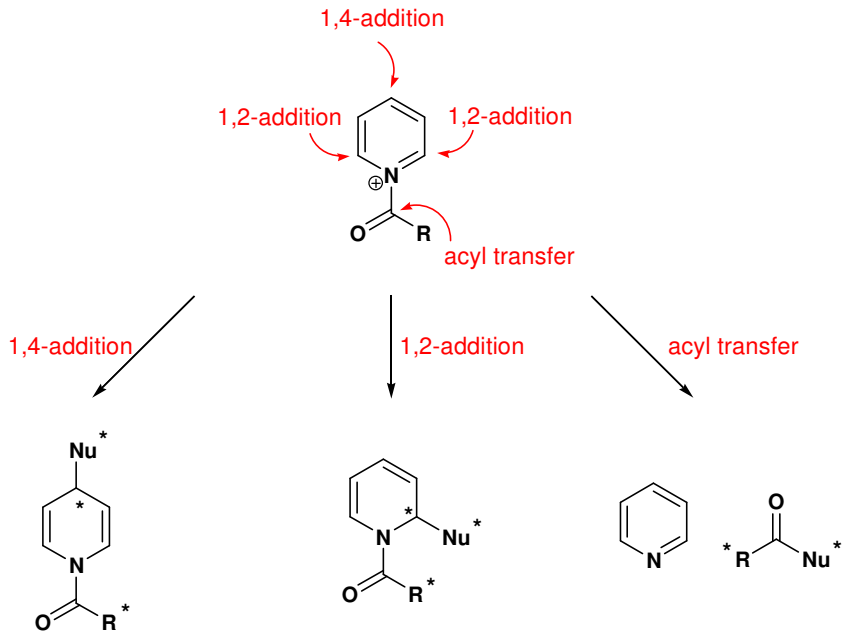
The Chemistry of 1-Acylpyridiniums

D. W. Lin



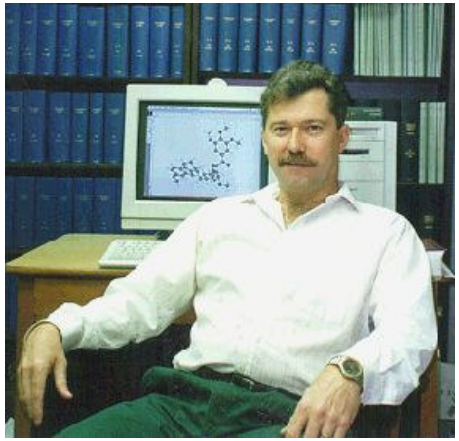
Despite the electron-deficient nature of pyridines, direct nucleophilic addition is difficult without activating the pyridine in some fashion. This review will cover the use of acylating agents to activate the ring -- and the acyl group -- to nucleophilic addition.

Other stratgies for activating the ring (which will not be covered in this review) include N-alkylation, N-fluorination, N-sulfonation, N-oxidation, and N-amination. For an overview of this chemistry, see Joule and Mills' *Heterocyclic Chemistry*, 4th Edition (**2000**), Chapters 4-5.

Notice that N-acylation, subsequent nucleophilic addition, and further functionalization reactions can rapidly produce stereochemically and functionally complex piperidine systems. This review will emphasize asymmetric methods for functionalizing pyridines.

Be sure to review the previous Baran Lab group seminar on a related topic, "Iminium and Pyridinium Photochemistry" (J. Richter, 2005).

A Big Player in The Acylpyridinium Field



Prof. Daniel Comins
North Carolina State University

B.S., SUNY Potsdam, 1972
Ph.D. (Robert Lyle, advisor), University of New Hampshire, 1977
Postdoctoral Associate (A.I. Meyers), Colorado State University, 1977-1979

Reviews on Related Topics

The chemistry of N-alkylpyridiniums is not covered in this seminar. For a representative review, see: J. Bosch, Bennasar, M.-L. *Synlett* **1995**, 587, and references therein.

A review covering catalytic enantioselective methods of addition to imines: T. Vilaivan, W. Banthumnavin, Y. Sritana-Anant. *Curr. Org. Chem.* **2005**, *9*, 1315.

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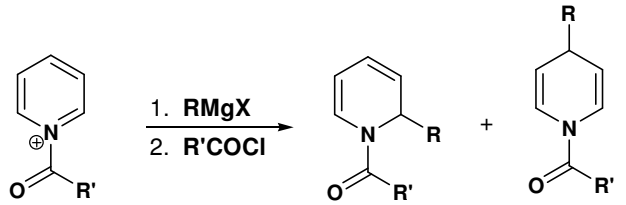
D. W. Lin

ADDITION OF NUCLEOPHILES INTO 1-ACYLPYRIDINIUM SALTS

A. Regioselectivity of Addition

Addition of Grignards into 1-acylpyridinium salts with unsubstituted C2 and C4 positions results in mixtures of C2- and C4-substituted dihydropyridines. 1,2-addition is typically favored, although selectivity is not large. 1,4-addition is favored if either the nucleophile **R** or acyl chloride **R'** is sterically demanding.

Use of organocuprates, however, strongly favors 1,4-addition, as seen below:



No Copper Additive

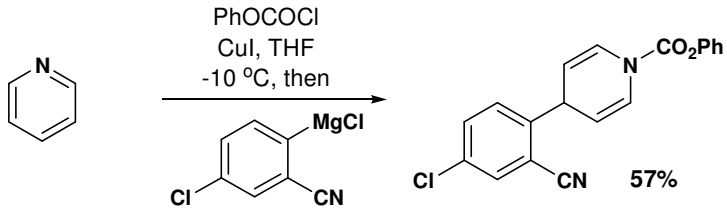
RMgX	acyl chloride (R')	overall yield,[a] %	ratio (3/4)[b]
C_2H_3MgBr	CH_3	76	70:30
C_2H_3MgBr	C_2H_3O	73	64:36
C_2H_3MgBr	$(CH_3)_3C$	73	52:48
C_6H_5MgCl	CH_3	70	93:7
C_6H_5MgCl	C_2H_3O	80	93:7
C_6H_5MgCl	C_6H_5	77	73:27
C_6H_5MgCl	$(CH_3)_3C$	66	52:48
$(CH_3)_2CHMgCl$	CH_3	56	51:49
$(CH_3)_2CHMgCl$	C_2H_3O	82	41:59
$(CH_3)_2CHMgCl$	$(CH_3)_3C$	80	13:87

With 5% CuI

RMgX[a]	acyl chloride (R')	overall yield,[b] %	ratio (3/4)[c]
C_6H_5MgCl	CH_3	65	0:100
C_2H_3MgBr	C_2H_3O	79	5.3:94.7
C_2H_3MgBr	C_6H_5	30	0:100
$(CH_3)_2CHMgCl$	C_2H_3O	62	1.6:98.4

D.L. Comins, A.H. Abdullah. *J. Org. Chem.* **1982**, *47*, 4315.

