Domino Ring-Opening/Recyclization Reactions of Doubly Activated Cyclopropanes as a Strategy for the Synthesis of Furoquinoline

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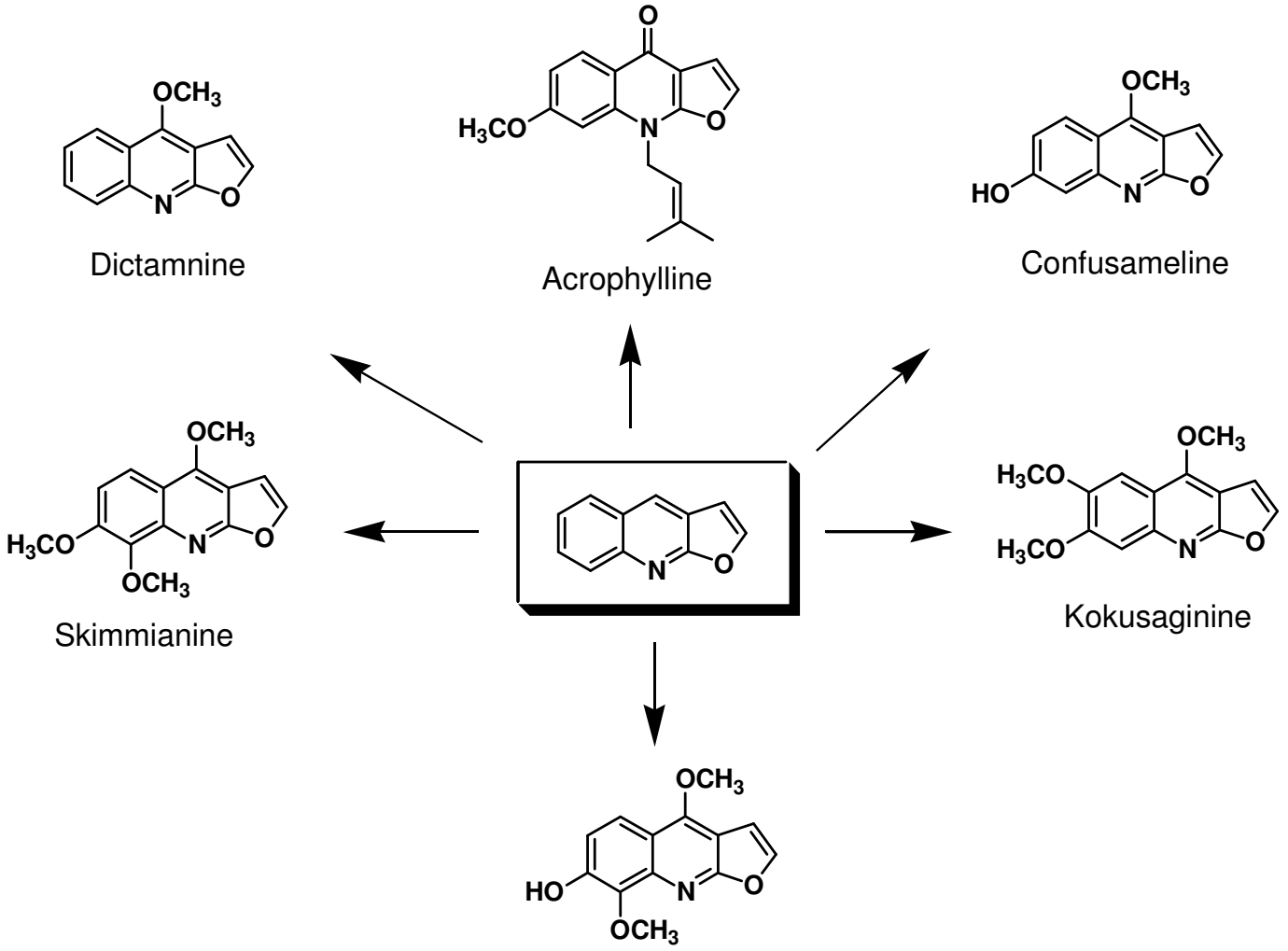
Angew. Chem. Int. Ed. 2007 Early View

