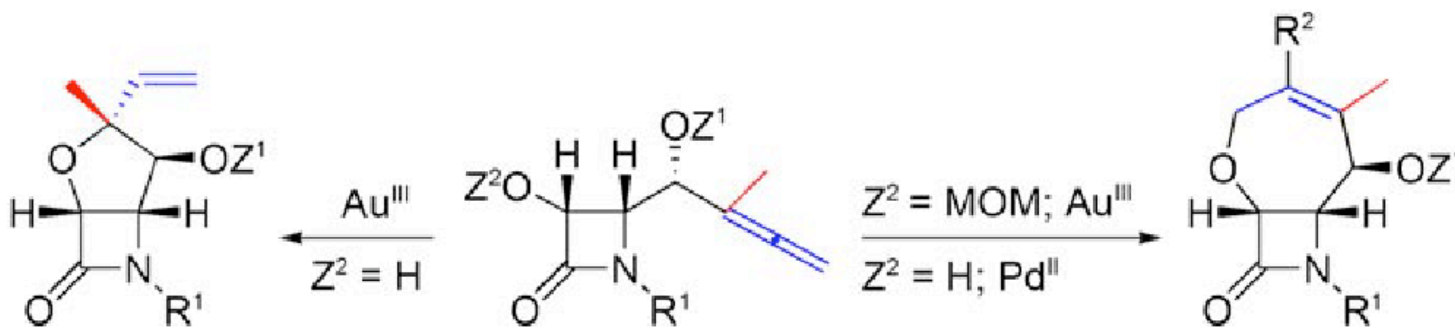
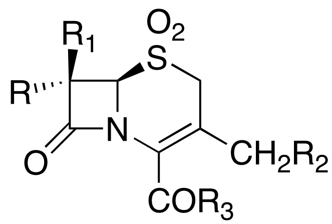
Metal-Catalyzed Regiodivergent Cyclization of γ-Allenols: Tetrahydrofurans versus Oxepanes

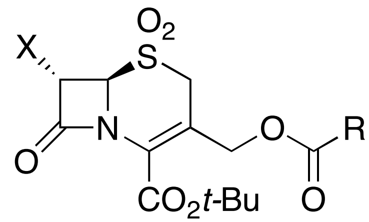
Alcaide*, B., Almendros, P. and Martinez del Campo, T. *Angew. Chem. Int. Ed.* Early view



