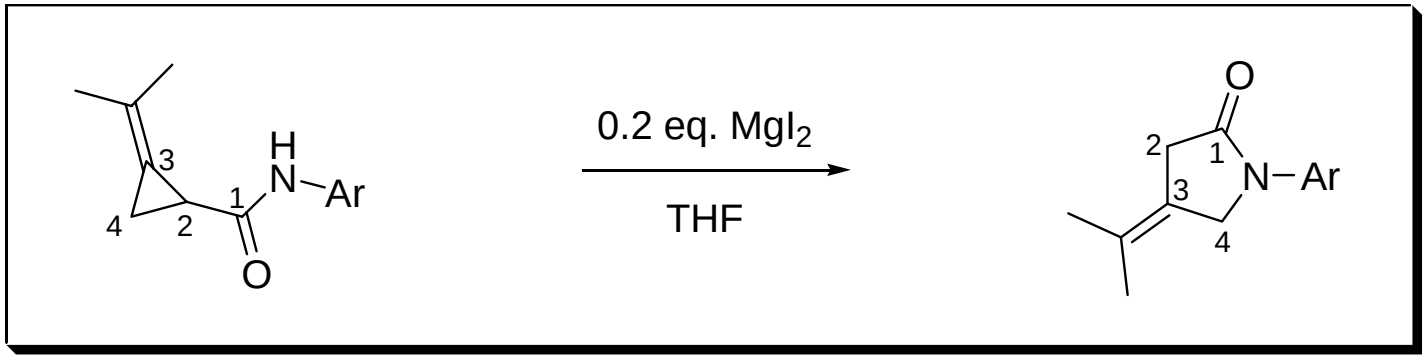
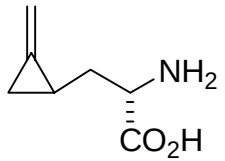
Magnesium Iodide Promoted Ring Expansion of Secondary Methylenecyclopropyl Amides



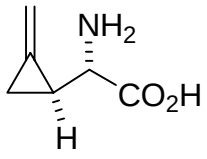
Mark Lautens
University of Toronto

Jennifer Davoren * 11/25/06 * Current Literature

Methylenecyclopropane Derivatives



hypoglycine



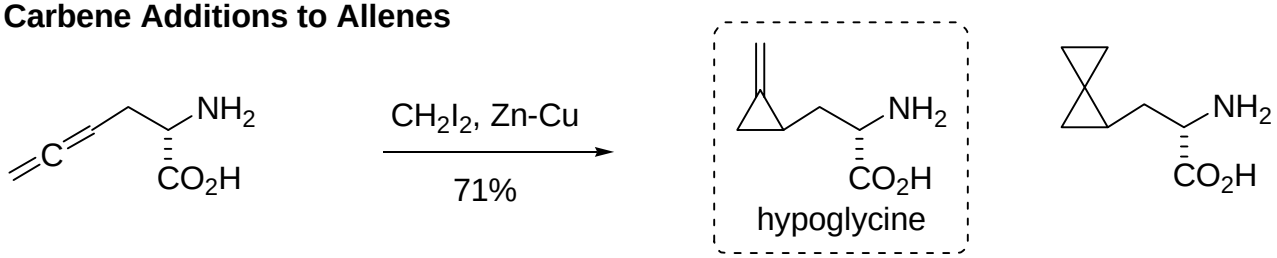
methylenecyclopropylglycine


methylenecyclopropane

- Hypoglycine is a naturally derived amino acid unripe fruit of the ackee tree *Blighia sapida*
  - Responsible for Jamaican vomiting sickness
- Methylenecyclopropylglycine was isolated from the kernels of litchi fruits
  - Causes hypoglycemia in mice and fasted rats
- Methylenecyclopropane is a stable volatile olefin (bp 11 °C), can be stored in a sealed tube for several years without decomposition

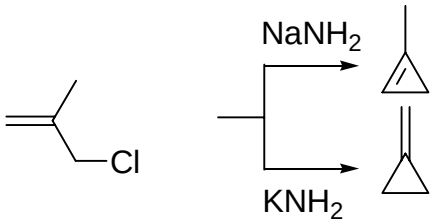
Synthesis of Methylenecyclopropane Derivatives

Carbene Additions to Allenes

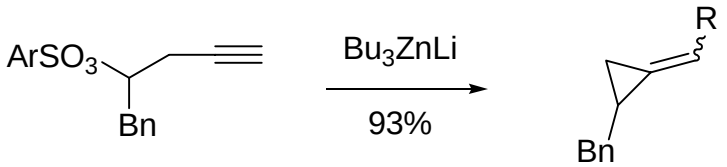


The formation of spiropentane derivatives is general and cannot normally be avoided, especially in simple monosubstituted allenes, even when using only a slight excess of the Simmons-Smith reagent

Eliminations



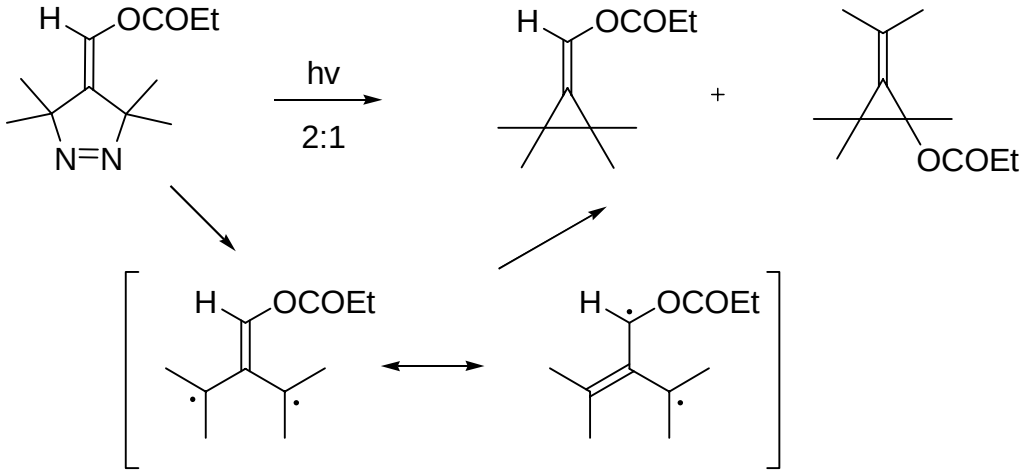
The base counterion plays an important role in the nature of products formed, as $NaNH_2$ gives the cyclopropene derivative, whereas KNH_2 gives MCP



