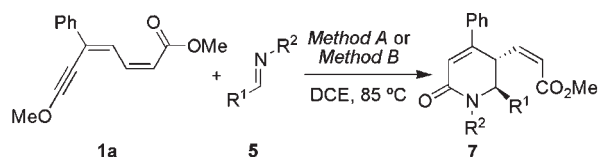
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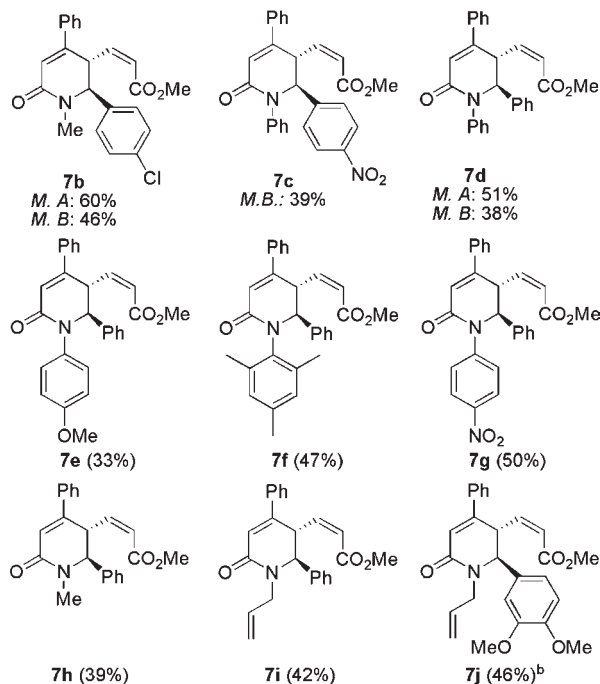
(13) For silver- or gold-catalyzed reactions see: Hashmi, A. S. K. In *Silver in Organic Chemistry*; Harmata, M., Ed.; John Wiley & Sons, Inc.: Hoboken, NJ, 2010; pp 357–379.

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*-methoxy phenyl (**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^a



Method A (M. A): AuClPEt₃ (5 mol %), AgSbF₆ (5 mol %)
 Method B (M. B): AgSbF₆ (5–10 mol %)



^a All yields are isolated yields based on the starting dienyne **1**. Numbers in brackets correspond to reactions performed under Method A conditions.
^b Reaction carried out with AuClPEt₃ (10 mol %), AgSbF₆ (10 mol %).

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 diaxial 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 for either (*E*)-1-phenyloct-1-en-3-yne **8** (a neutral enyne; Figure 1) or (*Z*)-methyl nona-2-en-4-ynoate **9** (an electron-deficient enyne), while just traces were detected by GC–MS 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. However, 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 dienyne **1** may also play some role in the reaction.

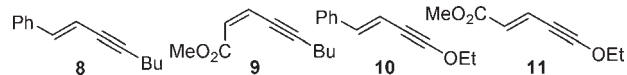


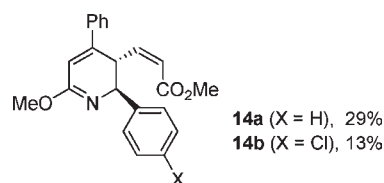
Figure 1. Other enyne systems tested under the reaction conditions.

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 required¹⁵ and led to *N*-unprotected *trans*-5,6-dihydropyridin-2-ones **13** in moderate yields (Scheme 3).

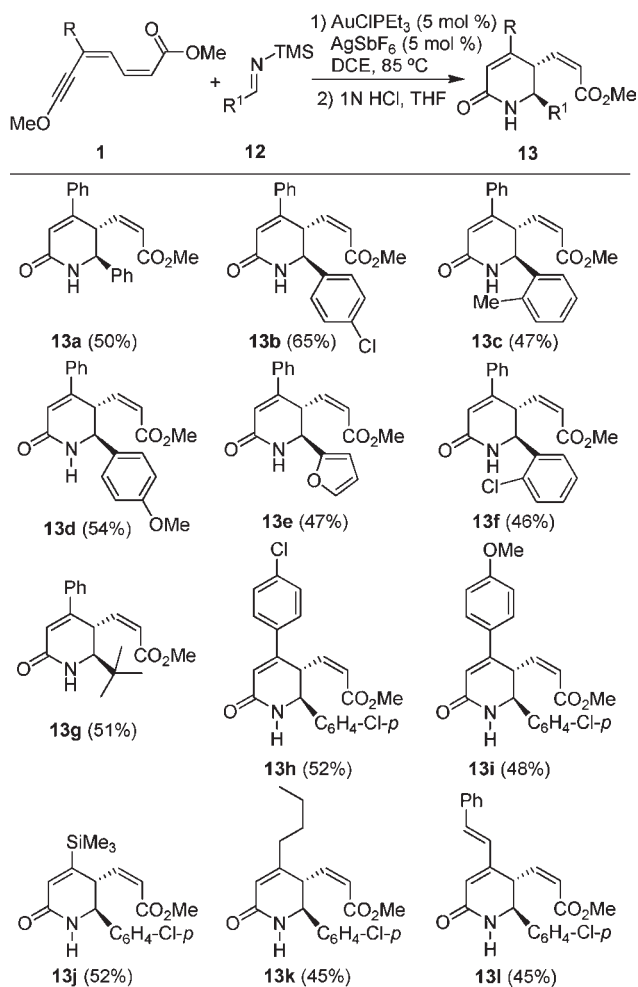
The scope of the reaction was explored regarding the substitution both at the dienyne and the silyl aldimine counterparts. Thus, several aryl groups with different electronic properties [phenyl (**13a**), bearing electron-donating

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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 benzaldehydes **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.



Scheme 3. Scope of the Intermolecular HDDA Cycloaddition Employing Silyl Aldimines^a



^a All yields are isolated yields based on the starting diyne **1**.

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 diyne 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).

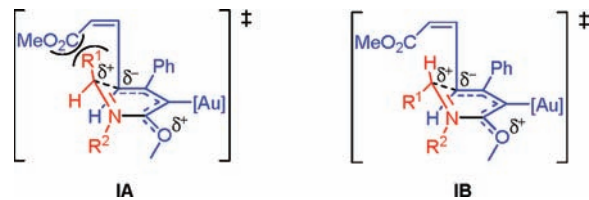


Figure 2. Proposed origin of the diastereoselectivity.

In summary, we have reported a novel catalyzed intermolecular heterodehydro-Diels–Alder reaction that occurs between push–pull 1,3-dien-5-yne **1** and aldimines or silylaldimines. 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. 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 laboratory 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, compound **7c** in CIF format. This material is available free of charge via the Internet at <http://pubs.acs.org>.