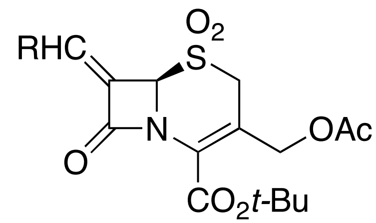
β-Lactams: Serine Protease Inhibitiors



Human Leucocyte Elastase Inhibitors



Porcine Pancreatic Elastase Inhibitors

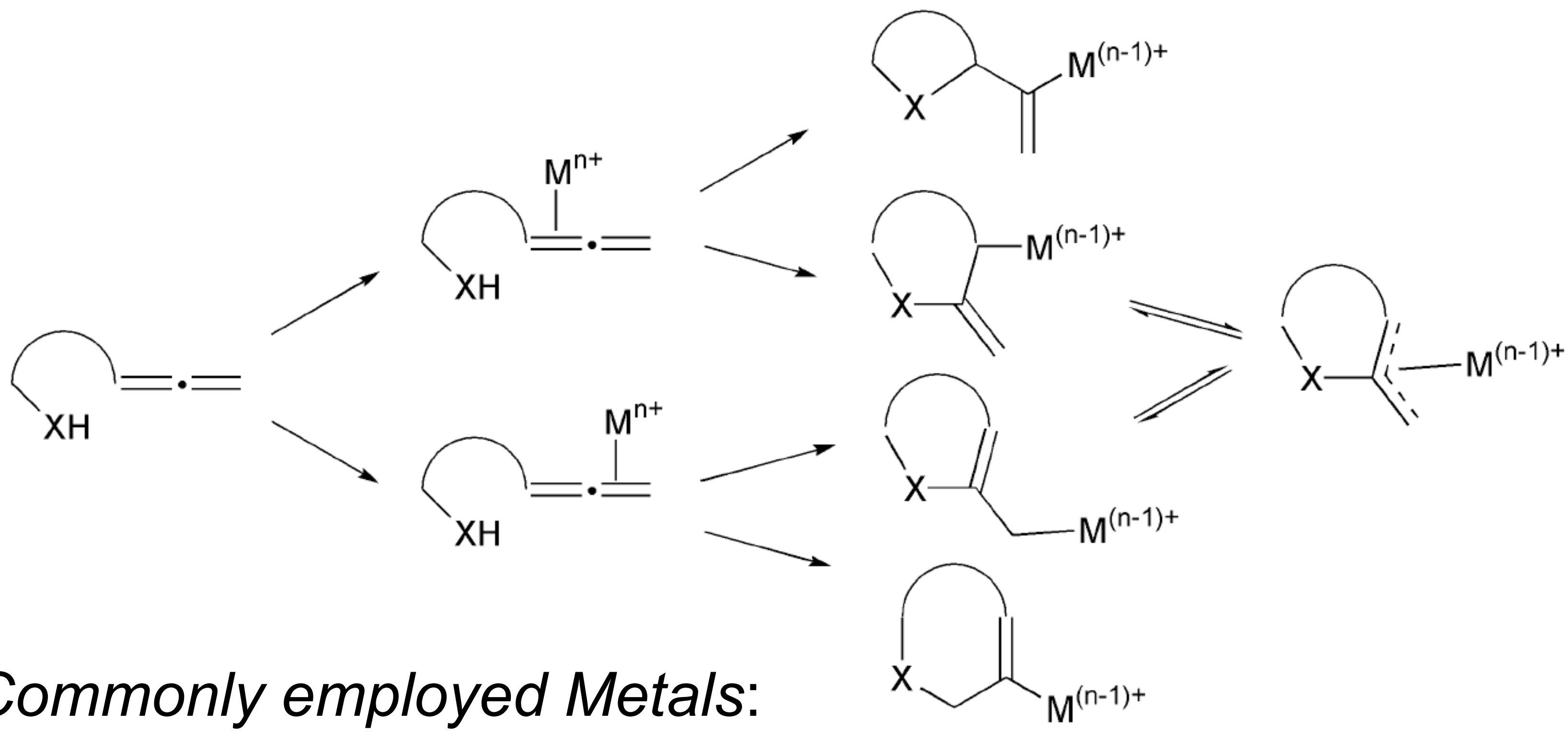


Cytotoxic

- Potent inhibitors of serine protease
- Poor selectivity
- Potent cytotoxicity against HT-1080 and MG-22A cell lines
- Monocyclic β latams: Phospholipase A_2 inhibition, antifungal activity

Veinburg, G. *et al.*, *Curr. Med. Chem.* **2003**, *10*, 1741-1751

Allene Activation Using Transition Metal Catalysis

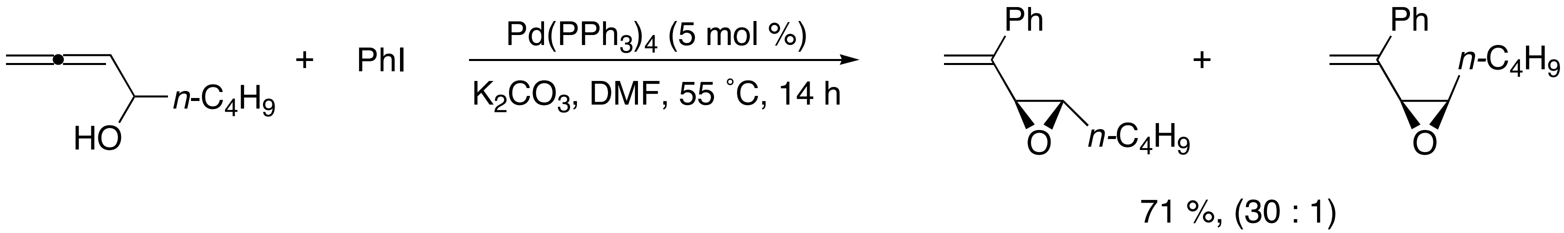


Commonly employed Metals:
Au^{+1}, Au^{+3}, Pd^{+2}, Ag^{+1}, Pt^{+2}

Bates, R. W. and Satcharoen, V., *Chem. Soc. Rev.* **2002**, *31*, 12-21
Ma, S., *Chem. Rev.* **2005**, *105*, 2829-2871