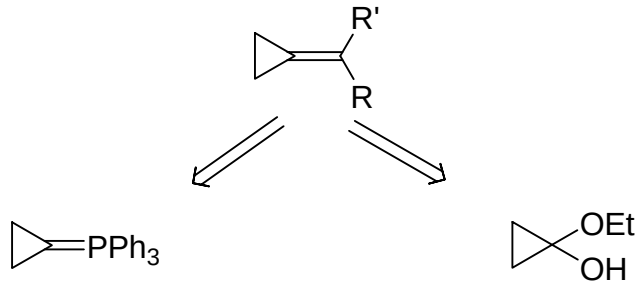
A nucleophilic alkene can be produced from an alkyne by the addition of an organometallic reagent

Synthesis of Methylenecyclopropane Derivatives

Elimination of N_2 from Pyrazolines

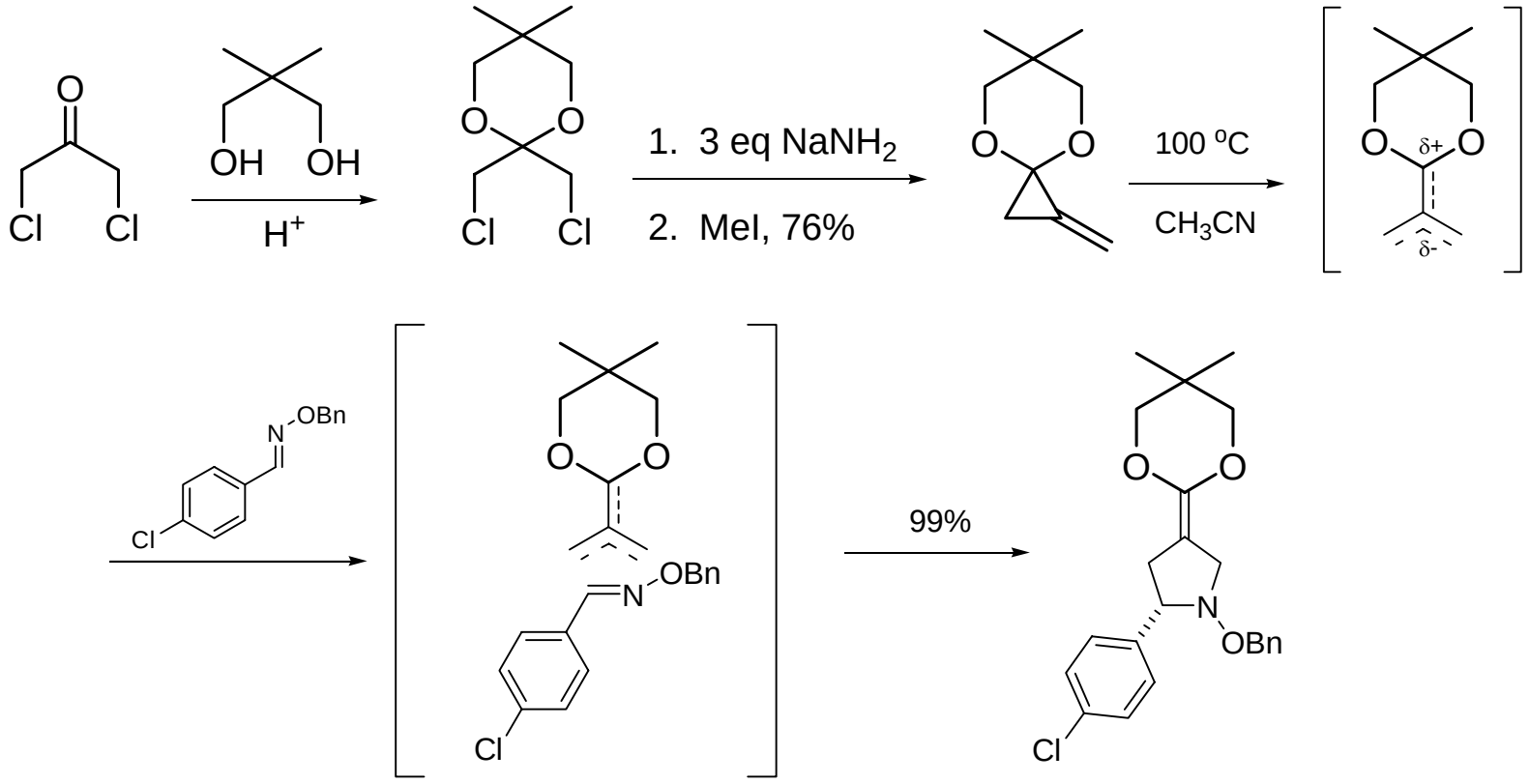


Wittig Olefinations



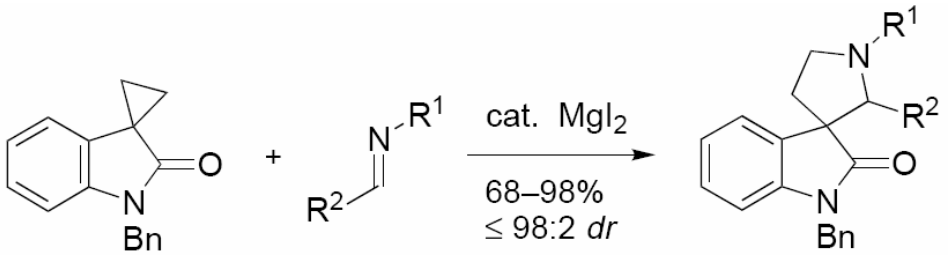
The route employing cyclopropylidene phosphorane has been the most utilized by researchers, because of the unavailability of cyclopropanone and the low reactivity of its synthetic equivalent cyclopropanone hemiacetal

