

Chemodivergence in Alkene/Allene Cycloetherification of Enallenols: Iron versus Noble Metal Catalysis

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Dedicated to Prof. Dr. Carmen Pardo on the occasion of her 65th birthday and retirement

A resplendent age of metal catalysis has bloomed in the last years. Particularly, gold and platinum complexes are excellent catalysts for the formation of C–C and C–heteroatom bonds.^[1] Recently, iron salts have emerged as powerful alternatives in view of their inexpensiveness and environmental friendliness.^[2] On the other hand, allenes are a class of compounds with two cumulative carbon-carbon double bonds, which are versatile synthetic intermediates in organic synthesis.^[3] A process which involves a selective chemical reaction, even if the structure of the substrate suggests numerous possibilities for reactivity, represents an attractive strategy. These substrates must have diverse reactive sites, at which different transformations can take place. In this context, carbon–heteroatom cyclization is of major interest. Although many efforts have been made in these fields, to the best of our knowledge, the chemodivergent metal-catalyzed heterocyclization of alcohols bearing both an allene and an alkene center has not yet been reported.^[4] The selective preparation of different oxacycles from the same enallenol requires two appropriate catalytic systems that are capable of chemodifferentiating between various alkene functions and developing a dissimilar role for each partner. Otherwise, a mixture of at least two different products is possible. As part of a program aimed at expanding the use of metal catalysis in heterocyclic and allene chemistry,^[5] we focused on finding a solution to the challenging problem of metal-cata-

lyzed chemodistinguishing (alkene versus allene) oxycyclization of enallenols. The results of our investigation using iron, platinum, and gold salts form the subject of this paper.

The structures of enallenols that we synthesized and used for chemodifferentiation are shown in Figure 1. Racemic enallenols **1a–d** were readily prepared beginning from the appropriate 4-oxoazetidine-2-carbaldehyde via regiocontrolled indium-mediated Barbier-type carbonyl–allenylation reaction in aqueous media using our previously described methodology.^[6] Optically active non- β -lactam precursors *syn-1e* and *anti-1e* were prepared from (*R*)-2,3-*O*-isopropylidene-glyceraldehyde, via metal-mediated sequential prenylation and allenylation, followed by protecting groups manipulation (Scheme S1, see Supporting Information).

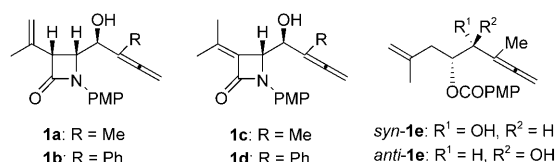


Figure 1. Structures of enallenols **1a–e**. PMP = 4-MeOC₆H₄.

Initially, we planned to study the cyclization of olefinic α -allenol **1a** under different metal catalysis. In a first series of runs, the cyclization of enallenol **1a** was catalyzed by precious metal salts (AgNO₃, [PtCl₂(CH₂=CH₂)₂], and AuCl₃) to afford the allene cycloisomerization adduct **2a** as the sole isomer (Table 1, entries 1–3).^[7] Further studies were designed to test the effects of different metal catalysis in the chemoselectivity of the hydroalkoxylation reaction. The possibilities of Lewis-acid catalyzed cyclization of unsaturated alcohol **1a** were first studied in the presence of different metallic chlorides.^[8] The reactivities of BiCl₃, InCl₃, and HfCl₄, were examined under catalytic amounts (20 mol %) in refluxing dichloromethane. However, complete conversion of enallenol **1a** was not detected by TLC and ¹H NMR

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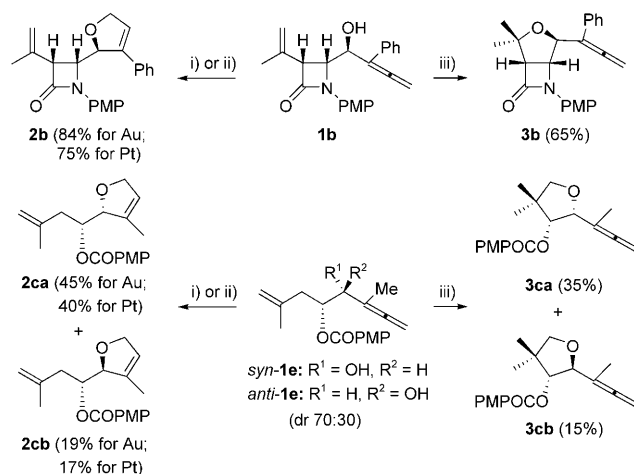
Table 1. Chemodivergent cycloetherification reaction of enallenol **1a** under modified metal-catalyzed or metal-promoted conditions.^[a]