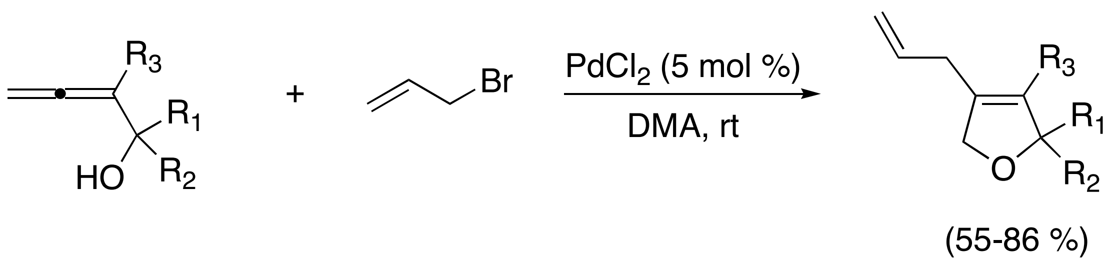
Allenes: Activation With Pd Catalysts

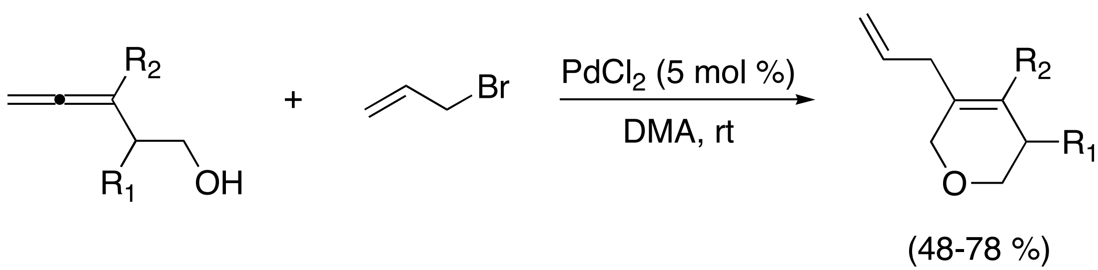
Pd⁰ catalysis



Ma, S.; Zhao, S., *J. Am. Chem. Soc.* **1999**, *121*, 7943

Pd^{+2} catalysis

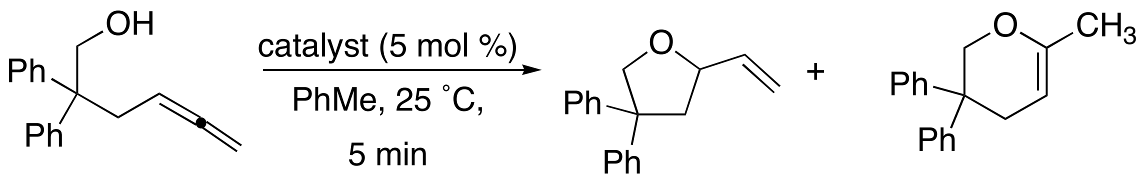




Ma, S.; Gao, W., *J. Org. Chem.* **1999**, *67*, 6104

Allenes: Activation with Au Catalysts

Au[+1] catalysis

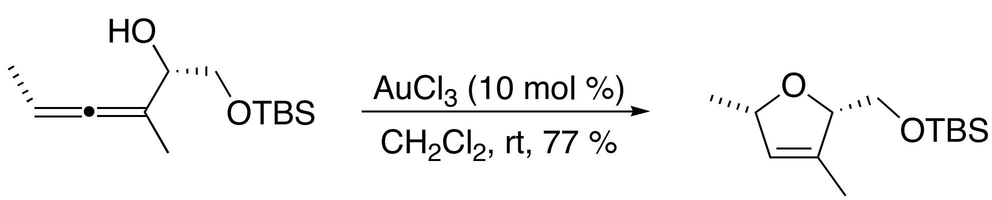


1 **2**

catalyst	**1** (%)	**2** (%)
Au[P(*t*-Bu)$_2$(*o*-biphenyl)]Cl + AgOTs	96	< 1
[PtCl(CH$_2$=CH$_2$)]$_2$/P(C$_6$H$_5$CF$_3$)$_3$	0	49