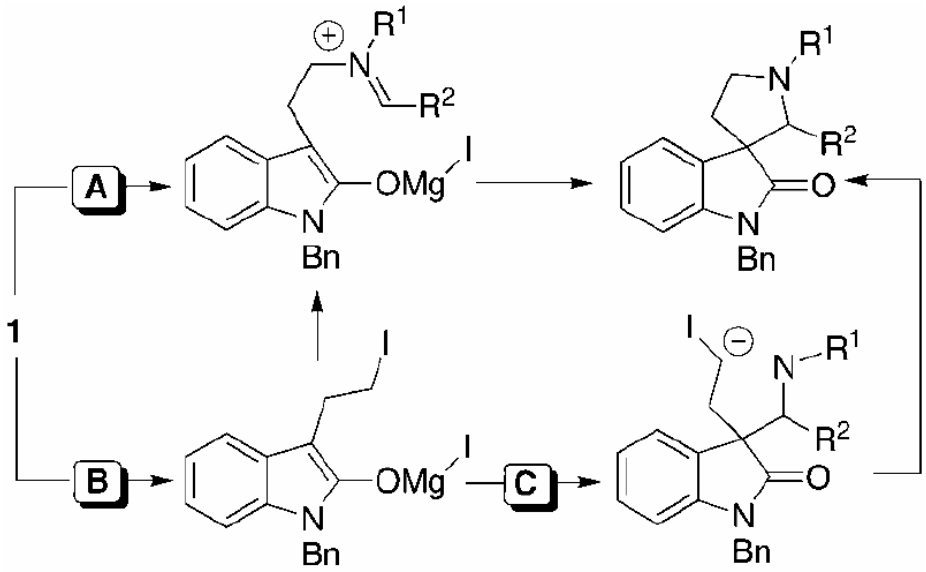
[3 + 2] Cycloaddition of Dipolar Trimethylenemethane (TMM) Derived From Methylenecyclopropanes



J. Org. Chem. **1998**, 63, 1694-1703

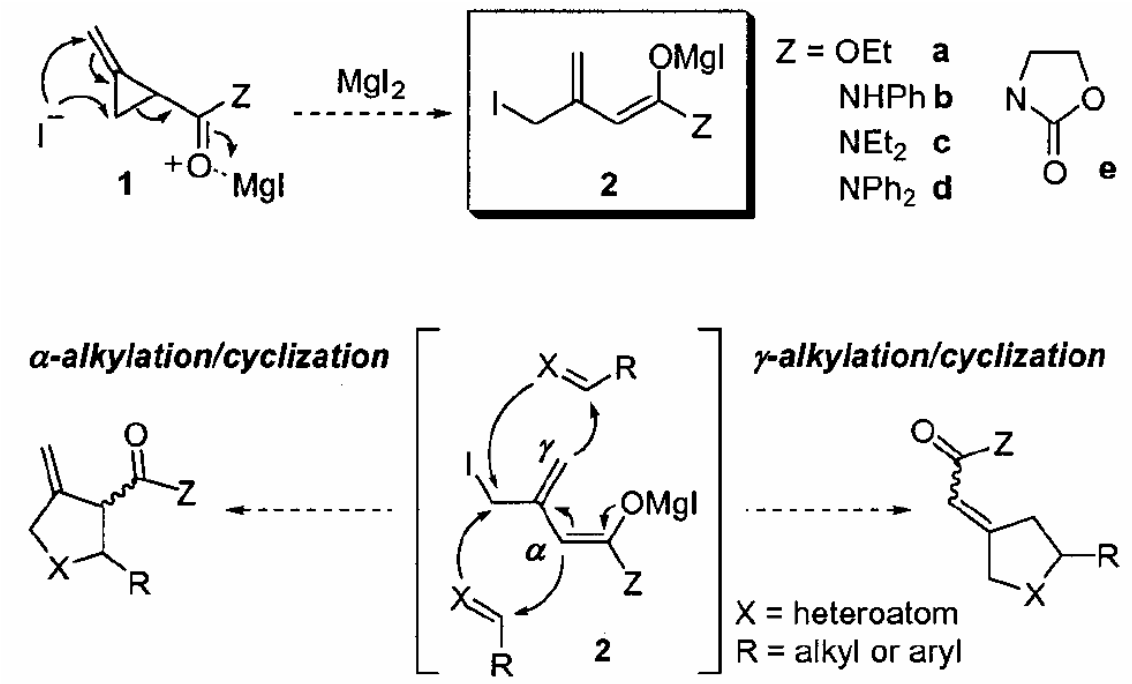
Carriera's Precedence





Angew. Chem., Int. Ed. **1999**, 38, 3186

Lauten's Early Work

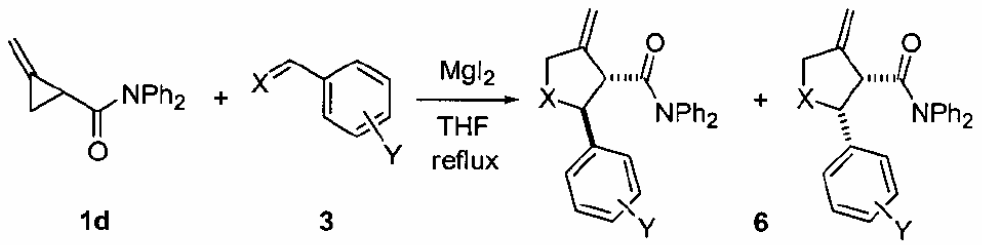


• Studies began with the reactions of several monoactivated MCP's of types **1a-1c** with aryl aldimines in the presence of stoichiometric MgI_2

- Reactions using ester **1a** and stoichiometric MgI_2 recovered starting material
- Whereas amides **1b** and **1c** gave complex mixtures even in the reactions with aryl aldehydes
- In contrast the diphenyl amide **1d** could be reacted with a variety of imines in good yields