William Paquette
2-17-07 Literature Presentation
Wipf Group

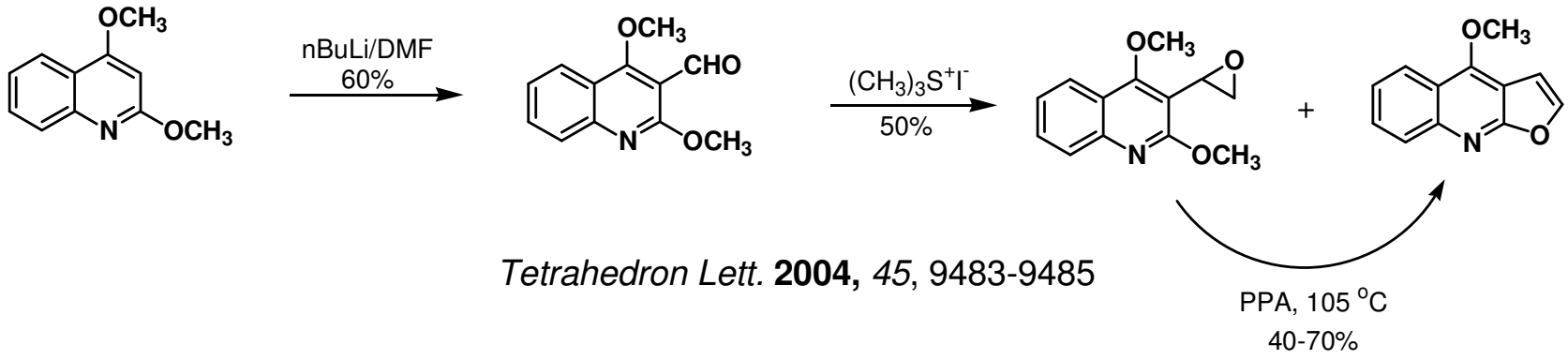
Structurally Related Furoquinoline Natural Products



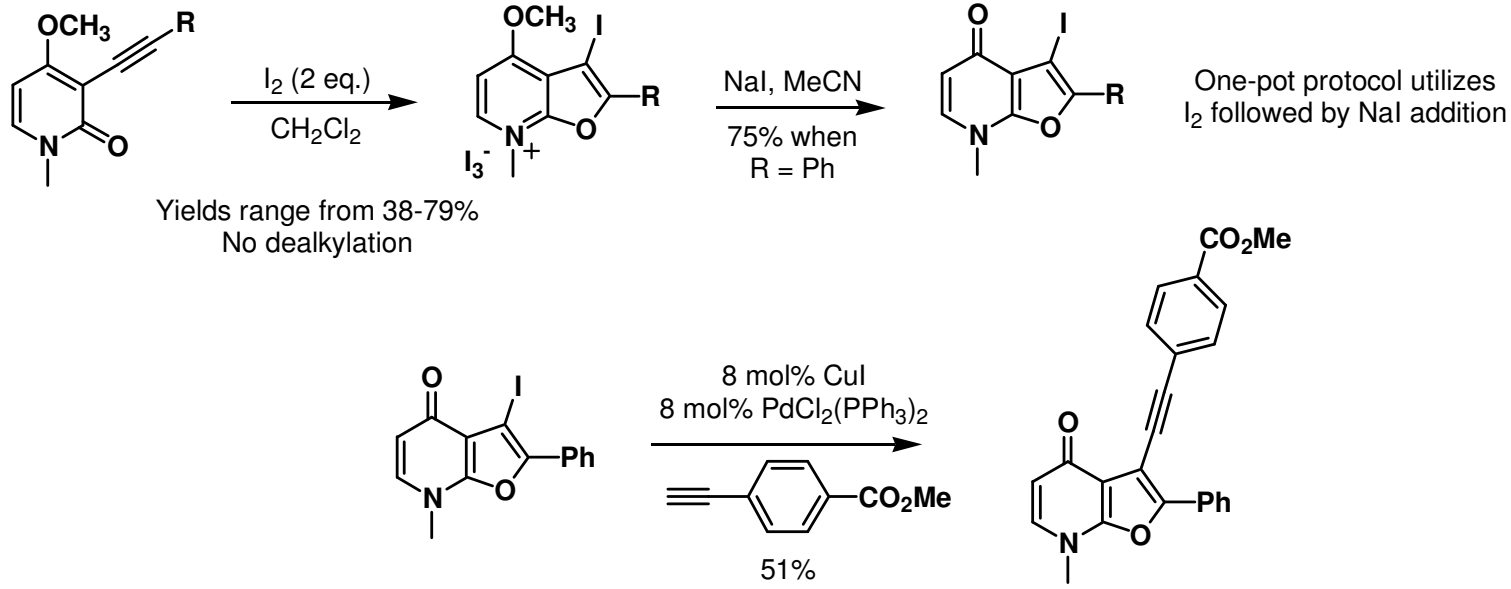
Possess wide range of biological properties including anti-allergic, anti-inflammatory, and cytotoxic