Process chemists at Merck have applied this method on a process scale:

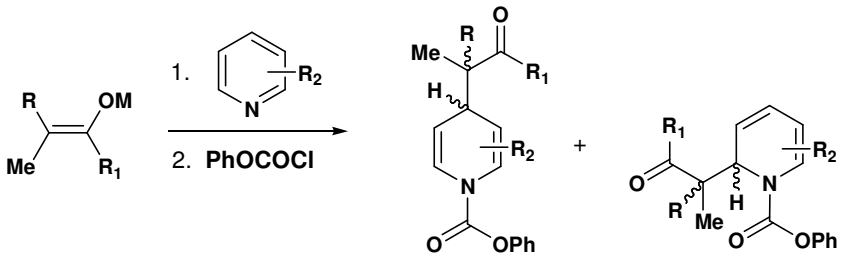


4.1.8. Phenyl 4-(4-chloro-2-cyanophenyl)pyridine-1(4*H*)-carboxylate (9a). General procedure for dihydropyridines. To a −30 °C solution of **2b** (835 g, 3.86 mol) in THF (10 L) was added *i*-PrMgCl (1.71 M in THF, 2.5 L, 4.25 mol) at a rate such that the temperature < −20 °C. Meanwhile, to a −10 °C solution of CuI (36 g, 190 mmol) in THF (10 L) was added pyridine (624 mL, 7.72 mol) and then phenyl chloroformate (532 mL, 4.25 mmol) such that the temperature < 0 °C. To this heterogeneous mixture was added the previously formed Grignard at a rate such that temperature < 0 °C. The resulting solution was aged at 0 °C for 30 min and allowed to warm up to rt. The reaction was then quenched with 10% aqueous NH_4Cl (20 L). EtOAc (20 L) was added and the blue aqueous layer was removed. The organic layer was washed with 10% aqueous NH_4Cl (20 L), 1 N HCl (20 L), and finally an aqueous 20% NaCl solution (20 L). The organic layer was then concentrated, solvent switched to MeOH and crystallized. The slurry was filtered and the filtercake washed with MeOH, yielding an off-white solid (584 g, 43%). Mp 128–130 °C; ^{1}H NMR

800 g scale!

G.N. Boice, et al. *Tet. Lett.* **2004**, *60*, 11367.

Titanium enolates also strongly favor 1,4-addition:



M = Li --> 50:50 (**1:2**)
M = Ti --> 70:30 to 98:2, typically 90:10 (**1:2**)

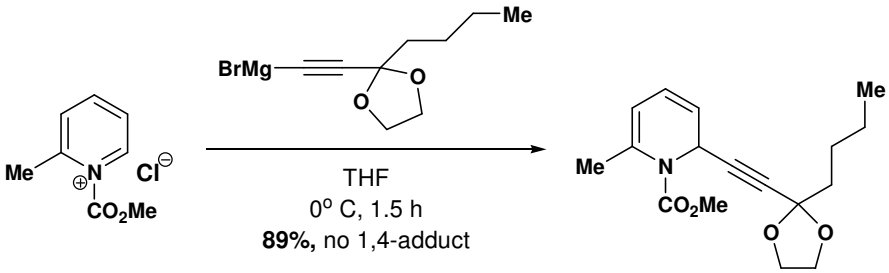
Ester enolates yield somewhat lower regioselectivity (typically 70:30 mixtures of **1:2** at best) than the corresponding ketone enolates.

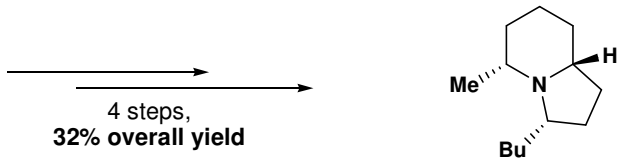
D.L. Comins, J.D. Brown. *Tet. Lett.* **1984**, *25*, 3297.

The Chemistry of 1-Acylpyridiniums

D. W. Lin

Certain nucleophiles - allyltin, allylindium, and alkynyl Grignard reagents - will undergo 1,2-addition regioselectively. For example:



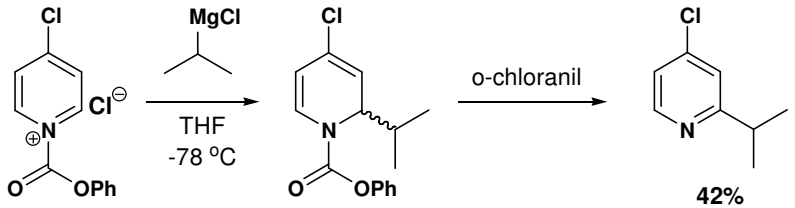


(±)-monomorine I

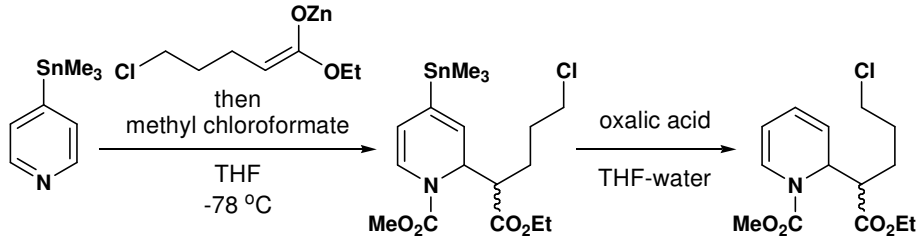
R. Yamaguchi, E. Hata, T. Matsuki, M. Kawanisi. *J. Org. Chem.* **1987**, *52*, 2094.

for 1,2-addition of allylstannanes see: R. Yamaguchi, M. Moriyasu, M. Yoshioka, M. Kawanisi. *J. Org. Chem.* **1985**, *50*, 287; and T.G.M. Dhar, C. Gluchowski. *Tet. Lett.* **1994**, *35*, 989.
for 1,2-addition of allylindium reagents see: T.-P. Loh, P.-L. Lye, R.-B. Wang, K.-Y. Sim. *Tet. Lett.* **2000**, *41*, 7779.

Generally, however, forcing 1,2-addition requires use of blocking groups or substituents at the C4 position.

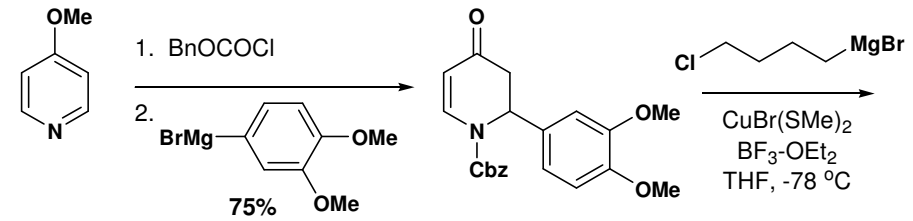


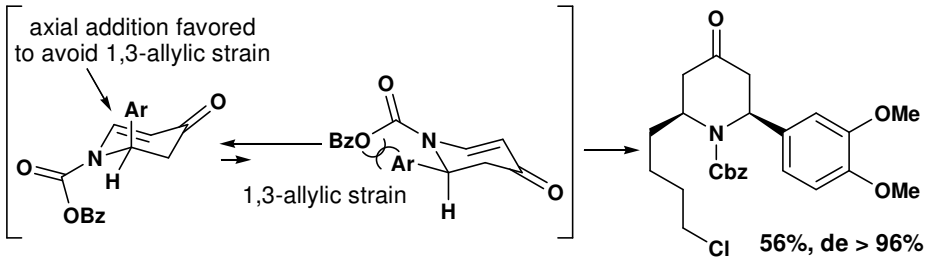
D.L. Comins, N.B. Mantlo. *J. Org. Chem.* **1985**, *50*, 4410.

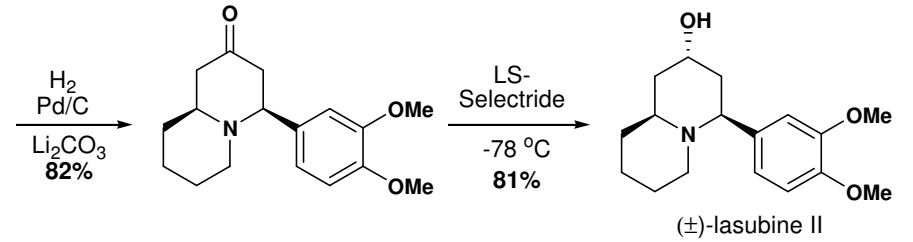


D.L. Comins, J.D. Brown. *Tet. Lett.* **1986**, *27*, 2219.