J. Am. Chem. Soc. **2002**. 124, 6312

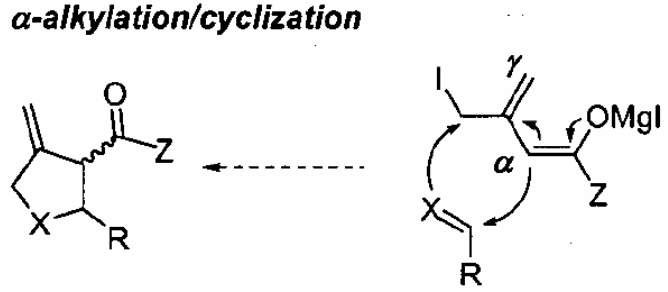
Reactions of MCP Amides: Bearing a Diphenyl Amide

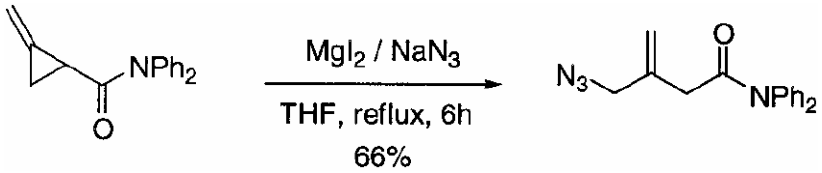


1d 3 6

entry	3	X	Y	time (h)	6	yield (%)	*d.r.* (trans:cis)
1	**a**	NTs	4-CF_3	10	**a**	65	1.6:1
2	**b**	NTs	4-NO_2	6	**b**	57	2.2:1
3	**c**	NTs	4-Br	10	**c**	85	2.3:1
4	**d**	NTs	4-OMe	6	**d**	78	5.3:1
5	**e**	NBs	H	6	**e**	81	4.1:1
6	**e**	NBs	H	15	**e**	76	3.8:1
7	**f**	NTs	2-Br	6	**f**	71	>20:1
8	**g**	NTs	2-CF_3	10	**g**	81	>20:1
9	**h**	NTs	2,4-dichloro	10	**h**	78	>20:1
10	**i**	NTs	2,4-dimethyl	10	**i**	82	>20:1

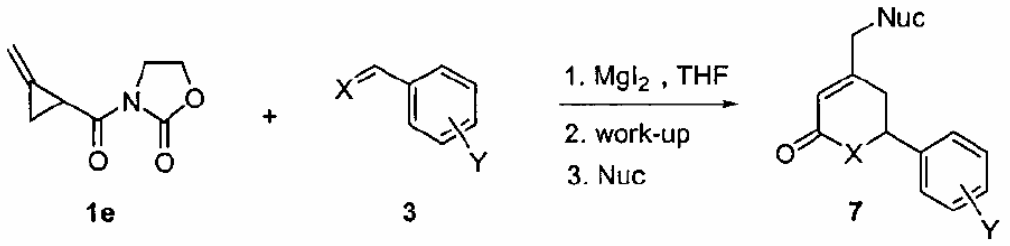
***α*-alkylation/cyclization**



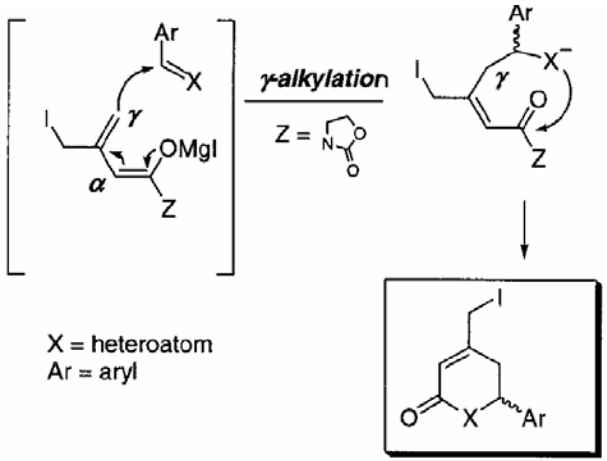


- In the case of aldimines bearing an *ortho*-substituent (entries 7-10) only the *trans* diastereomers were obtained.
- Stoichiometric MgI_2 is not required, the reactions could be carried out with 10-30 mol % of MgI_2 without any loss in yield (entries 3, 6, and 8-10).
- When 10 mol % MgI_2 was used, an increase in the reaction concentration to 0.2 M was required to ensure complete reaction (entry 6).
- Reactions with aryl iodides provided complex mixtures of products

Reactions of MCP Imides: Bearing a Oxazolidinone



entry	3	X	Y	method	7	Nuc	yield (%)
1	**c**	NTs	4-Br	A	**c**	N_3	78
2	**c**	NTs	4-Br	B	**c**	I	60
3	**j**	NTs	H	A	**j**	N_3	81
4	**g**	NTs	2-CF_3	B	**g**	Ts	75
5	**i**	NTs	2,4-dimethyl	A	**i**	OAc	72
6	**k**	O	H	A	**k**	N_3	88
7	**l**	O	2-Br	A	**l**	SPh	67
8	**m**	O	4-NO_2	B	**m**	OAc	71
9	**n**	O	3,4-OCH_2O	A	**n**	Ts	65
10	**o**	O	2,4-dichloro	B	**o**	N_3	74



- In contrast to the results with the diphenyl amide, the products were exclusively six-membered heterocycles bearing an allyl iodide and lacking the oxazolidone group
- Requires a stoichiometric amount of MgI_2 to go to completion
- The iodo-substituted products were not stable to silica flash chromatography
- A concerted [4+2] *hetero*- Diels-Alder reaction pathway could not be ruled out