Bioorg. Med. Chem. **2004,** *12*, 387-392

Synthesis of Furoquinoline and Furopyridone Scaffolds

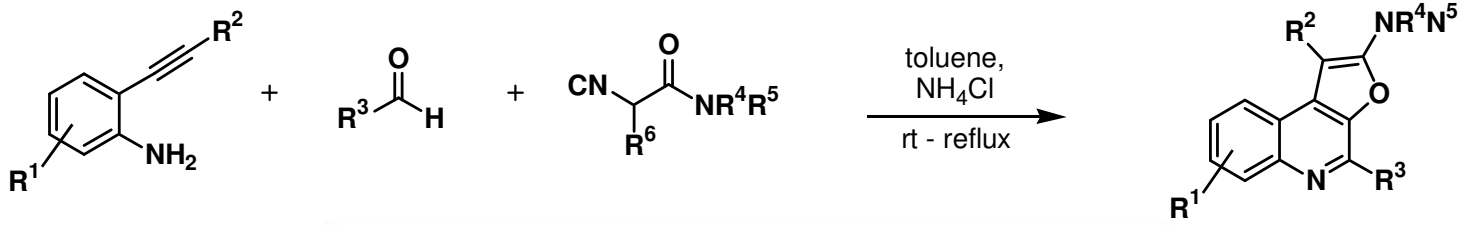


Tetrahedron Lett. **2004,** *45*, 9483-9485

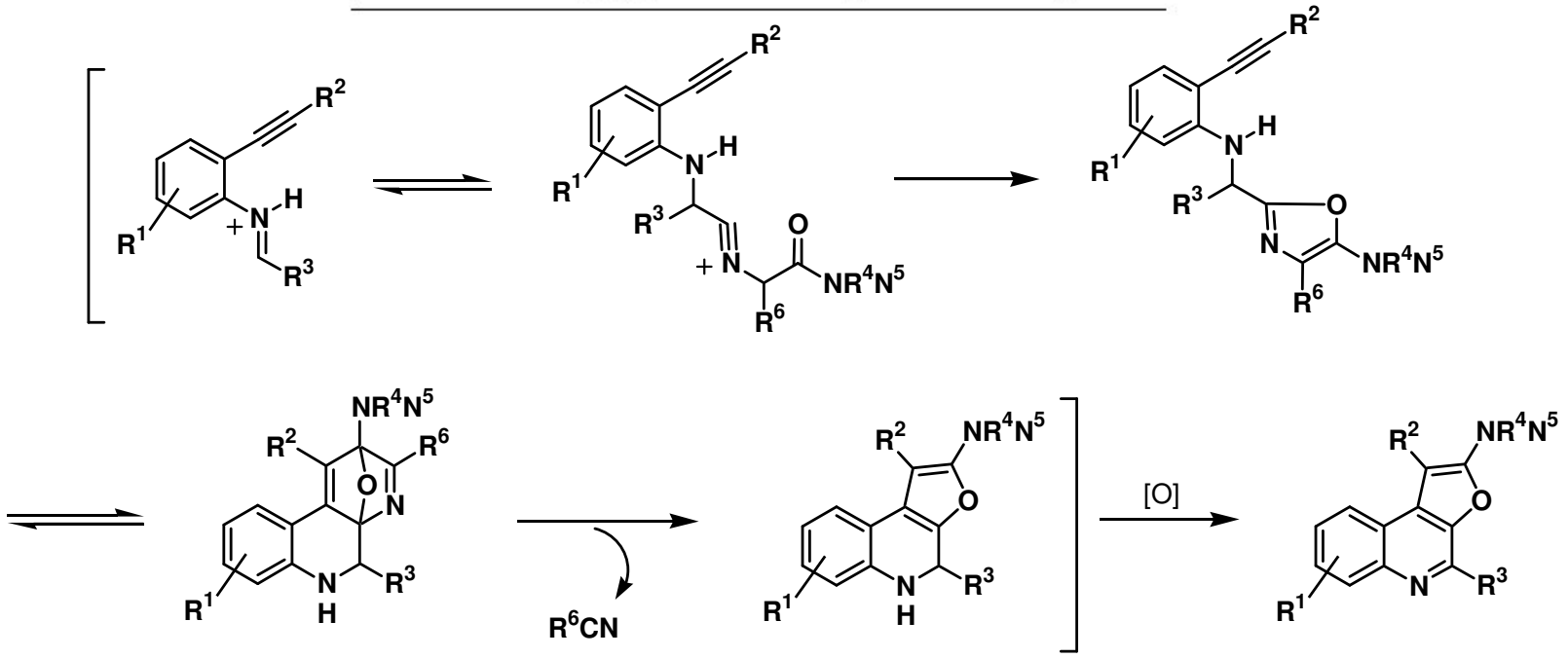


Org. Lett. **2006,** *8*, 1113-1116

Construction of Angular Furoquinolines via a Multicomponent Process

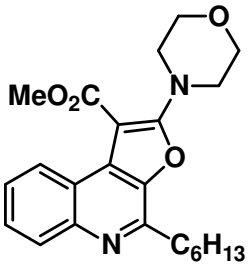


Entry	Additive	*t* [h]	Yield [%]
1	none	12	26
2	LiBr[b]	12	15
3	CSA[c]	12	22
4	NH_4Cl[b]	12	75