Widenhofer, R. A. *et al.*, *J. Am. Chem. Soc.* **2006**, *128*, 9066

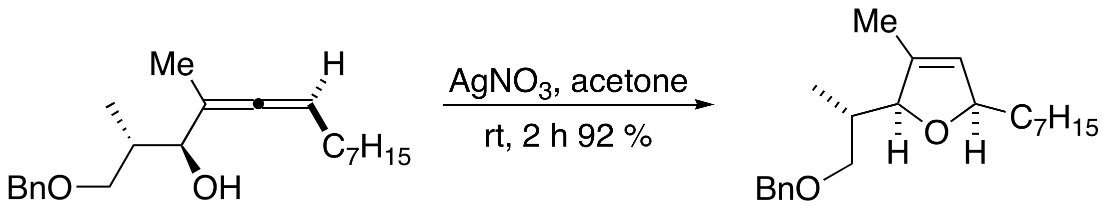
Au[+3] catalysis



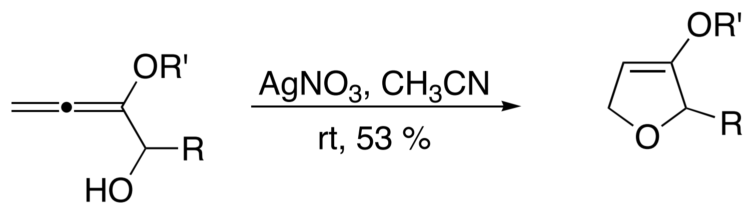
(*d.r.* = 94:6)

Hoffmann-Röder, A.; Krause, N., *Org. Lett.* **2001**, *3*, 2537

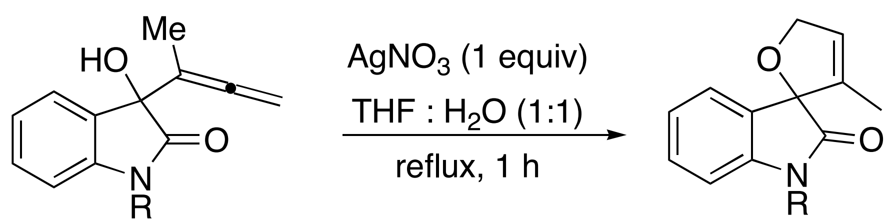
α-Allenols and Ag^{+1} Catalysis



Marshall, J. A. *et al.*, *J. Org. Chem.* **1995**, *60*, 5550



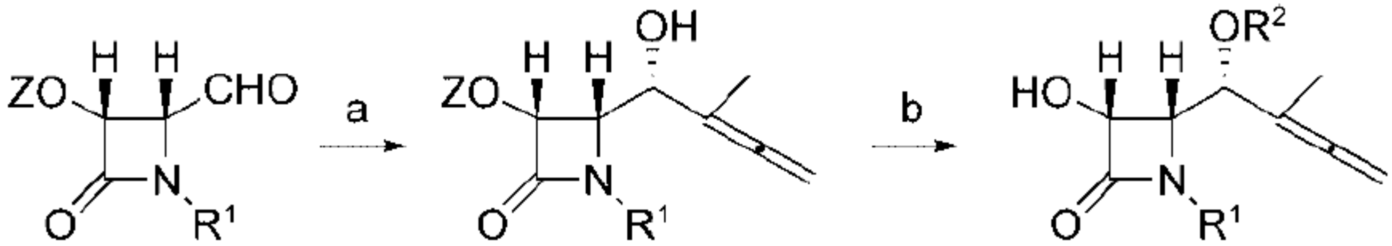
Flögel, O., Reißig, H.-U., Eur. *J. Org. Chem.* **2004**, 2797



R = Me (96 %)
R = H (100 %)

Alcaide, B. *et al.*, *J. Org. Chem.* **2006**, *71*, 2346

Synthesis of Allenols



(–)-**1a** R^1 = Bn	(+)-**2a** R^1 = Bn (68%)	(–)-**3a** R^1 = Bn, R^2 = TBS (70%)
(–)-**1b** R^1 = allyl	(–)-**2b** R^1 = allyl (61%)	(+)-**3b** R^1 = allyl, R^2 = TBS (71%)
(–)-**1a** R^1 = Bn	(+)-**2a** R^1 = Bn (68%)	(–)-**3c** R^1 = Bn, R^2 = MOM (79%)
(+)-**1c** R^1 = CH_2E	(+)-**2c** R^1 = CH_2E (65%)	(–)-**3d** R^1 = CH_2E, R^2 = MOM (61%)

Scheme 1. Synthesis of enantiopure monocyclic γ-allenols **3 a–d**. Reagents and conditions: a) In, 1-bromobut-2-yne, THF/NH_4Cl (aq. sat.), RT, 5 h. b) 1. TBSOTf, CH_2Cl_2, RT, 14 h; or MOMCl, Hünig's base, CH_2Cl_2, reflux, 2 h; 2. NaOMe, MeOH, RT, 0°C, 3 h. Z = 4-$MeOC_6H_4CO$, Bn = benzyl, E = CO_2Me, MOM = $MeOCH_2$, TBS = *tert*-butyldimethylsilyl, Tf = trifluoromethanesulfonyl.