Reactions of MCP Amides: Bearing a Secondary Amide

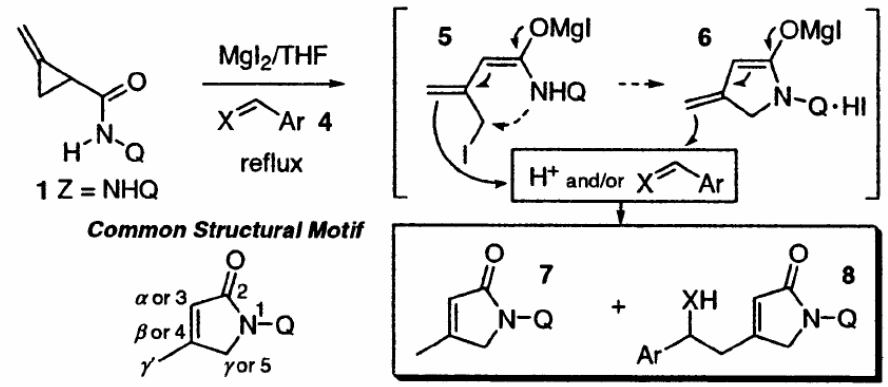
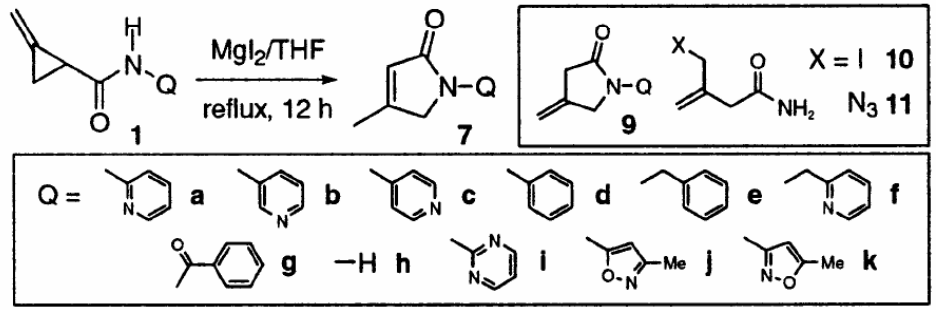


Table 1. Ring Expansion of Secondary MCP Amides



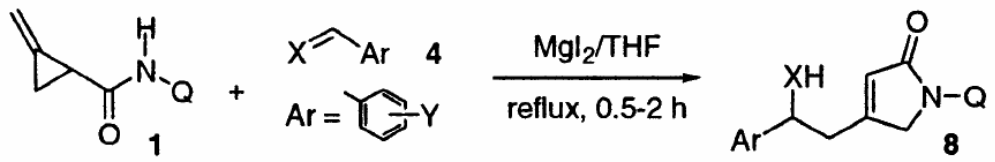
entry	1	product	yield (%)	entry	1	product	yield (%)
1	**a**	**7a**	89	5	**e**	**7e**	*d*
2	**b**	**7b**	95	6	**f**	**7f**	*d*
3	**c**	**7c**	87	7	**g**	**7g**	*d*
4	**d**	**7d**	80	8	**h**	**11**	67

- A different process for secondary MCP amides was observed
- In the absence of an electrophile underwent ring expansion to the isomeric five-membered unsaturated lactam **7**
- In the presence of a wide range of aryl aldimines or aldehydes products such as **8** were obtained

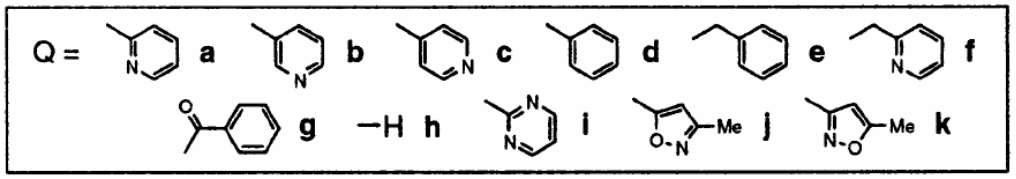
J. Am. Chem. Soc. **2003**, 125, 4028.

Reactions of MCP Amides: Bearing a Secondary Amide

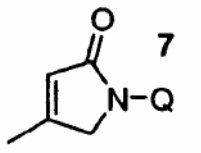
Table 2. Alkylative Ring Expansion of MCP **1a** (Q = Pyrid-2-yl)



entry	4	X	Y	equiv of MgI_2	[1] (M)	8	yield[a] (%)
1	**a**	NTs	4-Br	1.1	0.05	**aa**	45
2	**a**	NTs	4-Br	1.1	0.1	**aa**	53
3	**b**	NTs	2,4-dimethyl	1.1	0.05	**ab**	54
4	**b**	NTs	2,4-dimethyl	1.1	0.1	**ab**	68
5	**c**	NTs	4-OMe	1.1	0.1	**ac**	71
6	**d**	NTs	H	1.1	0.1	**ad**	72
7	**e**	NTs	2-CF_3	1.1	0.1	**ae**	76
8	**f**	O	H	1.1	0.1	**af**	62
9	**g**	O	3,4-OCH_2O	1.1	0.1	**ag**	72
10	**h**	O	4-CF_3	1.1	0.1	**ah**	81

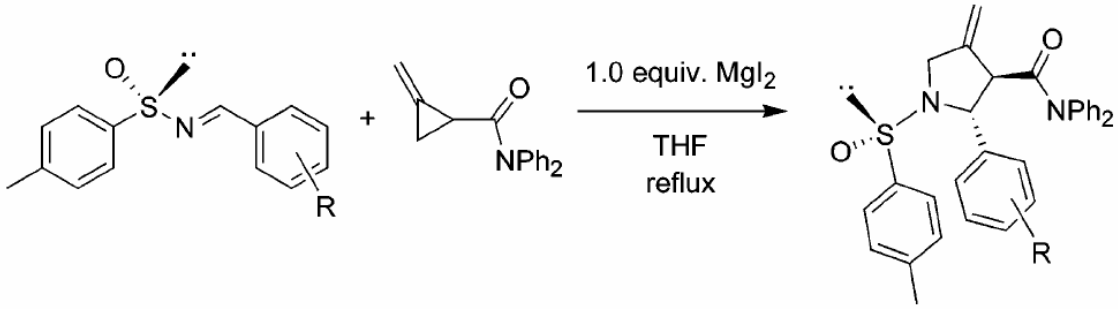


In each case, the monoalkylated product **7** was isolated in 10-30% yield



Diastereoselective Ring Expansion of MCP

Table 1. Aromatic Sulfinimine Scope for Diastereoselective MCP Amide Ring Expansion