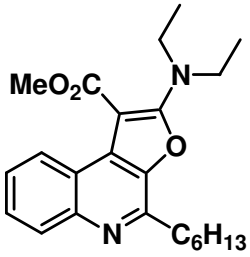


Angew. Chem. Int. Ed. **2002,** *41*, 3633-3635

Structural Diversity of Furoquinolines using a Multicomponent Strategy



75%



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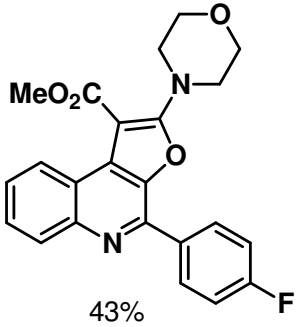
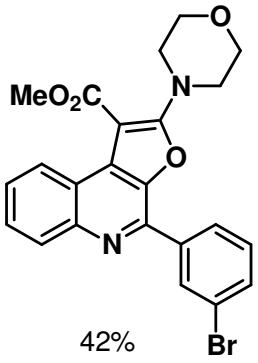


43%



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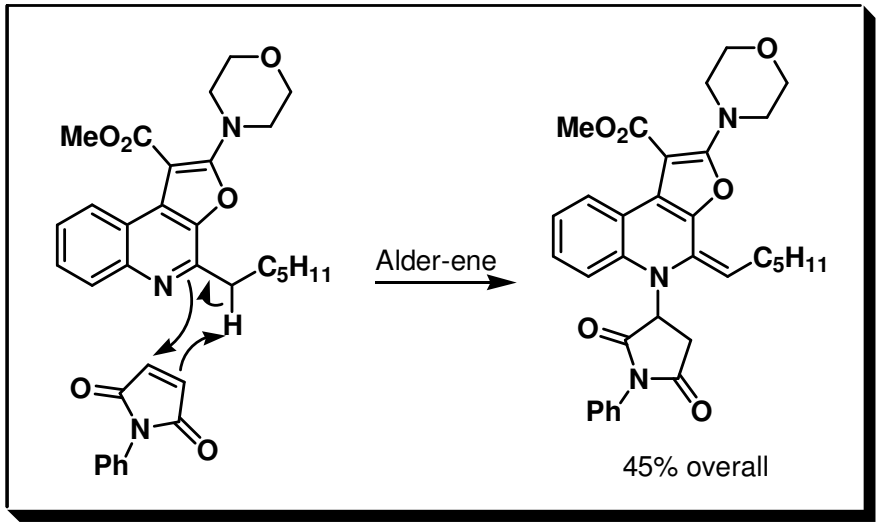
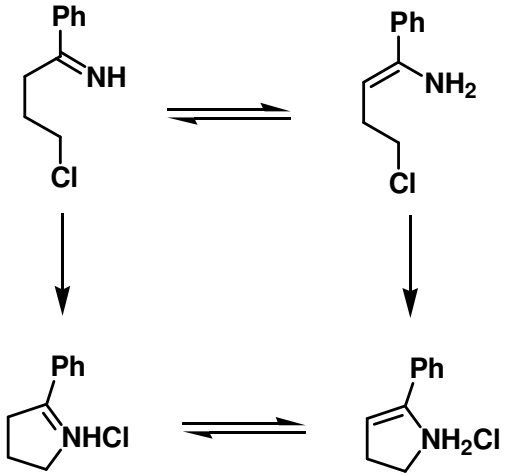
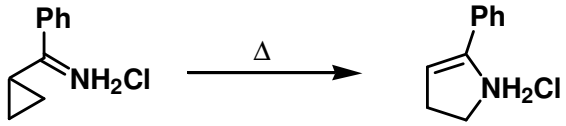


45% overall

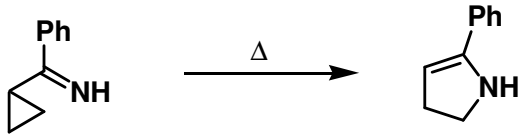
Cyclopropyl Fragmentation:
An Early Exploration into the Construction of Pyrrolines