Entry	Catalyst (mol %)	Conditions ^[a]	(2a / 3a) Ratio	Yield [%] ^[b]
1	AuCl ₃ (5)	A	100:0	65
2	AgNO ₃ (100)	B	100:0	55
3	[PtCl ₂ (CH ₂ =CH ₂) ₂] (5)	C	100:0	63
4	BiCl ₃ (150)	D	0:100	60
5	InCl ₃ (150)	D	0:100	60
6	HfCl ₄ (150)	D	0:100	70
7	FeCl ₃ (10)	E	0:100	83
8	HCl (10)	F	0:100	30

[a] Reaction conditions. A: 5 mol % AuCl₃, CH₂Cl₂, RT, 1 h; B: 1 equiv AgNO₃, acetone/H₂O 4:1, Δ, 0.5 h; C: 5 mol % [PtCl₂(CH₂=CH₂)₂], 10 mol % TDMPP, CH₂Cl₂, RT, 6 h; D: 1.5 equiv MCl₃, CH₂Cl₂, sealed tube, 70 °C, BiCl₃: 52 h, InCl₃: 56 h, HfCl₄: 48 h; E: 10 mol % FeCl₃, DCE, sealed tube, 80 °C, 24 h; F: 10 mol % HCl, DCE, sealed tube, 80 °C, 24 h. [b] Yield of pure, isolated product with correct analytical and spectral data. PMP = 4-MeOC₆H₄, TDMPP = tris(2,6-dimethoxyphenyl)phosphine. DCE = 1,2-Dichloroethane.

analysis of the crude reaction mixtures. Complete conversion was observed by heating a solution of enallenol **1a** in dichloromethane at 70 °C in a sealed tube using 1.5 equivalents of the metallic chloride (Table 1, entries 4–6). Since iron-catalyzed reactions have captured much recent attention, we decided to test the catalytic efficiency of FeCl₃. To our delight, this Fe^{III} salt was able to chemospecifically catalyze the cyclization in favour of the alkene component to exclusively afford the β-lactam-tetrahydrofuran hybrid **3a** in 83 % isolated yield (Table 1, entry 7).^[9] The lower limit of the iron-catalyst loading was 10 mol %. It deserves to be mentioned that the allene moiety is not altered under the oxycyclization reaction conditions. Besides the total chemoselectivity, the reaction was regioselective and only the five-membered ring ether was formed, without the presence of the isomeric six-membered ring. A control experiment that would rule out the participation of HCl as the active catalyst was undertaken. A strong difference of reactivity using FeCl₃ and HCl as catalysts was observed (compare entries 7 and 8). When enallenol **1a** was treated with hydrochloric acid (entry 8) with the same catalyst ratio, a 30 % yield of **3a** was obtained; highlighting the efficiency of FeCl₃ in the catalytic process.

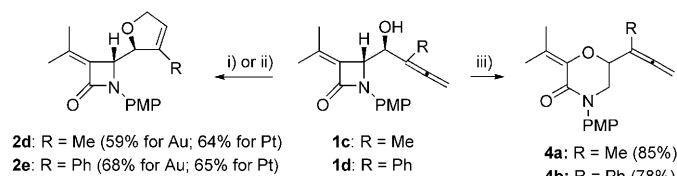
To further probe the scope of these chemodivergent transformations, we examined the olefinic phenylallenol **1b** and the non-β-lactam allenols **1c** (allenol **1c** was prepared as an inseparable *syn/anti* mixture 70:30). Under similar conditions, the corresponding dihydrofurans **2** and tetrahydrofurans **3** were chemospecifically obtained in good yields by precious metal and iron catalysis, respectively (Scheme 1). Fortunately, the diastereomeric adducts **2ca**, **2cb**, **3ca**, and **3cb**, from the selective cyclization of allenols *syn-1e* and *anti-1e*,



Scheme 1. Chemodivergent metal-catalyzed preparation of dihydrofurans **2** and tetrahydrofurans **3**. i) 5 mol % AuCl₃, CH₂Cl₂, RT, **2b**: 1 h; **2c**: 1.5 h. ii) 5 mol % [PtCl₂(CH₂=CH₂)₂], 10 mol % TDMPP, CH₂Cl₂, RT, **2b**: 6 h; **2c**: 12 h. iii) 10 mol % FeCl₃, DCE, sealed tube, 80 °C, **3b**: 24 h; **3c**: 20 h.

could be easily separated by gravity flow chromatography. Full chirality transfer has been accomplished from the starting enallenols *syn-1e* and *anti-1e*.