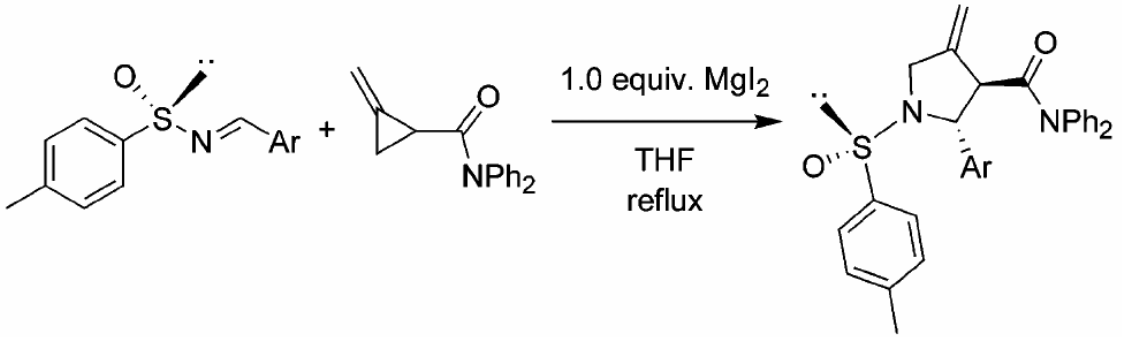


entry	R	time (h)	yield (%)	dr[a] (2*R*,3*R*)/(2*S*,3*S*)	*anti*/*syn*[a]
1	H	3.25	90	>20:1	>20:1
2	2-Br	6.5	63	>20:1	>20:1
3	3-Br	7.5	72	>20:1	>20:1
4	4-Br	7.5	80	>20:1	>20:1
5	4-MeO	7.0	76	>20:1	>20:1
6	4-NO_2	4.5	72	>20:1	>20:1
7	2-Me	6.0	65	>20:1	>20:1
8	4-Me	7.0	85	>20:1	>20:1
9	4-CF_3	4.0	94	>20:1	>20:1

Org. Lett. **2004**, 6, 3309

Diastereoselective Ring Expansion of MCP

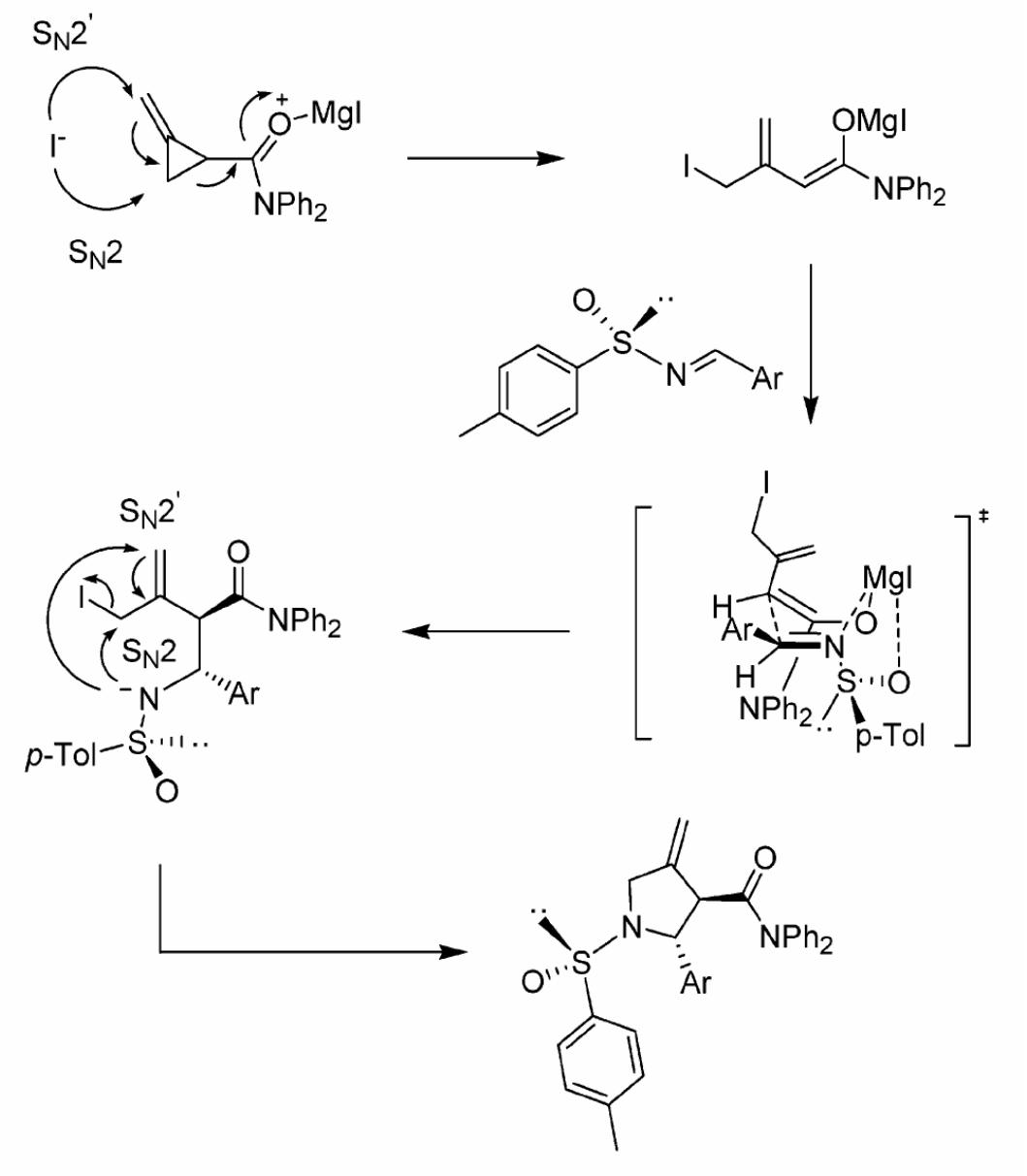
Table 2. Hetereoaromatic Sulfinimine Scope for Diastereoselective MCP Amide Ring Expansion



entry	Ar	time (h)	yield (%)	dr	(2*R*,3*R*)/(2*S*,3*S*)	*anti*/*syn*
1	3-pyridyl	16	82		>20:1	>20:1
2	4-pyridyl	3.25	76		>20:1	>20:1
3	2-furyl	11	82		>20:1	1.1:1
4	3-furyl	3.25	85		>20:1	84:16