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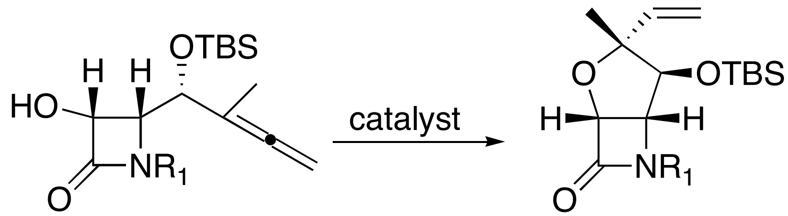
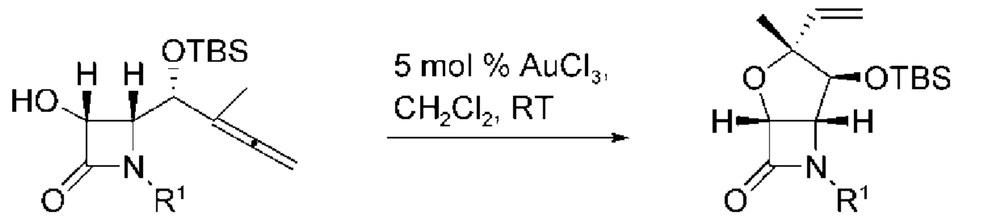
Hydroalkoxylation: Initial Attempts



Catalysts: $AgNO_3$ (54 %), poor diastereoselectivity

$[PtCl_2(CH_2{=}CH_2)]_2$, (12 %), only diastereomer



(–)-**3a** R^1 = Bn
(+)-**3b** R^1 = allyl

(+)-**4a** R^1 = Bn (57%)
(+)-**4b** R^1 = allyl (58%)

Scheme 2. Gold-catalyzed heterocyclization reaction of γ-allenol derivatives **3a** and **3b**. Reaction time: 48 h.

Synthesis of quaternary center in excellent diastereoselectivity

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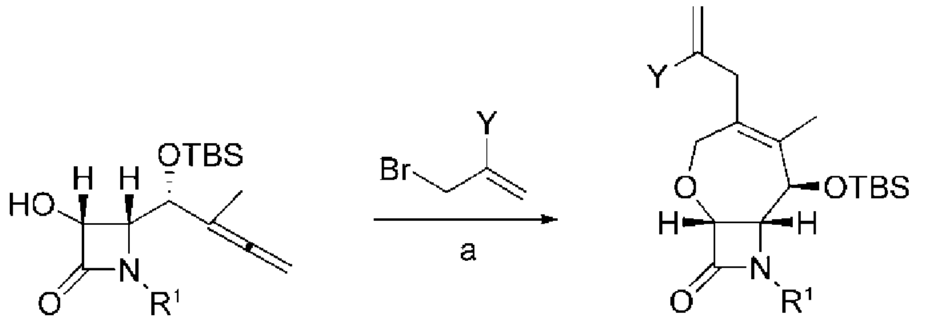
Hydroalkoxylation: Catalytic Pd^{+2}



(–)-**3a** R^1 = Bn	(–)-**5a** R^1 = Bn, Y = H (83%)
(–)-**3a** R^1 = Bn	(–)-**5b** R^1 = Bn, Y = Me (67%)
(–)-**3a** R^1 = Bn	(–)-**5c** R^1 = Bn, Y = Br (63%)
(+)-**3b** R^1 = allyl	(+)-**5d** R^1 = allyl, Y = H (94%)

Scheme 3. Palladium-promoted preparation of seven-membered oxa-cycles **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 γ-allenols