Comins has employed this blocking method in an elegant synthesis of lasubine II:







(±)-lasubine II

J.D. Brown, M.A. Foley, D.L. Comins. *J. Am. Chem. Soc.* **1988**, *110*, 7445.

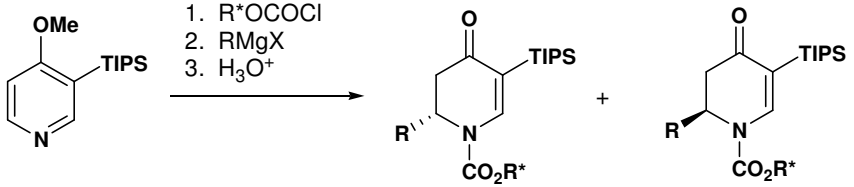
The Chemistry of 1-Acylpyridiniums

D. W. Lin

STRATEGIES FOR ASYMMETRIC 1,2-ADDITION

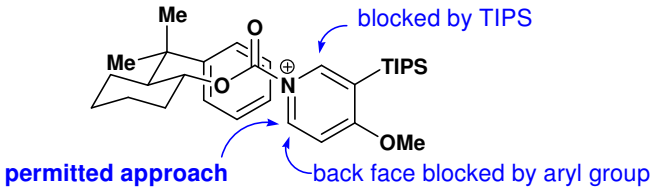
Comins' Chiral Auxiliary for 1,2-Addition

Comins has developed a chiral acylating group which directs the stereoselectivity of 1,2-additions into the pyridinium ring. This group, when employed on a 3-silyl-4-methoxypyridine, permits highly diastereoselective 1,2-additions.



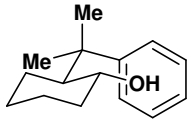
major diastereomer with (-)-auxiliary | **major diastereomer with (+)-auxiliary**

This substrate has been chosen carefully to maximize diastereoselectivity. The bulky TIPS group directs addition to C_6 over C_2, and the C_4-methoxy group blocks C_4 addition. The chiral auxiliary blocks access to one face of the pyridinium salt.

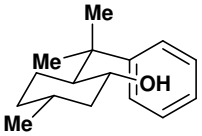


chiral auxiliary	RMgX	yield,[b] %	de[c]
(−)-menthol	PhMgCl	88	50
(−)-8-phenylmenthol	PhMgCl	82	65
(−)-menthol	PhMgCl	87	44
(−)-8-phenylmenthol	PhMgCl	88	94
(−)-8-cyclohexylmenthol	PhMgCl		60
(−)-8-phenylmenthol	*o*-MePhMgCl	81	60
(−)-8-(4-phenoxyphenyl)menthol	*o*-MePhMgCl	78	78
(−)-8-phenylmenthol	*c*-HexMgBr	90	81
(−)-8-(4-phenoxyphenyl)menthol	*c*-HexMgBr	67	90
(−)-8-phenylmenthol	*p*-MeOPhMgBr	77	73
(−)-8-(4-phenoxyphenyl)menthol	*p*-MeOPhMgBr	88	90
(−)-8-phenylmenthol	vinylMgBr	81	85
(−)-8-(4-phenoxyphenyl)menthol	vinylMgBr	80	88
(−)-8-phenylmenthol	*n*-PrMgCl	88	91[d]
(−)-*trans*-2-(α-cumyl)cyclohexanol	*n*-PrMgCl	98	90
(+)-*trans*-2-(α-cumyl)cyclohexanol	PhMgCl	90	92

D.L. Comins, S.P. Joseph, R.R. Goehring. *J. Am. Chem. Soc.* **1994**, *116*, 4719.



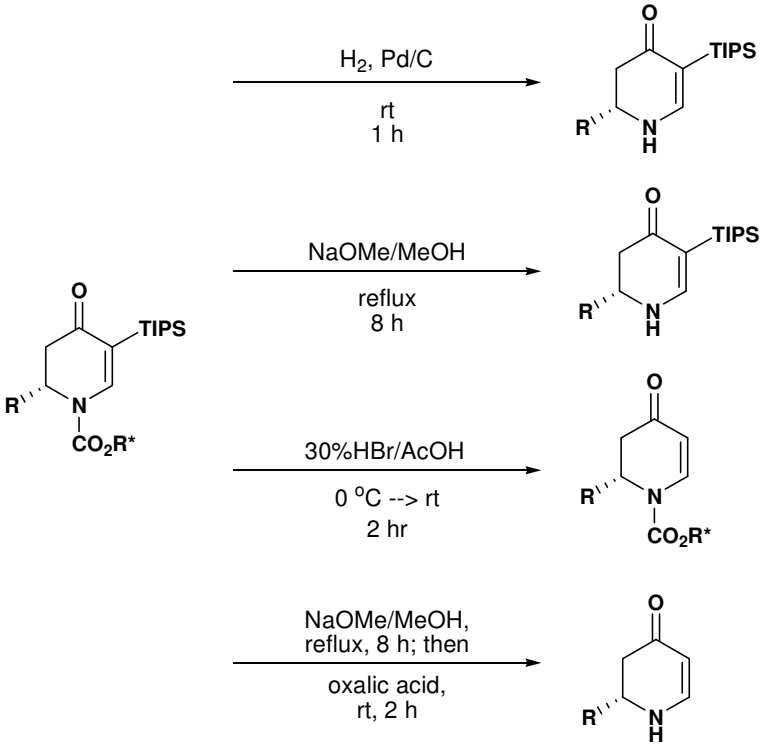
(-)-trans-2-(α-cumyl)cyclohexanol (TCC)
see reference below for route



(-)-8-phenylmenthol
commercially available

for preparing enantiopure auxiliary, see: D.L. Comins, Y.C. Myoung. *J. Org. Chem.* **1990**, *55*, 292.

Deprotection of either the TIPS group or the auxiliary is straightforward:

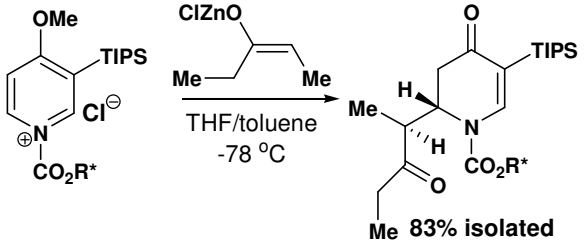


D.L. Comins, S.P. Joseph, R.R. Goehring. *J. Am. Chem. Soc.* **1994**, *116*, 4719.