Cyclopropyl Ketimine - HCl



Free Cyclopropyl Ketimine

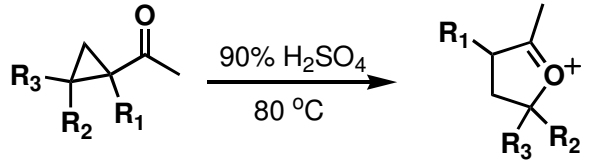


Determined to be more thermally stable

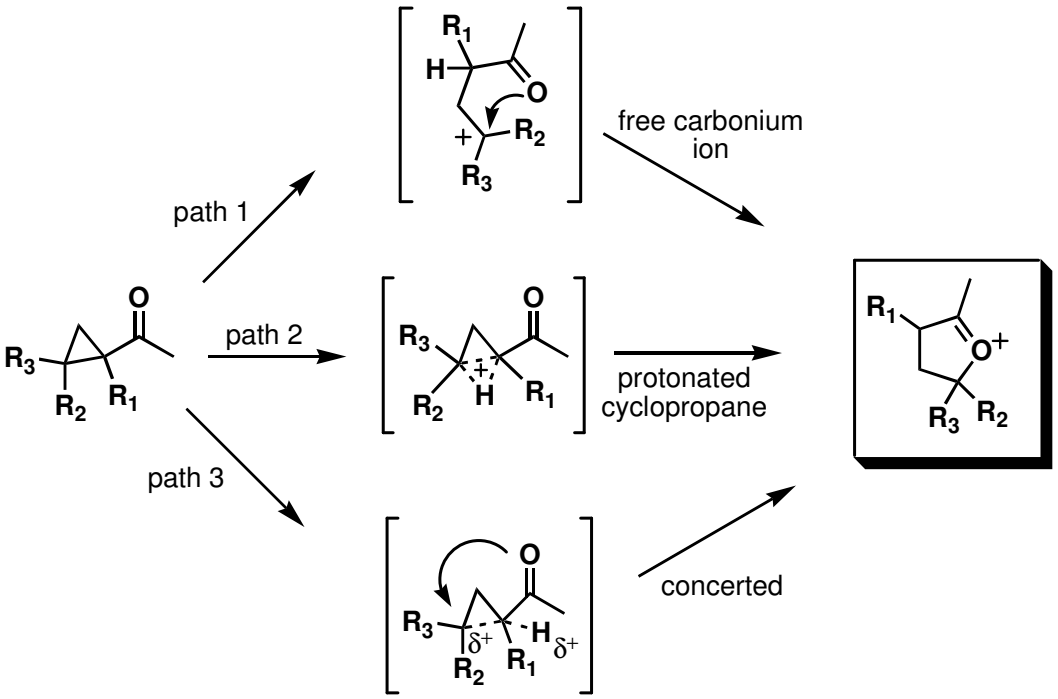
- The HCl salt derivative was found to undergo cyclopropyl ring fragmentation at lower temperature
- Therefore the cyclopropyl ring has an increased tendency to rupture in the presence of acid

J. Am. Chem. Soc. **1929,** *51*, 1174-1187

Rearrangement of Cyclopropyl Ketones in the presence of a Brönsted Acid

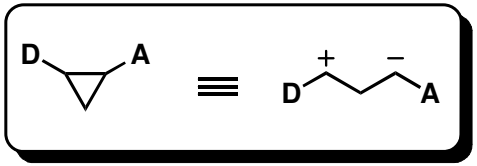


R_1 = H or CH_3
R_2 = H, CH_3, or Ph
R_3 = H or CH_3

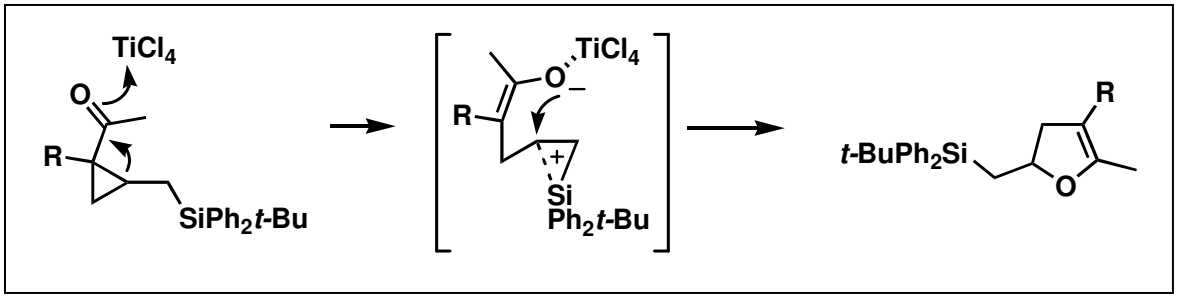


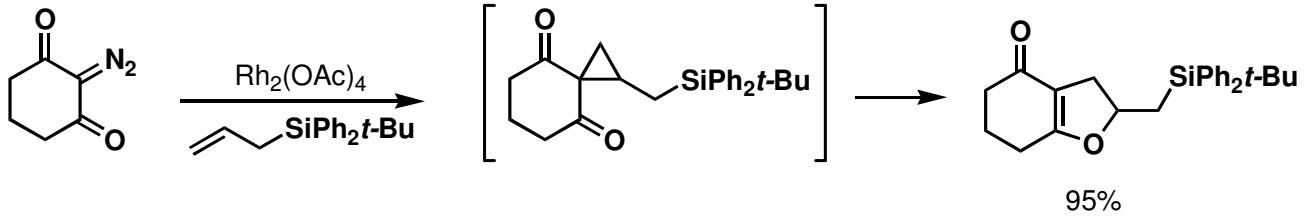
J. Am. Chem. Soc. **1969,** *91*, 5915-5918

Silicon-Assisted Construction of Dihydrofurans
Application of a Donor-Accceptor Cyclopropane