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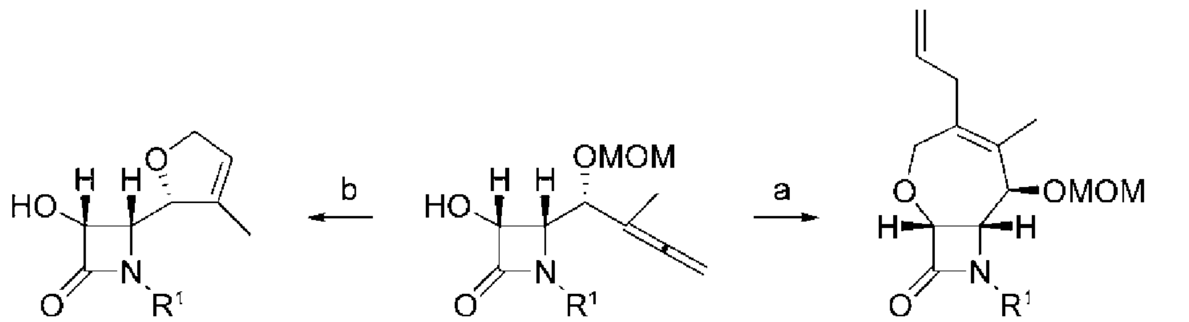
Hydroalkoxylation: Au^{+3}/ Pd^{+2} Catalysts



(+)-**6a** R^1 = Bn (37%) (–)-**3c** R^1 = Bn (–)-**5e** R^1 = Bn (52%)

(+)-**6b** R^1 = CH_2CO_2Me (49%) (–)-**3d** R^1 = CH_2CO_2Me (–)-**5f** R^1 = CH_2CO_2Me (80%)

Scheme 4. Metal-catalyzed heterocyclization reactions of γ-allenol derivatives **3c** and **3d**. Reagents and conditions: a) 1. $PdCl_2$ (5 mol%), allyl bromide, DMF, RT, **5e**: 5 h; **5f**: 6 h; 2. MOMCl, Hünig's base, CH_2Cl_2, reflux, 2 h. b) $AuCl_3$ (5 mol%), CH_2Cl_2, RT, **6a**: 22 h; **6b**: 16 h.

Reversal of the regioselectivity in Au^{+3}-catalyzed reaction

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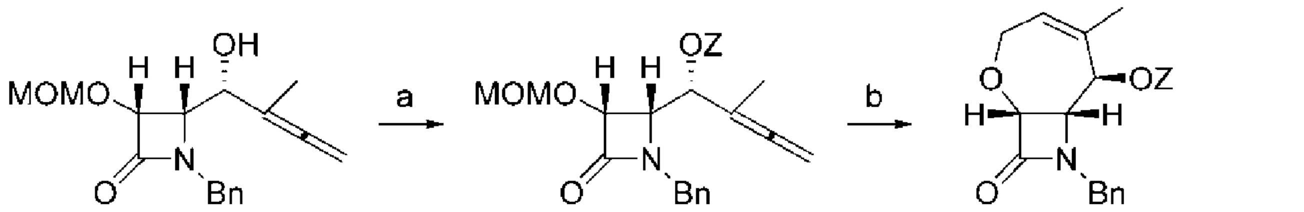
Cyclization of **7**: Au^{+3} Catalysis



(+)-**2d** (–)-**7a** Z = 4-BrC_6H_4CO (60%) (+)-**8a** Z = 4-BrC_6H_4CO (58%)

(+)-**2d** (–)-**7b** Z = PMPCO (60%) (+)-**8b** Z = PMPCO (45%)

Scheme 5. Au^{III}-catalyzed heterocyclization reaction of MOM-protected γ-allenol derivatives **7a** and **7b**. Reagents and conditions: a) 4-BrC_6H_4COCl or PMPCOCl, Et_3N, DMAP, CH_2Cl_2, reflux, **7a**: 6 h; **7b**: 8 h. b) $AuCl_3$ (5 mol%), CH_2Cl_2, RT, **8a**: 72 h; **8b**: 72 h. DMAP = 4-(dimethylamino)pyridine, PMP = 4-$MeOC_6H_4$.

