

Communication

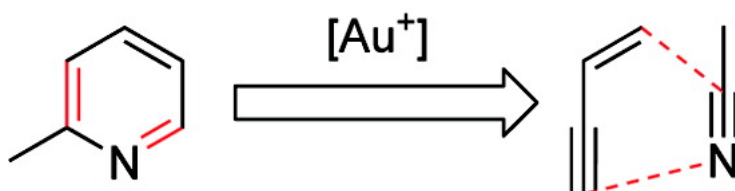
**Gold-Catalyzed Intermolecular Hetero-Dehydro-Diels–Alder
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Intermolecular HDDA Cycloaddition



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Gold-Catalyzed Intermolecular Hetero-Dehydro-Diels–Alder Cycloaddition of Captodative Dienynes with Nitriles: A New Reaction and Regioselective Direct Access to Pyridines

José Barluenga,^{*,†} Manuel Ángel Fernández-Rodríguez,[‡] Patricia García-García,[†] and Enrique Aguilar^{*,†}

Instituto Universitario de Química Organometálica “Enrique Moles”, Unidad Asociada al CSIC, Universidad de Oviedo, Julián Clavería 8, 33006-Oviedo, Spain and Instituto de Investigaciones Químicas y Ambientales de Barcelona (IIQAB)-CSIC, Jordi Girona 18-26, 08034-Barcelona, Spain

Received December 20, 2007; E-mail: barluenga@uniovi.es, EAH@uniovi.es

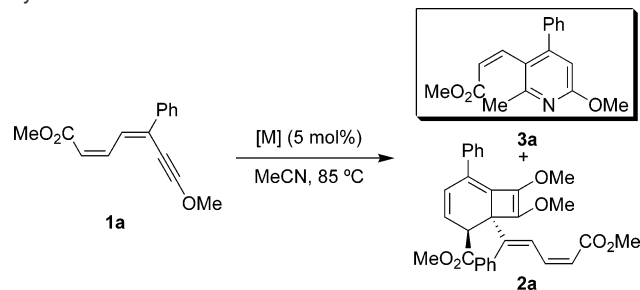
The Diels–Alder reaction is undoubtedly the most powerful synthetic tool for the formation of six-membered cyclic structures. However, the well-documented and closely related dehydro-Diels–Alder reaction (DDAR) has been fairly less developed. That is probably due to geometric constrictions, derived from the lineal disposition imposed by the *sp*-hybridization of the triple bond carbons. The state of the art for DDAR is mainly confined to intramolecular versions,¹ while intermolecular approaches are limited to the employment of highly reactive intermediates such as benzyne² or to photochemical activation.³

On the other hand, a resplendent age of metal catalysis, particularly gold,⁴ has bloomed in the last years. The notorious ability of gold derivatives to activate triple bonds for the attack of different nucleophiles has resulted in the development of an impressive array of organic transformations, mainly intramolecular cyclizations.⁵ Remarkably, relatively few gold-catalyzed intermolecular cycloadditions have been reported.⁶

We have recently described an efficient and simple procedure for the synthesis of captodative dienynes **1** (from commercially available 2-methoxyfurane and Fischer alkynyl carbene complexes),⁷ which could be appropriate substrates for metal-catalyzed transformations; in fact, we have envisioned that the attack of an unsaturated nucleophile to the metal-complexed triple bond could be followed by cyclization. In this communication we present the results using nitriles⁸ as nucleophiles: tetrasubstituted pyridines⁹ are regioselectively formed by a novel approach, this one being the first case of a catalyzed intermolecular *hetero-dehydro-Diels–Alder* reaction (HDDAR).¹⁰