R = COMe, 81%
R = CO_2Et, 70%
R = H, NR

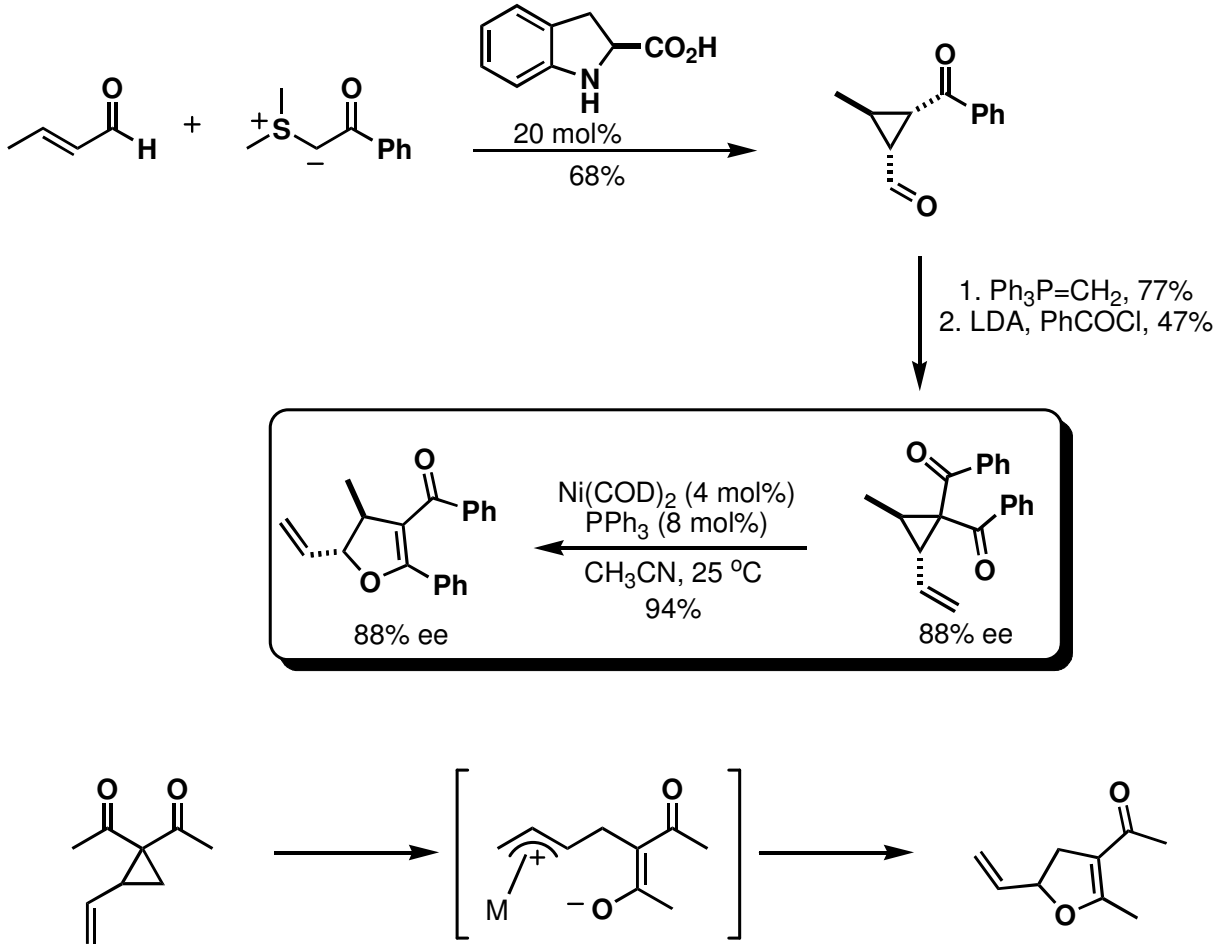




95%

Org. Lett. **2001,** *3*, 2717-2719

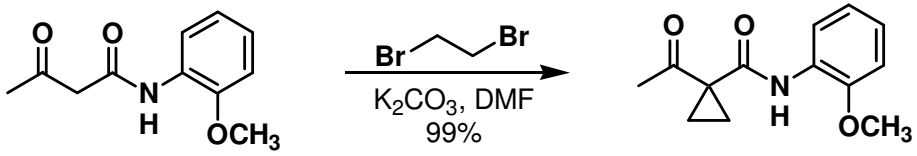
Nickel-Catalyzed Rearrangement of Activated Cyclopropanes: *Synthesis of Highly Functionalized Dihydrofurans*