Next, we decided to test these selective cycloetherification reactions in substrates **1c** and **1d**. As expected, both the gold- and platinum-catalyzed oxycyclizations did totally control the reaction toward the corresponding dihydrofurans **2d** and **2e** (Scheme 2). Worth of note, in contrast to the iron-

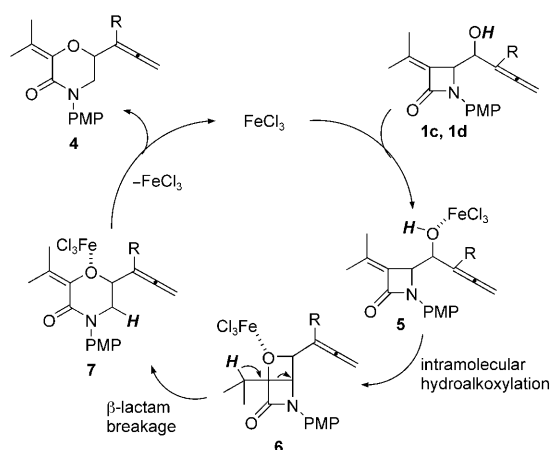


Scheme 2. Chemodivergent metal-catalyzed preparation of dihydrofurans **2** and morpholinones **4**. i) 5 mol % AuCl₃, CH₂Cl₂, RT, **2d**: 1.5 h; **2e**: 2 h. ii) 5 mol % [PtCl₂(CH₂=CH₂)₂], 10 mol % TDMPP, CH₂Cl₂, RT, **2d**: 4 h; **2e**: 5 h. iii) 10 mol % FeCl₃, DCE, sealed tube, 80 °C, **4a**: 1.5 h; **4b**: 2.5 h.

catalyzed reaction of δ-olefinic α-allenols **1a** and **1b** which lead to tetrahydrofurans, the reaction of γ-olefinic α-allenols **1c** and **1d** under identical conditions gave allenic morpholin-3-ones **4a** and **4b** as the sole products (Scheme 2),^[10] through an exclusive 4-*trig* cyclization by attack of the hydroxy group to the proximal alkene carbon followed by β-lactam ring opening.^[11] Additionally, we performed an experiment in which enallenol **1c** was treated with 10 mol % HCl and we observed the formation of morpholin-3-one **4a** in very low yield (10 %). This result indicates that FeCl₃ is the real catalytic species of our reactions.^[12]

Probably, AuCl₃ and [PtCl₂(CH₂=CH₂)₂] enhance the reactivity of the enallenol moiety through selective complexation to the 1,2-diene site,^[13] while FeCl₃ may activate the

enallenol group by coordination to the hydroxyl moiety. The formation of morpholin-3-ones **4** should proceed by a pathway that involve full, or partial, C–O bond formation at the β -lactam stage in the transition state. The hydroxyl-iron complex **5** is formed initially through coordination of the iron trichloride to the oxygen atom of enallenols **1**. Accordingly, the Lewis acid FeCl_3 considerably increases the Brønsted acidity of the hydroxyl protons of γ -olefinic α -allenols **1**. Next, chemo- and regioselective intramolecular protonation of the alkene moiety with concomitant 4-*exo* oxy-cyclization forms species **6**, which rapidly evolves to intermediates **7** through selective β -lactam ring cleavage. Finally, demetalation affords heterocycles **4** and regenerates the iron catalyst (Scheme 3). An alternative pathway involving coordination of FeCl_3 to the olefinic double bond cannot be ruled out at the moment. The morpholin-3-one formation must be driven by relief of the strain associated with the four-membered ring on forming a more stable six-membered ring.



Scheme 3. Mechanistic explanation for the Fe-catalyzed preparation of morpholinones **4**.

In conclusion, the chemodifferentiation between an alkene and an allene moiety using iron- or precious-metal catalysis, respectively, was presented, which showed unprecedented chemodivergence. Besides, an iron-catalyzed tandem cycloetherification/ β -lactam ring cleavage to afford allenic morpholin-3-ones was accomplished. Mechanistic consideration and reactivity of differently substituted enallenols are under investigation.

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Keywords: alkenes • allenes • chemoselectivity • heterocycles • iron

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