The initial assays were carried out with dienyne **1a** in neat acetonitrile. Thus, spontaneous dimerization of **1a** to form **2a** was observed on standing or when warmed in the absence of catalyst (Table 1, entry 1). Several catalytic metals (Pt, Cu, Ag, or Pd) also produced dimerization or the formation of complex reaction mixtures. However, the [4 + 2]-cycloaddition reaction could be achieved with different gold catalysts; for instance, AuCl₃ and AuCl gave 61% and 46% isolated yields of adduct **3a** (entries 2 and 3). The reactivity of Au(I) cationic catalysts was modulated by employing several ligands such as phosphines (entries 4–8) or *N*-heterocyclic carbenes (entry 9), which display a broad range of electron-donating abilities; among them, the system AuCIPeT₃/AgSbF₆ exhibited the best result (entry 5). Interestingly, the reaction yield was further improved by the employment of 1,2-dichloroethane (DCE) as solvent, and the amount of acetonitrile could be reduced to 20 equiv (entry 10).¹¹

Table 1. Catalyst Screening for the Intermolecular HDDA Cycloaddition of **1a**



entry	[M]	2a ^a	3a ^a
1	none	33	
2	AuCl ₃		61
3	AuCl		46
4	AuCIPPh ₃ /AgSbF ₆		(63), 60
5	AuCIPeT ₃ /AgSbF ₆		(69), 67
6	AuCIP(<i>p</i> -MeO-C ₆ H ₄) ₃ /AgSbF ₆		(34)
7	AuCIP(<i>p</i> -CF ₃ -C ₆ H ₄) ₃ /AgSbF ₆		(23)
8	AuCIP(<i>o</i> -Me-C ₆ H ₄) ₃ /AgSbF ₆		(52)
9	AuCl(IPr) ^b /AgSbF ₆		(51)
10 ^c	AuCIPeT ₃ /AgSbF ₆		(72), 70

^a Isolated yield based on the starting dienyne **1a**; in brackets, yield estimated by ¹H NMR (400 Hz) employing ^tBuOAc as internal standard. ^bIPr: 1,3-bis(diisopropylphenyl)imidazol-2-ylidene. ^cReaction carried out with acetonitrile (20 equiv) and **1a** in DCE (0.1 M).

Once the optimum conditions for the desired transformation were established, we turned to analyze its scope and limitations. A wide variety of dienynes **1** and a set of commercially available nitriles were tested. Thus, substitution at the 4-position of the pyridine ring includes phenyl groups (Table 2, entries 1–7), aromatic rings with electron-withdrawing (entry 8) or electron-donating groups (entry 9), and primary and tertiary alkyl (entries 10, 11), and alkenyl (entries 12, 13) groups. On the other hand, primary, secondary, and tertiary alkyl (entries 1–3), aromatic (entry 4), heteroaromatic (entries 5–6), and olefinic (entry 7) nitriles, besides acetonitrile (entries 8–13), reacted with 1,3-dien-5-ynes **1**. In all cases, the reaction proceeded satisfactorily yielding the expected pyridines **3**. Only one regioisomer was detected as established by NMR experiments (COSY, HSQC, HMBC, NOESY).

In order to analyze the substrate electronic requirements, the intermolecular HDDAR conditions were tested in simpler substrates: (a) (*E*)-1-phenyloct-1-en-3-yne **4** (a neutral enyne) did not evolve under the optimized reaction conditions; (b) (*Z*)-methyl nona-2-en-4-ynoate **5** (an electron-deficient enyne) just underwent partial double bond isomerization, while (c) (*E*)-1-ethoxy-oct-3-en-1-yne

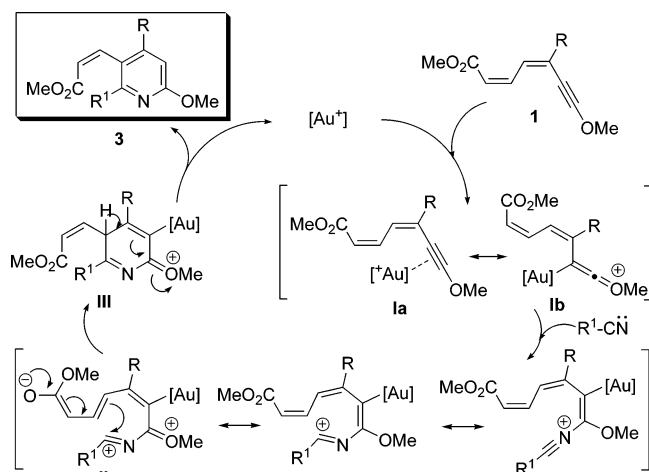
[†] Instituto Universitario de Química Organometálica “Enrique Moles”.