The Chemistry of 1-Acylpyridiniums

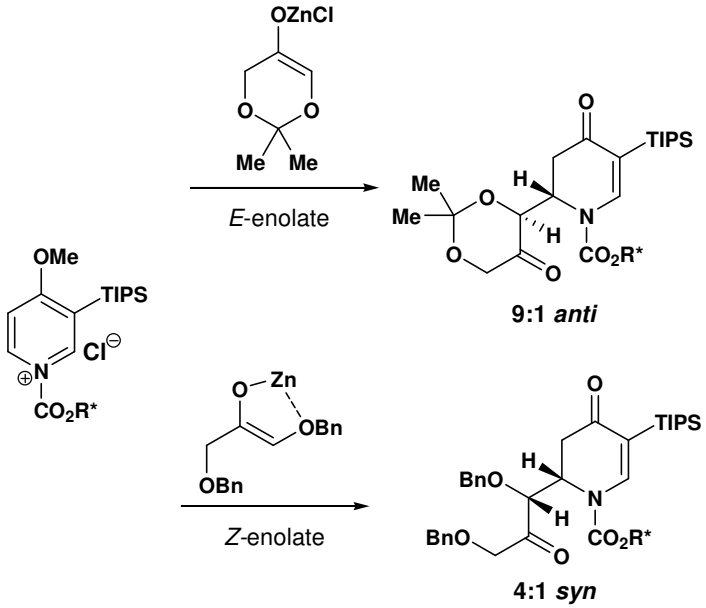
D. W. Lin

This strategy can also be applied to the 1,2-addition of enolates to define two asymmetric centers with *anti*-stereochemistry:



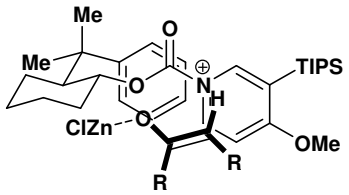
D.L. Comins, J.T. Kuethe, H. Hong, F.J. Lakner. *J. Am. Chem. Soc.* **1999**, *121*, 2651.

Good enolate facial selectivity is observed:



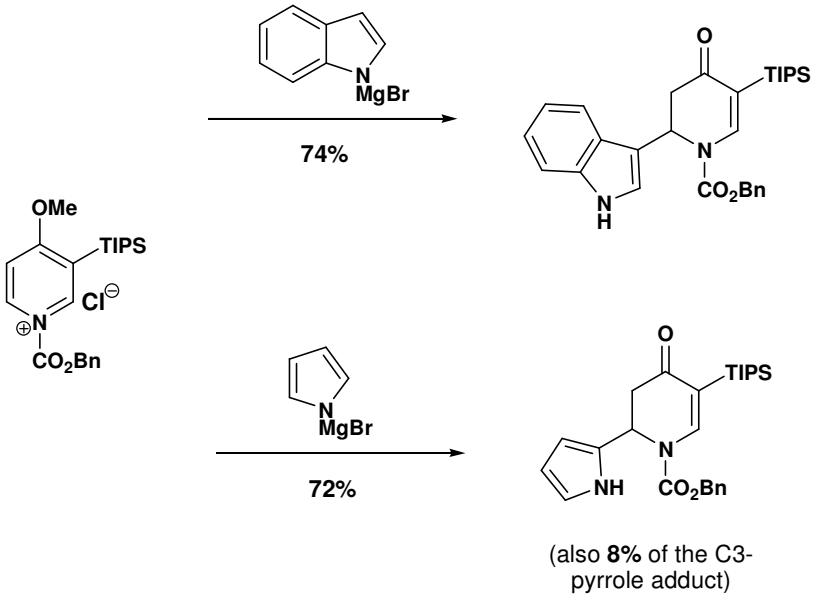
D.L. Comins, J.T. Kuethe, H. Hong, F.J. Lakner. *J. Am. Chem. Soc.* **1999**, *121*, 2651.

The postulated transition state for *E*-enolate addition, yielding *anti*-stereochemistry:



D.L. Comins, J.T. Kuethe, H. Hong, F.J. Lakner. *J. Am. Chem. Soc.* **1999**, *121*, 2651.

Interestingly, the pyrrole and indole anions can be used as nucleophiles as well:



(also **8%** of the C3-pyrrole adduct)

J.T. Kuethe, D.L. Comins. *J. Org. Chem.* **2004**, *69*, 2863.

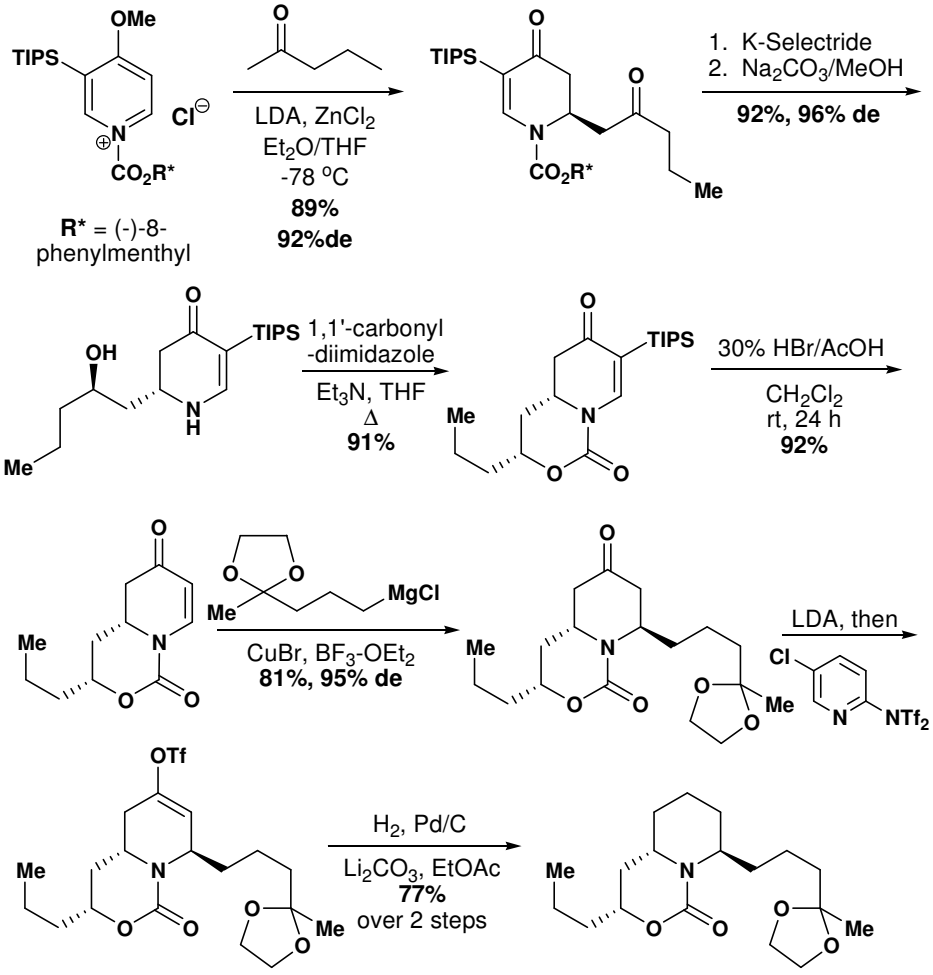
The Chemistry of 1-Acylpyridiniums

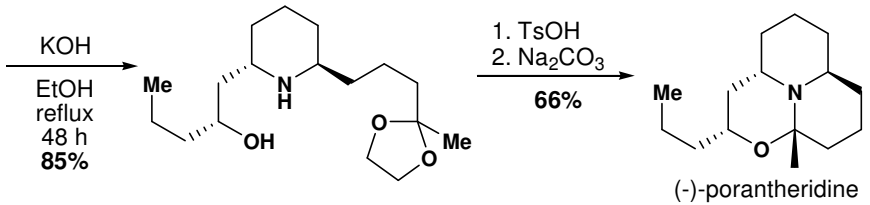
D. W. Lin

Applications to Total Synthesis

Comins and coworkers have applied this chiral auxiliary methodology in a number of elegant, imaginative total syntheses.