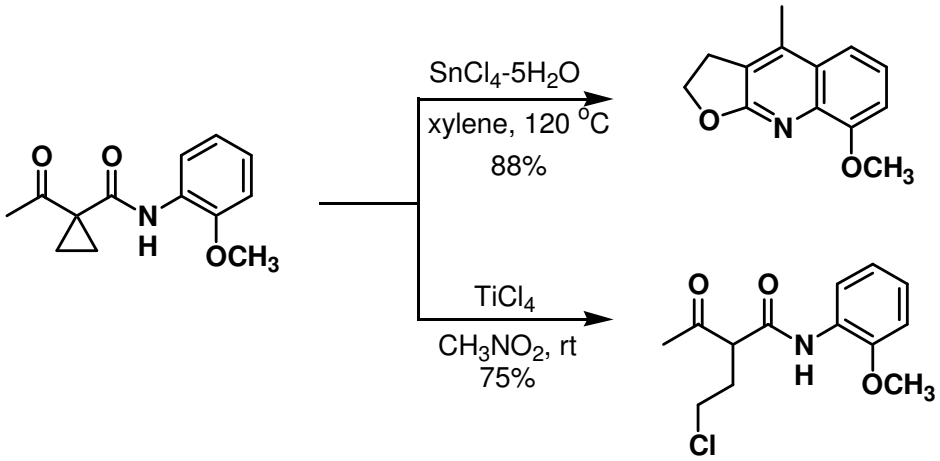


Org. Lett. **2006,** *8*, 573-576

Domino Ring-Opening Reaction of Doubly Activated Cyclopropanes: *Strategic Synthesis of Furoquinolines*

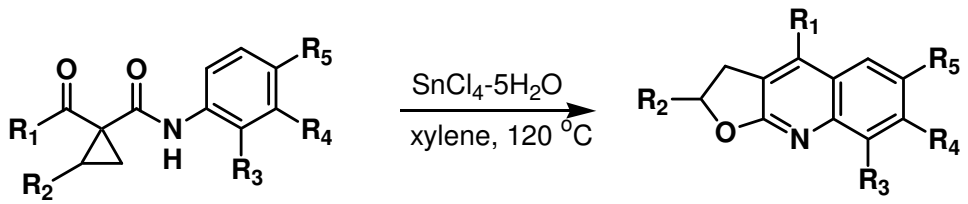
***Angew. Chem. Int. Ed.* 2007 Early View**

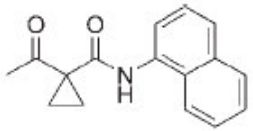
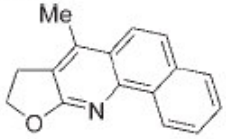
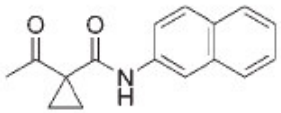
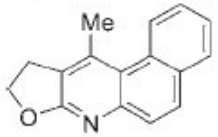




Entry	Lewis acid (equiv)	Solvent	T [°C]	t [h]	Yield of **2a** [%][a]
1	$SnCl_4 \cdot 5H_2O$ (1.2)	xylene	120	4.5	88
2	$FeCl_3 \cdot 6H_2O$ (1.2)	xylene	120	6.0	52
3	$BF_3 \cdot OEt_2$ (1.2)	xylene	120	5.0	28
4	anhydrous $FeCl_3$ (1.2)	xylene	120	7.0	27
5	anhydrous $SnCl_4$ (1.2)	xylene	120	4.5	45
6	$SnCl_4 \cdot 5H_2O$ (0.5)	xylene	120	0.5	11[b]
7	$SnCl_4 \cdot 5H_2O$ (1.2)	toluene	110	8.0	58
8	$SnCl_4 \cdot 5H_2O$ (1.2)	benzene	80	40.0	63
9	$SnCl_4 \cdot 5H_2O$ (1.2)	nitromethane	101	10.0	45