[‡] Instituto de Investigaciones Químicas y Ambientales de Barcelona.

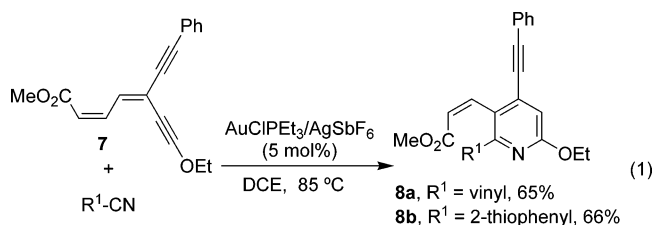
Table 2. Scope of the Intermolecular HDDA Cycloaddition

Entry	1	R	R ¹	3	Yield (%) ^a
1	1a	Ph	Pr	3b	64
2	1a	Ph	^t Pr	3c	60
3	1a	Ph	^t Bu	3d	55
4	1a	Ph	Ph	3e	67
5	1a	Ph	2-furyl	3f	69
6	1a	Ph	2-thiophenyl	3g	73
7	1a	Ph	vinyl	3h	75
8	1b	<i>p</i> -Cl-C ₆ H ₄	Me	3i	62
9	1c	<i>p</i> -MeO-C ₆ H ₄	Me	3j	66
10	1d	Bu	Me	3k	71
11	1e	^t Bu	Me	3l	61
12	1f	1-cyclohexenyl	Me	3m	75
13	1g	Ph	Me	3n	64

^a Isolated yield based on the starting diyne 1.

Scheme 1

6 (electron-rich enyne) did polymerize with all the tested catalysts, even at low temperature ($-20\text{ }^{\circ}\text{C}$). Apparently, the electronic nature of the conjugated system is crucial for the intermolecular HDDAR to occur: a push–pull (captodative) system is required. This assumption is supported by the fact that, for diyne **7**, which presents two triple bonds of different electronic nature, only the electron-rich one partakes in the HDDAR (eq 1).



A mechanism that would explain the formation of pyridines **3** is depicted in Scheme 1. An initial coordination of the triple bond to the gold catalyst $[\text{Au}^+]$ would take place to form intermediate **Ia**, which presents a resonance structure **Ib**, due to the electron-donating group linked to the triple bond. The push–pull substitution on the

dienyne would therefore facilitate the regioselective nucleophile attack of the nitrile, leading to the formation of species **IIa**. Both steps: triple bond activation and subsequent nucleophile attack are well documented for gold-mediated transformations.⁵ A cyclization may occur through resonance structure **IIb** or, alternatively, by intramolecular nucleophile attack through structure **IIc**. This last option would involve the electron-withdrawing ester group in the reaction mechanism and would explain why the reaction with **6** evolves by other routes. Consequently, dihydropyridine **III** would be formed and a final metal decoordination would render the reaction products **3** and allow the incorporation of the gold catalyst into a new cycle.

In summary, we present here the first example of a catalyzed intermolecular hetero-dehydro-Diels–Alder reaction which occurs between captodative 1,3-dien-5-yne and nonactivated nitriles. The sequence is promoted by both gold(I) and gold(III) catalysts and leads to the regioselective formation of tetrasubstituted pyridines. Labeling and designed NMR experiments directed to prove the proposed mechanism and work to expand this new methodology to other unsaturated nucleophiles are currently underway in our labs and will be reported in due course.

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Supporting Information Available: Experimental procedures and characterization data for the new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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- Regarding the catalyst loading, a 5 mol% provided the highest yield in a reasonable reaction time. Other tested solvents (THF, toluene, 1,2-dimethoxyethane), lower reaction temperatures, or less equiv of nitrile led to longer reaction times and/or poor yields.

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