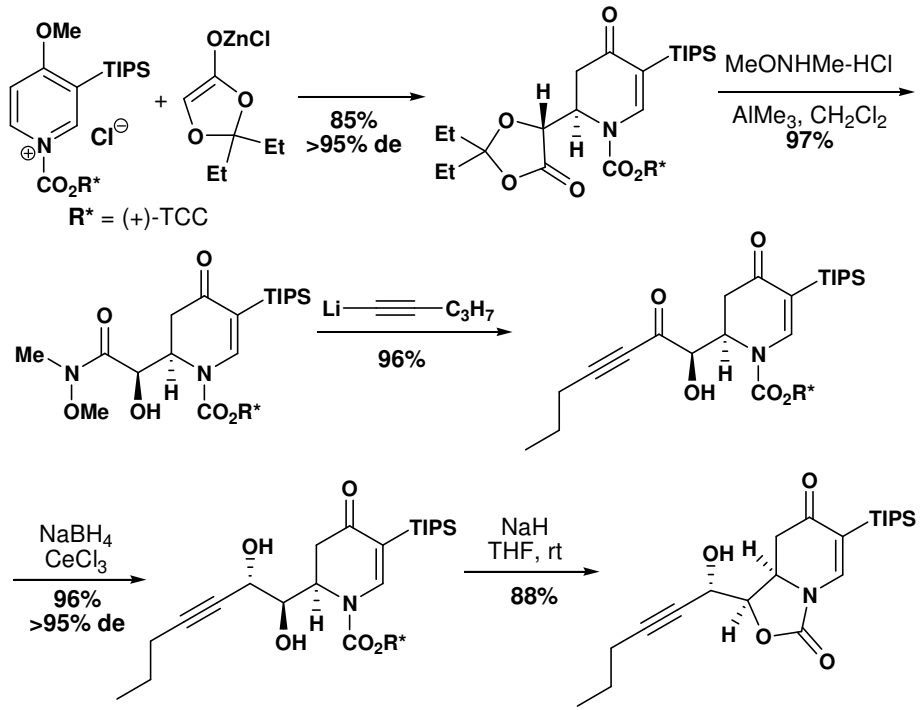
(-)-porantheridine





D.L. Comins, H. Hong. *J. Am. Chem. Soc.* **1993**, *115*, 8851.

(+)-Cannabisativine

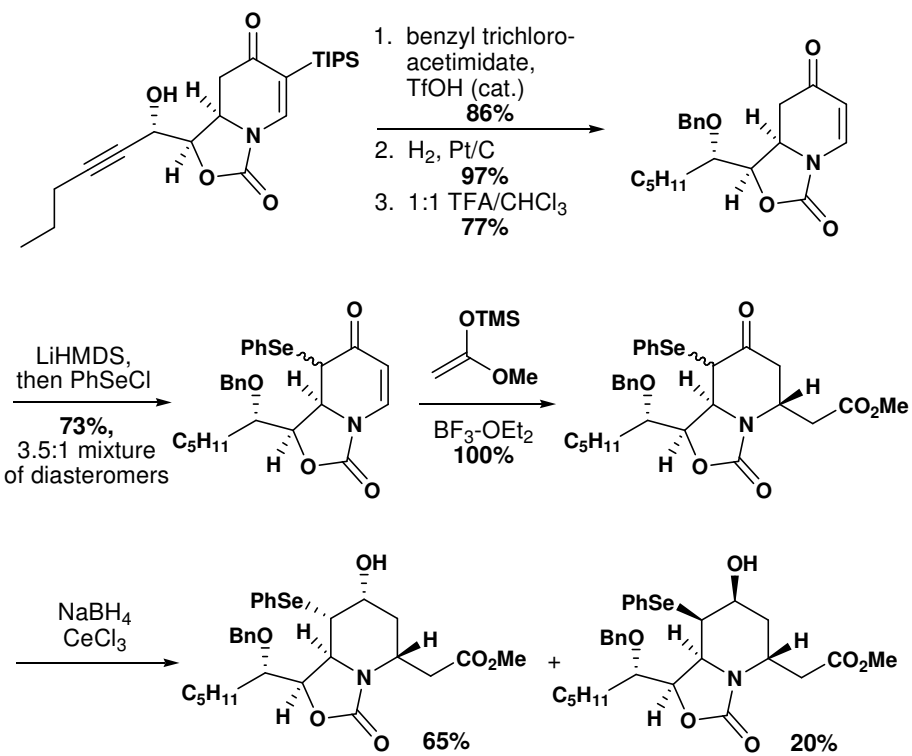


J.T. Kuethe and D.L. Comins. *J. Org. Chem.* **2004**, *69*, 5219.

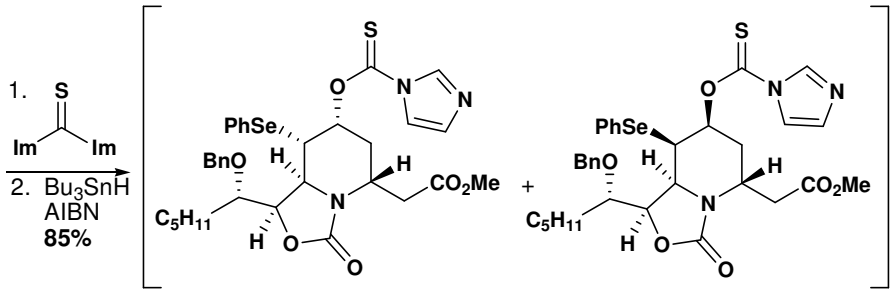
The Chemistry of 1-Acylpyridiniums

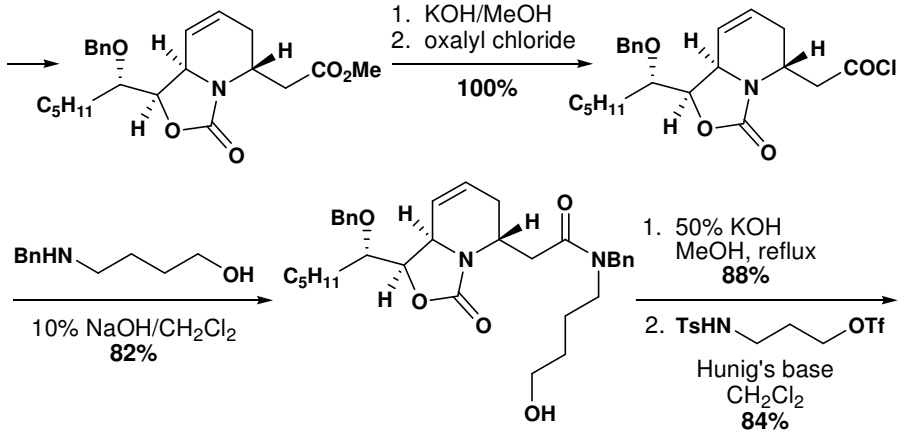
D. W. Lin

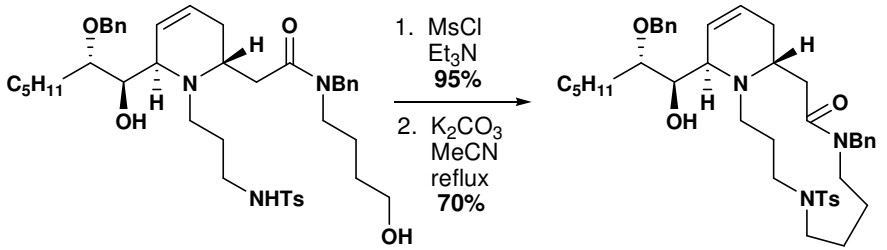
(+)-Cannabisativine (cont'd)

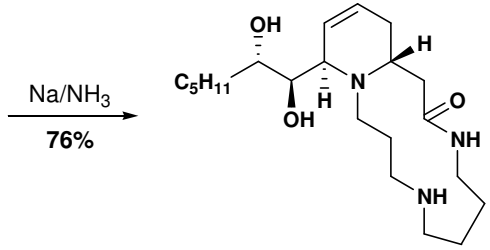


In both diastereomers, hydride addition occurs on the face opposite the bulky SePh group. For the next step, both diastereomers will be carried through separately.