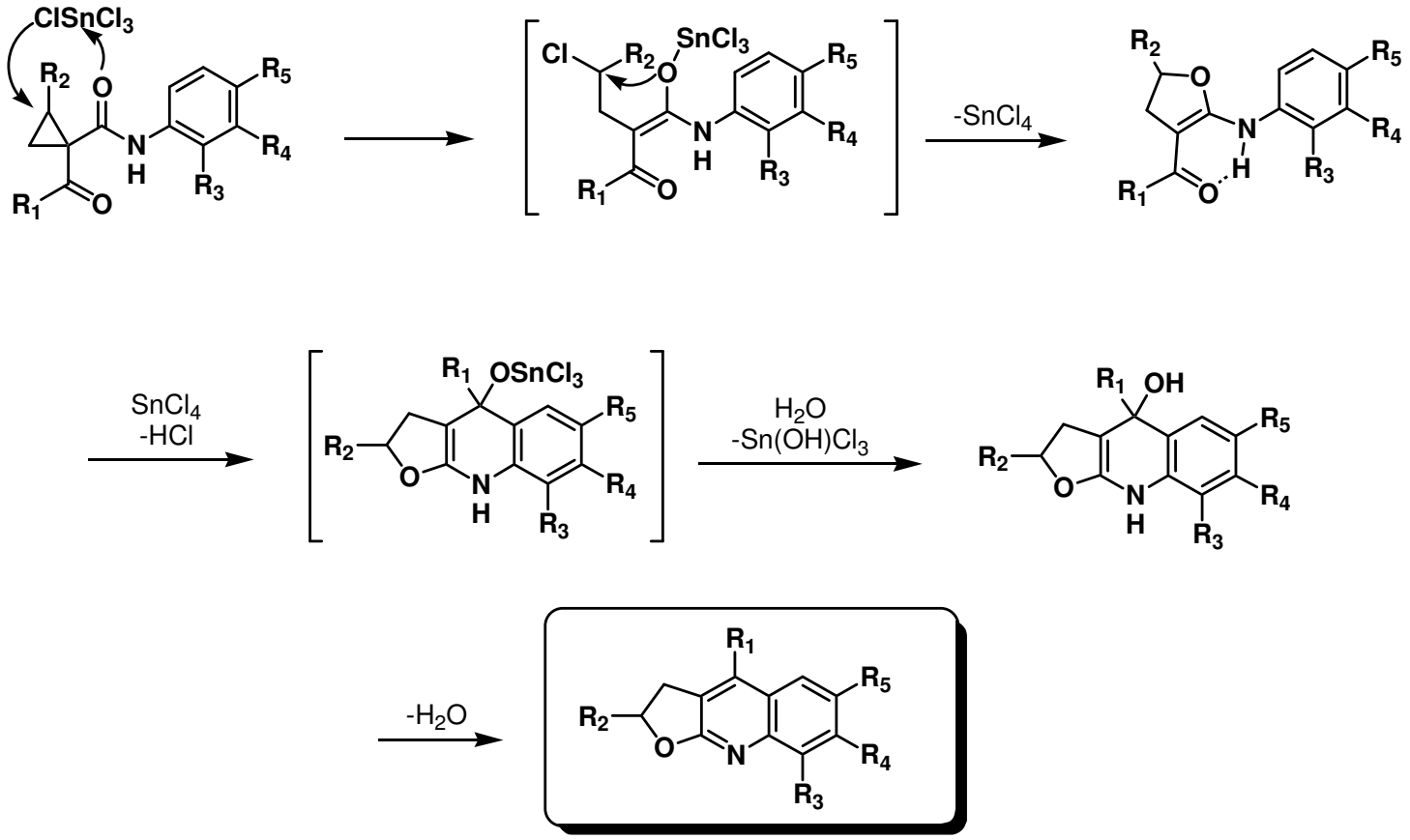
Generality and Scope of the Domino Reaction



Entry	Substrate 1						t [h]	Product	Yield [%][b]
	1	R^1	R^2	R^3	R^4	R^5			
1	**1b**	Me	H	Me	H	H	4.0	**2b**	90
2	**1c**	Me	H	Me	H	Me	5.5	**2c**	87
3	**1d**	Me	H	H	H	H	1.0	**2d**	75
4	**1e**	Me	H	H	H	Cl	0.5	**2e**	57
5	**1f**	Me	H	H	H	Me	1.5	**2f**	86
6	**1g**	Me	H	H	Cl	H	0.5	**2g**	56
7	**1h**	Me	H	H	Me	H	1.3	**2h**	91
8	**1i**	Me	H	H	H	CH_3CO	0.5	**2i**	0
9	**1j**						0.5		68
10	**1k**						0.5		75
11	**1l**	Me	Me	H	H	H	1.5	**2l**	93
12	**1m**	Me	Me	OMe	H	H	5.0	**2m**	85
13	**1n**	*p*-$MeOC_6H_4$	H	H	H	H	0.5	**2n**	45

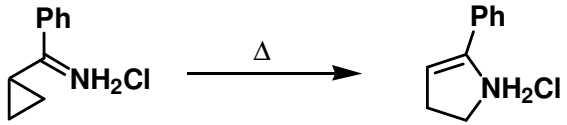
[a] Reactions were carried out with $SnCl_4 \cdot 5\,H_2O$ (1.2 mmol) and **1** (1.0 mmol) in xylene (3 mL) at 120 °C for 0.5–5.5 h. [b] Yield of the isolated product.

Mechanistic Hypothesis for the Construction of *Furo[2,3-b]quinolines*

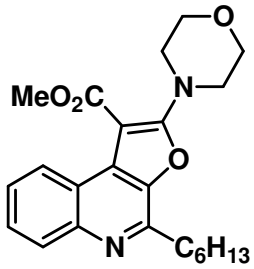


Summary

•Acyl (and ketimine) cyclopropane derivatives possess unique synthetic utility and have garnered interest in the organic community since the late 1920's



•Rapid access to novel heterocyclic structures with various points of diversity provide a cornucopia of compounds with potential biological activity



•Utilizing the inherent reactivity of doubly activated acyl cyclopropanes provides access to various functionalized dihydropyrans and furoquinolines in rapid fashion