- For the pyridyl series (entries 1-2), the diastereoselectivity was found to be excellent in all cases.
- In the furyl series, however, the diastereoselectivity decreased when the oxygen was *ortho* to the imine substituent

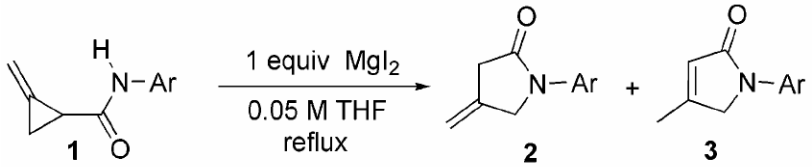
Proposed Mechanism of Diastereoselective MCP Ring Expansion



- The enolate must attack the sulfinimine v*ia* a boat TS to give the observed *anti* relationship
- The sulfoxide adopts a conformation in this boat transition state to minimize 1,3-allylic strain while maximizing the stabilization of this intermediate via coordination of the magnesium to the oxygen of the sulfoxide.
- Presumably the presence of an *ortho* heteroatom in the sulfinimine results in low diastereoselectivity due to competing coordination of magnesium to the *ortho* heteroatom
- The pyrrolidine products could be deprotected in 94% using TFA

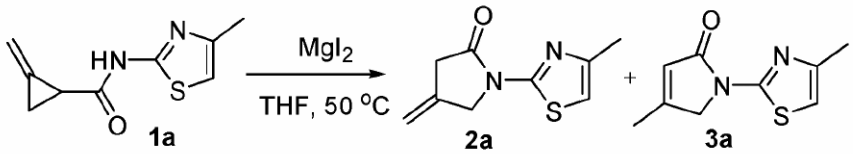
Synthesis of β,γ-Unsaturated Lactams via a MgI_2 Promoted Ring Expansion of Secondary MCP Amides

Initial MgI_2 Ring Expansion



Ar = Ph		10%	80%
= 2-pyridyl		9%	89%

Table 1. Effect of Catalyst Loading and Concentration on Reaction Selectivity and Yield

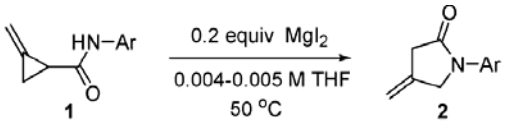


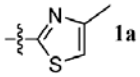
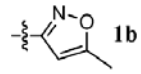
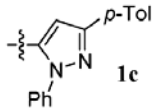
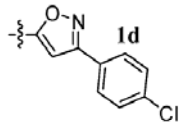
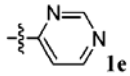
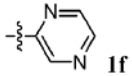
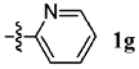
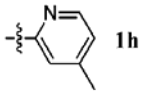
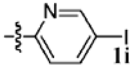
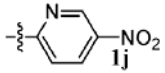
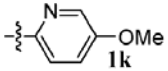
MgI_2 loading (equiv)	concentration (M)	yield (%)	**2a**:**3a** ratio
1.0	0.10	75	1:6.3
0.5	0.10	53	1:2.0
0.2	0.10	49	1:1.3
0.2	0.05	91	>10:1
0.2	0.02	96	>20:1
0.2	0.005	98	>20:1

- Initial investigations established that THF and MgI_2 were optimal as both solvent and Lewis acid
- The use of dilute reaction conditions and substoichiometric amounts of MgI_2 were crucial to obtaining the exo isomer in excellent yield and selectivity

Org. Lett. **2006**, 8, 5521

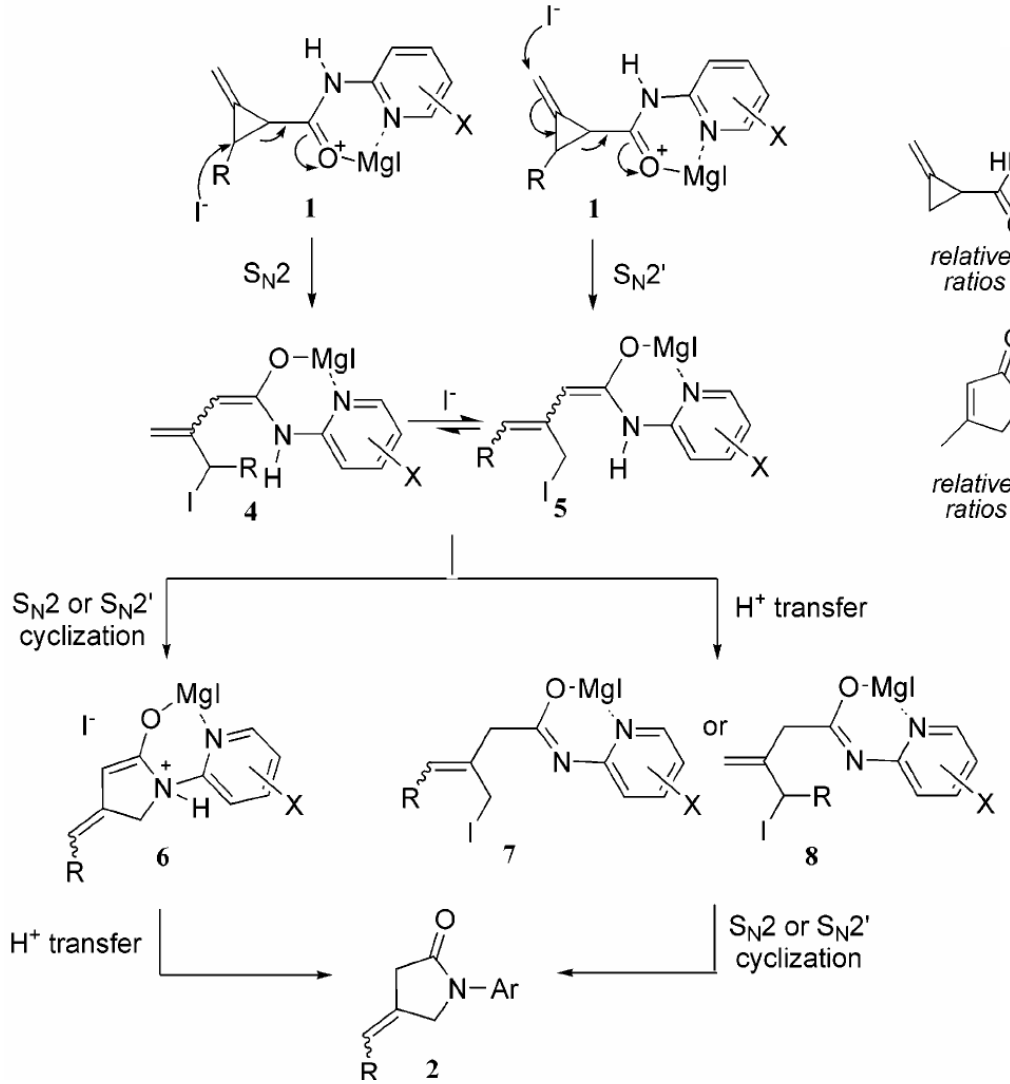
Scope of MgI_2 Promoted Ring Expansion of Secondary MCP Amides