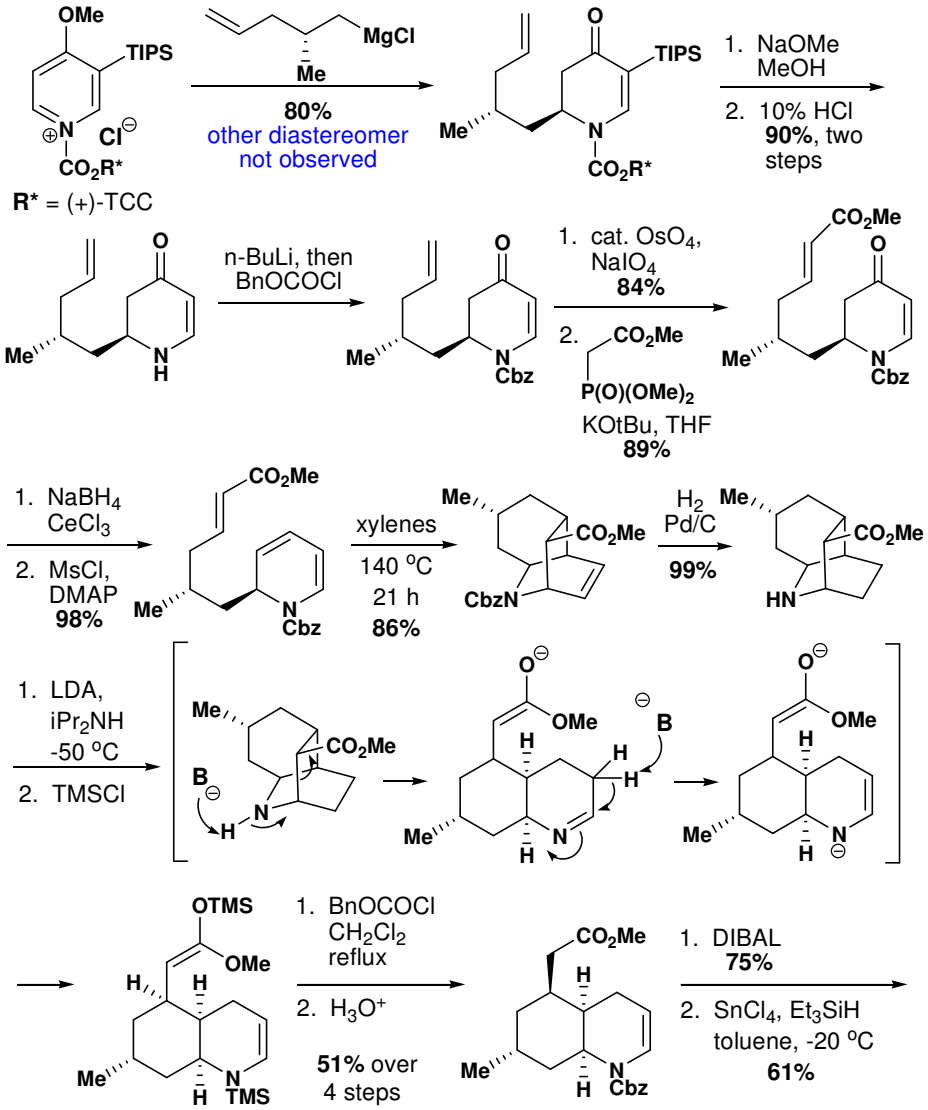
(+)-cannabisativine

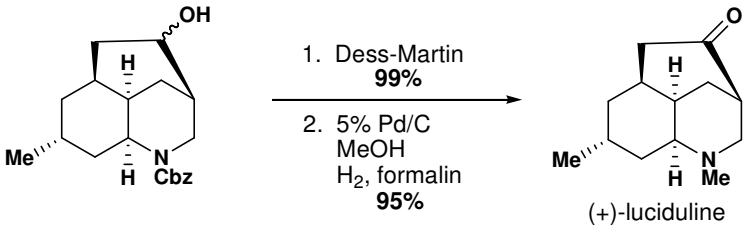
J.T. Kuethe and D.L. Comins. *J. Org. Chem.* **2004**, *69*, 5219.

The Chemistry of 1-Acylpyridiniums

D. W. Lin

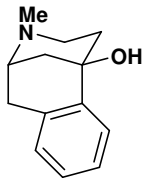
(+)-Luciduline





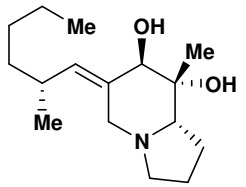
D.L. Comins, C.A. Brooks, R.S. Al-awar, R.R. Goehring. *Org. Lett.* **1999**, *1*, 229.

Comins' group has synthesized a number of other alkaloids using his chiral acylpyridinium methodology, including:



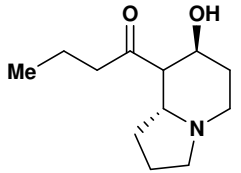
(+)-benzomorphan

D.L. Comins, Y.-m. Zhang, S.P. Joseph. *Org. Lett.* **1999**, *1*, 657.



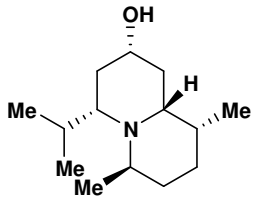
(+)-allopumiliotoxin 267A

D.L. Comins, S. Huang, C.L. McArdle, C.L. Ingalls. *Org. Lett.* **2001**, *3*, 469.



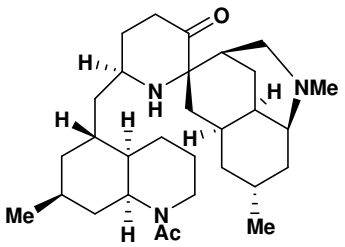
(+)-elaeokanine C

D.L. Comins, H. Hong. *J. Am. Chem. Soc.* **1991**, *113*, 6672.



plumerinine
(incorrect structure)

D.L. Comins, X. Zheng, R.R. Goehring. *Org. Lett.* **2002**, *4*, 1611.



