Metal-Catalyzed Regiodivergent Cyclization of $\gamma$-Allenols: Tetrahydrofurans versus Oxepanes

**β-Lactams: Serine Protease Inhibitors**

- Potent inhibitors of serine protease
- Poor selectivity
- Potent cytotoxicity against HT-1080 and MG-22A cell lines
- Monocyclic β-lactams: Phospholipase A2 inhibition, antifungal activity

Allene Activation Using Transition Metal Catalysis

Commonly employed Metals: 
Au$^{+1}$, Au$^{+3}$, Pd$^{+2}$, Ag$^{+1}$, Pt$^{+2}$

Ma, S., Chem. Rev. 2005, 105, 2829-2871
Allenes: Activation With Pd Catalysts

**Pd$^0$ catalysis**

\[
\text{HO} + \text{PhI} \xrightarrow{\text{Pd(PPh$_3$)$_4$ (5 mol \%)} \atop \text{K$_2$CO$_3$, DMF, 55 °C, 14 h}} \text{Ph} + \text{n-C$_4$H$_9$}
\]

71 %, (30 : 1)


**Pd$^{+2}$ catalysis**

\[
\begin{align*}
\text{HO} & + \text{Br} \xrightarrow{\text{PdCl$_2$ (5 mol \%) \atop \text{DMA, rt}}} \text{R$_3$} \\
\text{R$_1$} & + \text{OH} \xrightarrow{\text{PdCl$_2$ (5 mol \%) \atop \text{DMA, rt}}} \text{R$_2$}
\end{align*}
\]

(55-86 %)

Allenes: Activation with Au Catalysts

**Au$$^1$$ catalysis**

\[
\begin{align*}
&\text{catalyst (5 mol %)} & \text{PhMe, 25 °C, 5 min} \\
&\text{1 (P(t-Bu)2(o-biphenyl))Cl + AgOTs} & 96 \quad < 1 \\
&\text{[PtCl(CH2=CH2)]2/P(C6H5CF3)3} & 0 \quad 49
\end{align*}
\]


**Au$$^3$$ catalysis**

α-Allenols and Ag\(^{+1}\) Catalysis

![Chemical Structure]


![Chemical Structure]


![Chemical Structure]

Synthesis of Allenols

Scheme 1. Synthesis of enantiopure monocyclic γ-allenols 3a–d.
Reagents and conditions: a) In, 1-bromobut-2-yne, THF/NH₄Cl (aq. sat.), RT, 5 h. b) 1. TBSOTf, CH₂Cl₂, RT, 14 h; or MOMCl, Hünig’s base, CH₂Cl₂, reflux, 2 h; 2. NaOMe, MeOH, RT, 0°C, 3 h. Z = 4-MeOC₆H₄CO, Bn = benzyl, E = CO₂Me, MOM = MeOCH₂, TBS = tert-butyldimethylsilyl, Tf = trifluoromethanesulfonyl.

Alcaide, B. et al., Angew. Chem. Int. Ed. Early View
Hydroalkoxylation: Initial Attempts

Catalysts: AgNO$_3$ (54 %), poor diastereoselectivity

$\text{[PtCl}_2(\text{CH}_2=\text{CH}_2)\text{]}_2$, (12 %), only diastereomer

Scheme 2. Gold-catalyzed heterocyclization reaction of $\gamma$-allenol derivatives $3\text{a}$ and $3\text{b}$. Reaction time: 48 h.

Synthesis of quaternary center in excellent diastereoselectivity

Alcaide, B. et al., Angew. Chem. Int. Ed. Early View
Hydroalkoxylation: Catalytic Pd$^{+2}$

Scheme 3. Palladium-promoted preparation of seven-membered oxacycles 5a–d. Reagents and conditions: a) PdCl$_2$ (5 mol%), DMF, RT. Reaction times: 16, 24, 21, and 24 h for 5a–d, respectively. DMF = N,N-dimethylformamide.

Unprecedented Pd$^{+2}$-catalyzed cyclization of $\gamma$-allenols

Alcaide, B. et al., Angew. Chem. Int. Ed. Early View
Hydroalkoxylation: \( \text{Au}^{+3} / \text{Pd}^{+2} \) Catalysts

Scheme 4. Metal-catalyzed heterocyclization reactions of \( \gamma \)-allenol derivatives 3c and 3d. Reagents and conditions: a) 1. \( \text{PdCl}_2 \) (5 mol%), allyl bromide, DMF, RT, 5e: 5 h; 5f: 6 h; 2. MOMCl, Hünig’s base, \( \text{CH}_2\text{Cl}_2 \), reflux, 2 h. b) \( \text{AuCl}_3 \) (5 mol%), \( \text{CH}_2\text{Cl}_2 \), RT, 6a: 22 h; 6b: 16 h.

Reversal of the regioselectivity in \( \text{Au}^{+3} \)-catalyzed reaction

Alcaide, B. et al., Angew. Chem. Int. Ed. Early View
Cyclization of 7: Au$^{+3}$ Catalysis

Scheme 5. Au$^{III}$-catalyzed heterocyclization reaction of MOM-protected γ-allenol derivatives 7a and 7b. Reagents and conditions: a) 4-BrC$_6$H$_4$COCl or PMPCOCl, Et$_3$N, DMAP, CH$_2$Cl$_2$, reflux, 7a: 6 h; 7b: 8 h. b) AuCl$_3$ (5 mol%), CH$_2$Cl$_2$, RT, 8a: 72 h; 8b: 72 h. DMAP = 4-(dimethylamino)pyridine, PMP = 4-MeOC$_6$H$_4$.

Directing effect of the MOM group
Synthesis of fused oxepines using Au$^{+3}$ catalysis

Alcaide, B. et al., Angew. Chem. Int. Ed. Early View
Proposed Mechanism for Au$^{+3}$ Catalysis

Alcaide, B. et al., Angew. Chem. Int. Ed. Early View
Proposed Mechanism: Pd$^{2+}$ Catalysis

Alcaide, B. et al., *Angew. Chem. Int. Ed.* Early View
Conclusions

• Synthesis of fused bicyclic β-lactams bearing a quaternary center was accomplished in good yield and excellent diastereocontrol

• An efficient *metal-controlled* regiodivergent synthesis of tetrahydrofurans and tetrahydrooxepins has been developed

• The directing effect of the -MOM group afforded reversal of regiochemistry in Au$^{+3}$-mediated cyclization

• Elucidation of the reaction mechanism and its scope is under investigation