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

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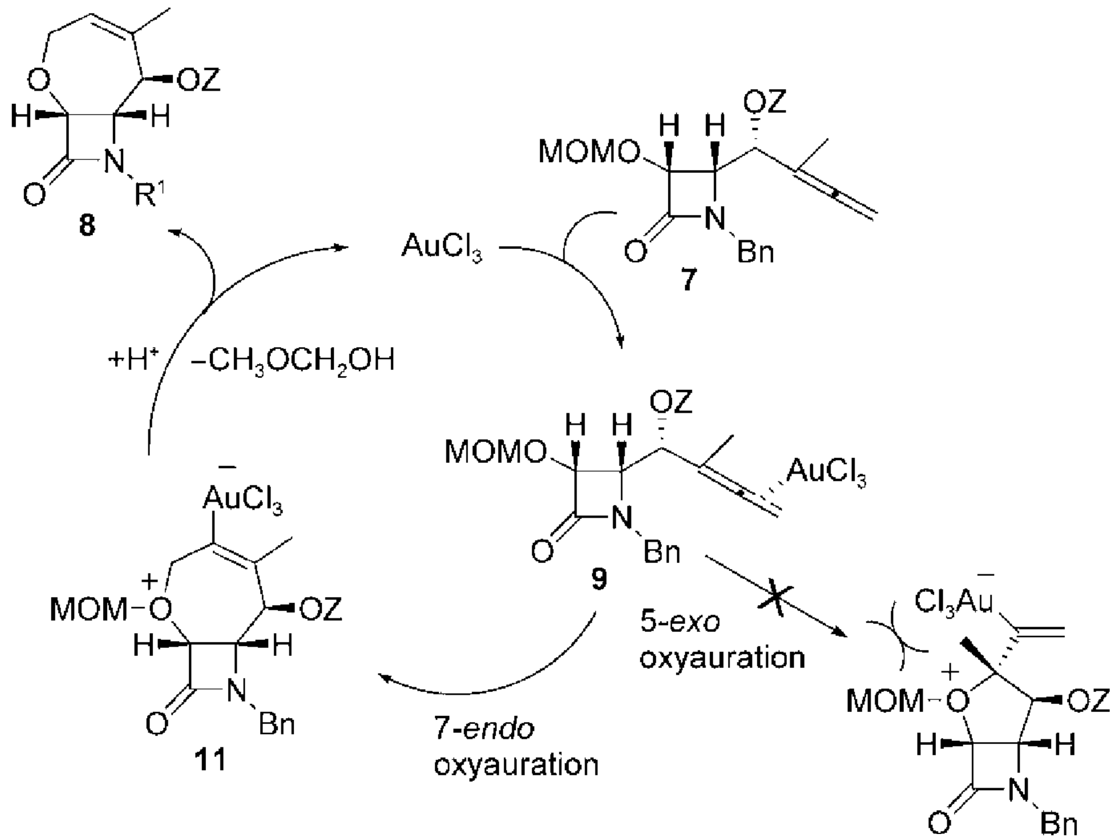
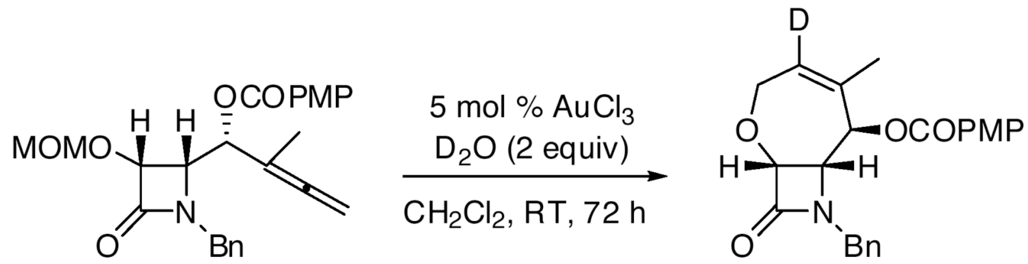
Proposed Mechanism for Au^{+3} Catalysis