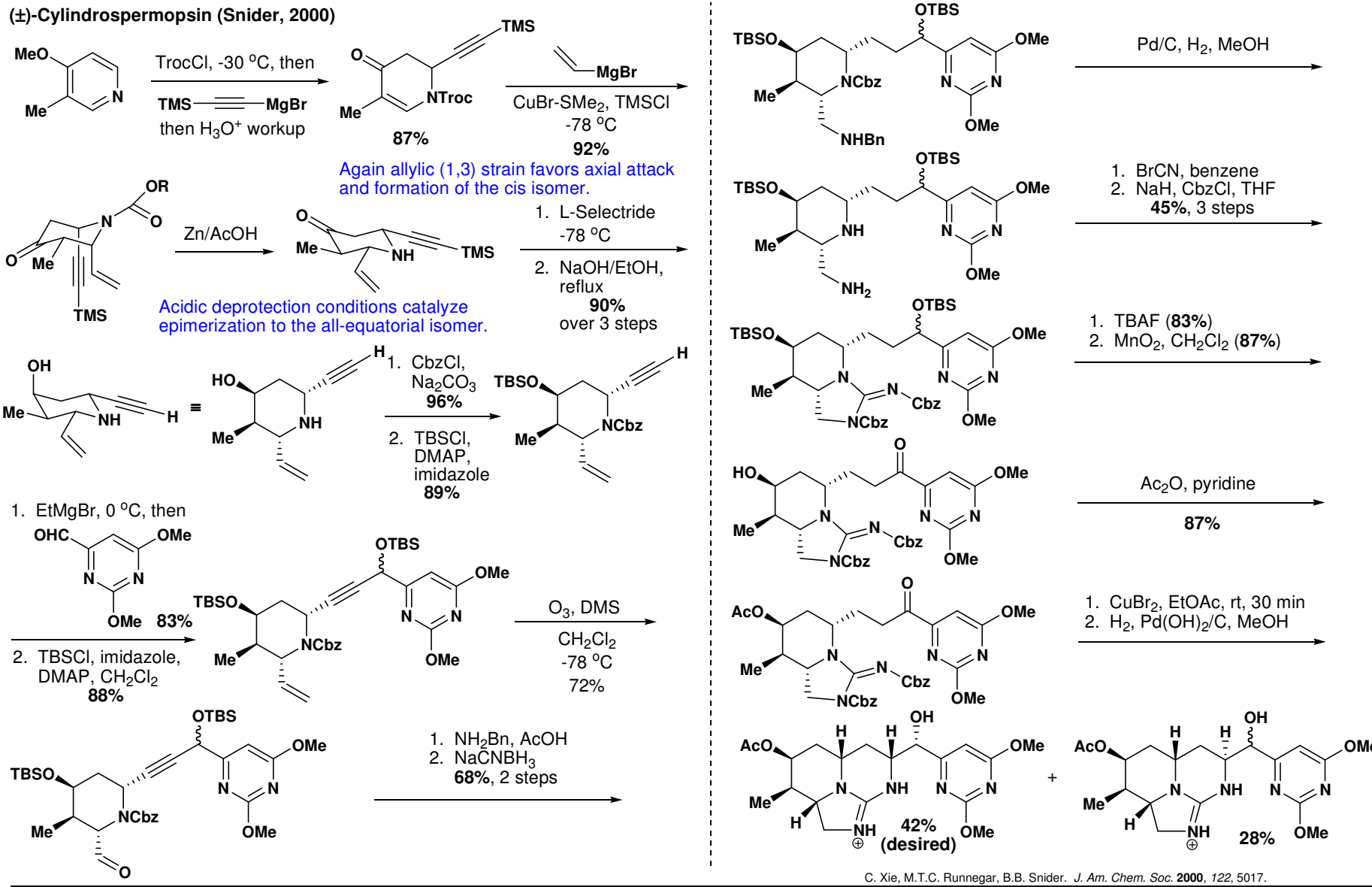
spirolucidine
(model studies)

D.L. Comins, A.L. Williams. *Org. Lett.* **2001**, *3*, 3217.

The Chemistry of 1-Acylpyridiniums

D. W. Lin

(±)-Cylindrospermopsin (Snider, 2000)

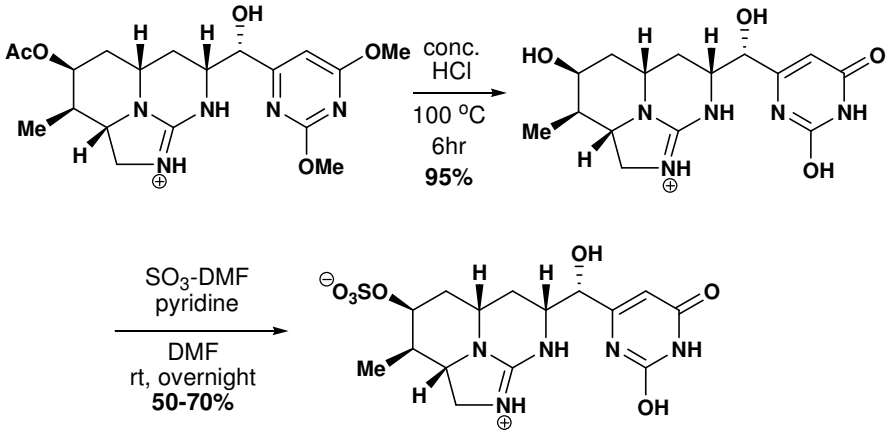


C. Xie, M.T.C. Runnegar, B.B. Snider. *J. Am. Chem. Soc.* **2000**, *122*, 5017.

The Chemistry of 1-Acylpyridiniums

D. W. Lin

(±)-Cylindrospermopsin (Snider, 2000), cont'd.

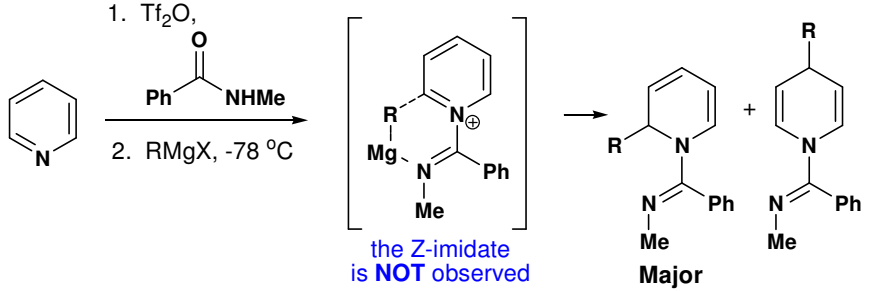


(±)–cylindrospermopsin

C. Xie, M.T.C. Runnegar, B.B. Snider. *J. Am. Chem. Soc.* **2000**, *122*, 5017.

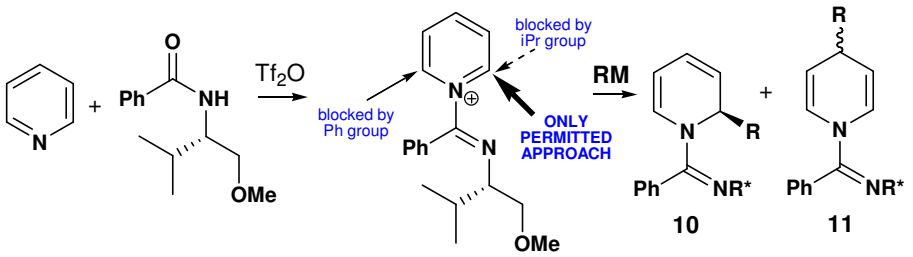
Charette's Chiral Auxiliary for 1,2-Addition

Andre Charette and coworkers at the Universite de Montreal have developed a new chiral auxiliary which can direct enantioselective addition to unsubstituted pyridinium rings. This relies on an *E*-imidate species where the nitrogen directs the addition of organometallics to the C2 position with high regioselectivity:



Treatment of the dihydropyridine with DDQ in THF at room temperature will regenerate the aromatic pyridine, now with a C2 substituent.

Charette also developed a chiral version of the imidate, based on valinol, which exhibits robust regio- and diastereoselectivity.