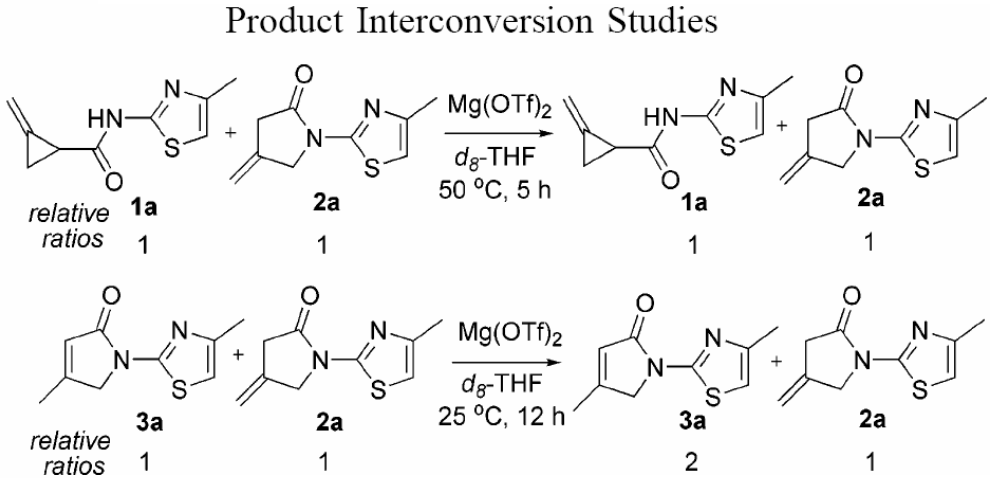


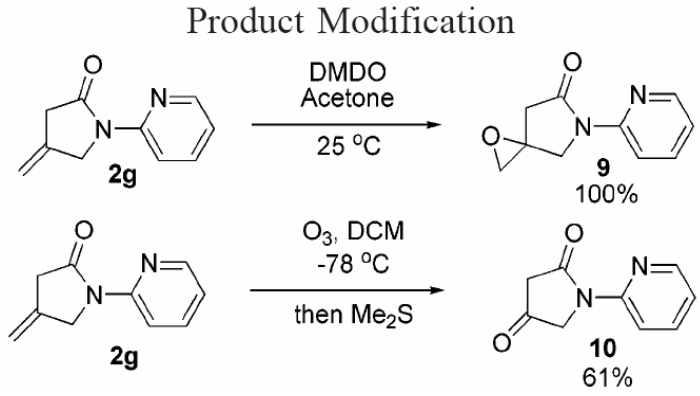
entry	MCP	time (h)	yield[a] (%)	exo:endo ratio[b]
1	 **1a**	12	98	>20:1
2	 **1b**	12	92	>20:1
3	 **1c**	60	79 (90)[c]	>20:1
4	 **1d**	24	trace	-
5	 **1e**	4	93	17:83
6	 **1f**	12	81[d]	9:1
7	 **1g**	12	93	9:1
8	 **1h**	2.5	92	3:1
9	 **1i**	7	99	>20:1
10	 **1j**	4	100	1:3
11	 **1k**	34	55[e]	3:1

- Several substituted azoles (1-3) afforded the corresponding ring-expanded products in excellent yield and selectivity
- The use of an analogous isoxazole substrate bearing an oxygen adjacent to the amido functionality resulted in no observable ring expansion (4)
    - This result suggests that a nitrogen atom adjacent to the amido functionality is crucial to obtaining the desired exo product in good selectivity and yield
- Mild electron withdrawing groups and electron rich groups gave ring expanded products in excellent yields and selectivities
    - Conversely electron withdrawing groups gave poor exo-selectivities (5 & 10)
- Interestingly, MCPs substituted at either the exo methylene or cyclopropyl carbon also provided ring-expanded products in moderate to good yields with high selectivities of the exo product

Proposed Mechanism of MgI_2 Promoted Ring Expansion







Conclusions

- MgI_2 promoted ring expansion of MCP's to either 5 or 6 membered rings
- Unique mechanistic pathways observed depending on the type of amide used; ie. diphenyl amides vs. secondary amides vs. oxazolidinones
- Diastereoselective variant was developed using the diphenyl amide