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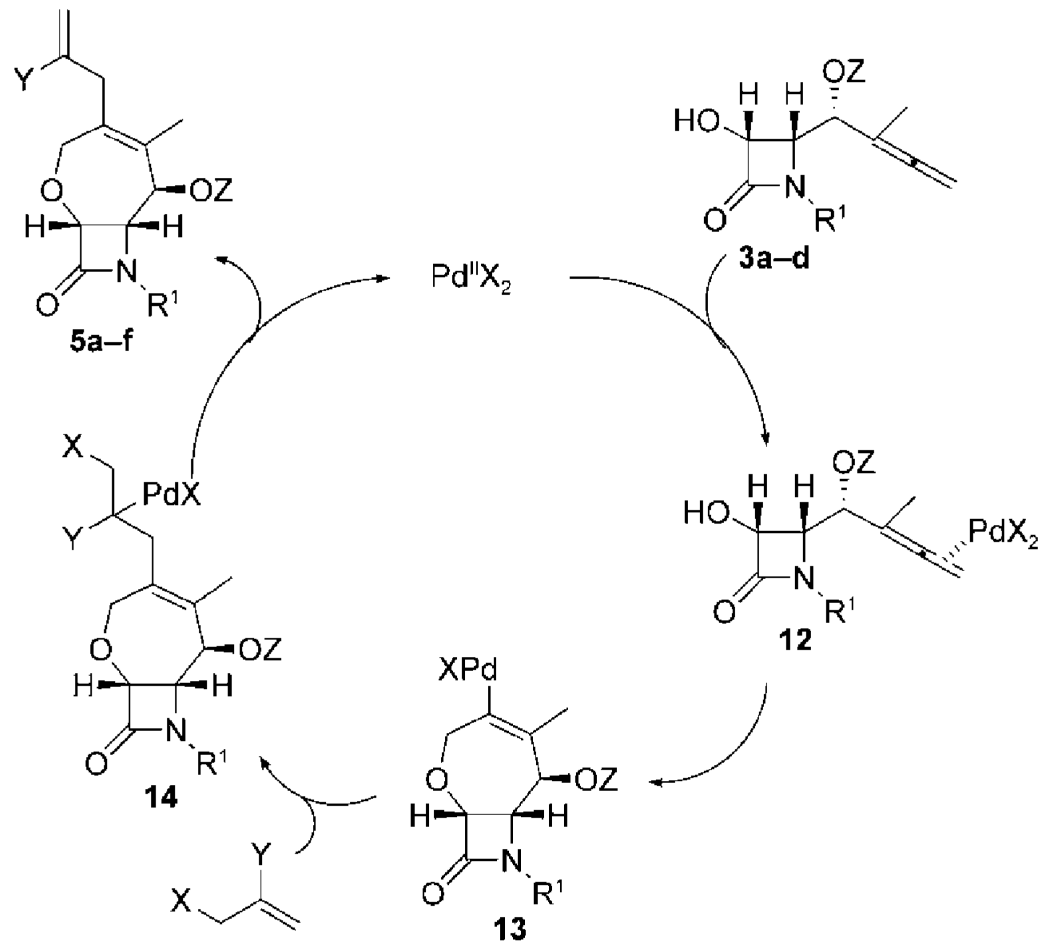
Proposed Mechanism: Pd^{+2} Catalysis



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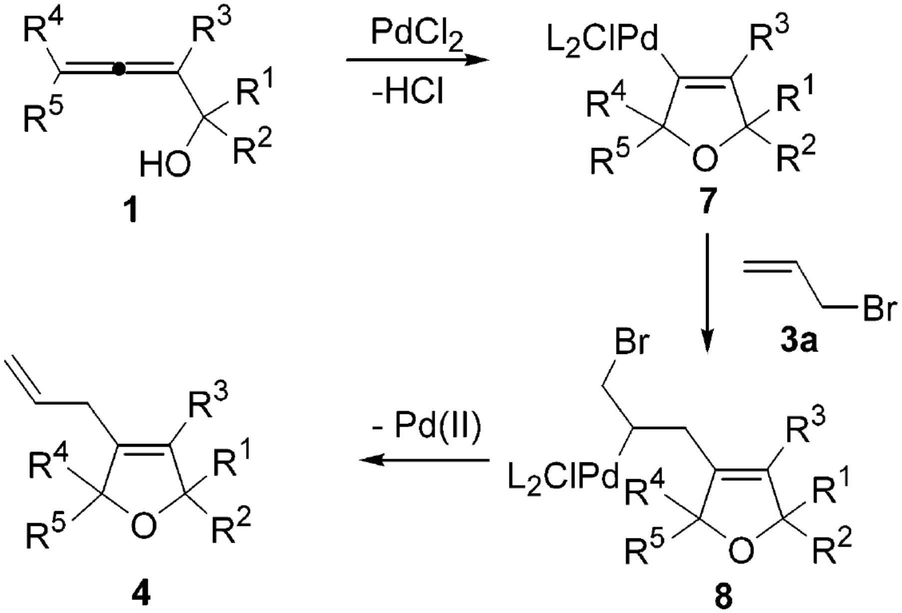
Conclusions

- 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


PdCl2
-HCl
3a
- Pd(II)
1
7
8
4