RM	10/11[a]	d.r.[a]	yield (%)
MeMgBr	>95/5	>95/5	77
EtMgBr	75/25	>95/5	79[b]
Et_2Zn	>95/5	>95/5	73[c]
PhMgBr	90/10	>95/5	74
PhMgBr[c,d]	>95/5	>95/5	89
2-FurylMgBr	>95/5	>95/5	68
1-HexynylMgBr	>95/5	>95/5	65

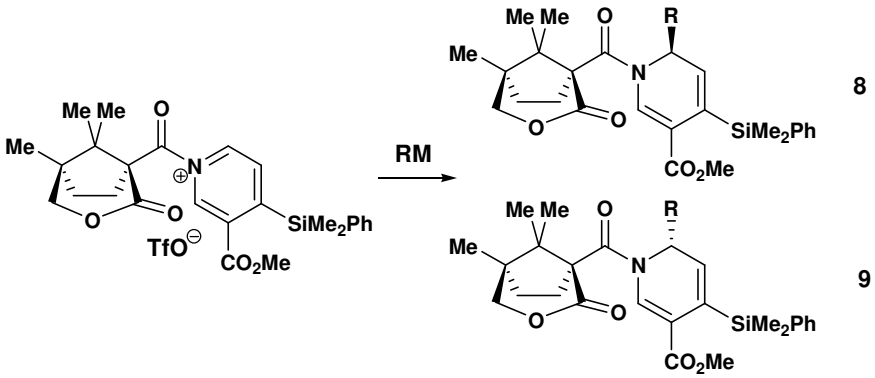
A.B. Charette, M. Grenon, A. Lemire, M. Pourashraf, J. Martel. *J. Am. Chem. Soc.* **2001**, *123*, 11829.

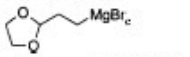
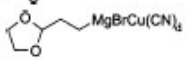
The Chemistry of 1-Acylpyridiniums

D. W. Lin

Wanner's Chiral Auxiliary for 1,2-Addition

Klaus Wanner has developed an alternative chiral auxiliary for diastereoselective additions to acylpyridiniums. He has found that using silyl triflate additives allow access to electron-deficient pyridines, although the diastereoselectivities and yields are more modest in these cases than those explored by Comins and Charette.



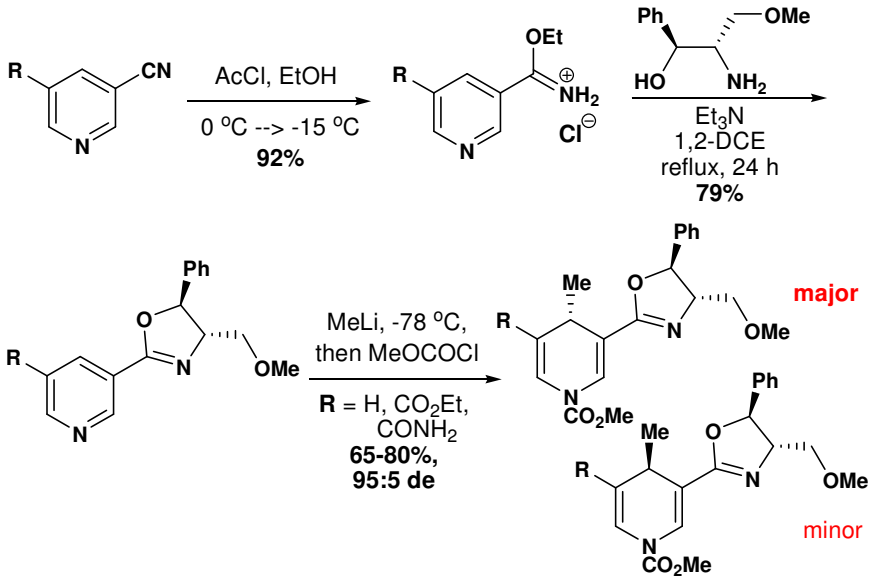
Reagent	Additive	Time (h)[a]	Yield (%) 8+9	d.s.[b] 8/9
PhMgBr[c]	–	1	0	–
PhMgBr[c]	Me_3SiOTf	1	27	24.0/76.0
PhCu(CN)MgBr[d]	Me_3SiOTf	3	47	50.5/49.5
	Me_3SiOTf	3	41	87.2/12.8
	Me_3SiOTf	3	62	65.2/34.8

C.E. Hoesl, M. Maurus, J. Pabel, K. Polborn, K. Th. Wanner. *Tet.* **2002**, *58*, 6757.

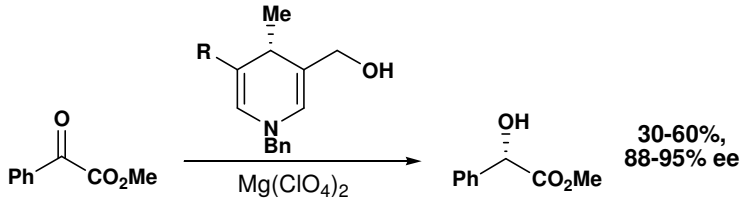
STRATEGIES FOR ASYMMETRIC 1,4-ADDITION

All strategies reported to date for asymmetric 1,4-addition also involve use of chiral auxiliaries, with auxiliaries installed at C3 to direct diastereoselective addition to C4.

Meyers' Chiral Auxiliary



Intriguingly, Meyers elaborates this enantiopure dihydropyridine into a mimic of the biological reductant NADH that enantioselectively reduces methyl mandelate:



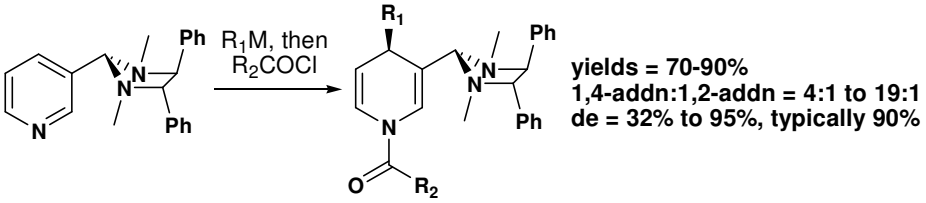
A.I. Meyers, T. Oppenlaender. *J. Am. Chem. Soc.* **1986**, *108*, 1989.

Asymmetric reductions with chiral dihydropyridines are beyond the scope of this review. Interested readers should consult the following for an introduction to the field: V.A. Burgess, S.G. Davies, R.T. Skerlj. *Tet. Asymm.* **1991**, *2*, 299.

The Chemistry of 1-Acylpyridiniums

D. W. Lin

Mangeney and coworkers have constructed a similar auxiliary with the C3 aldehyde:

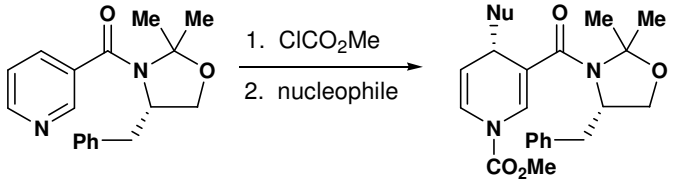


yields = 70-90%
1,4-addn:1,2-addn = 4:1 to 19:1
de = 32% to 95%, typically 90%

P. Mangeney, et al. *J. Org. Chem.* **1994**, *59*, 1877.

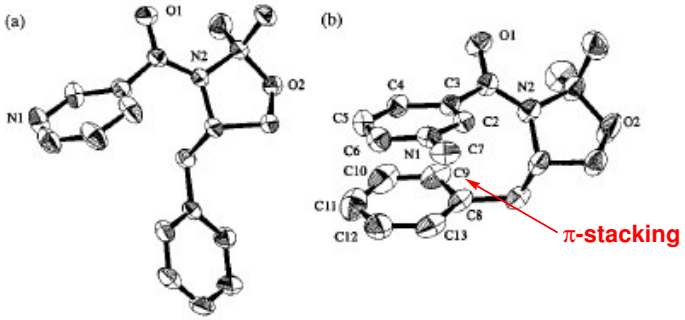
Yamada's Chiral Auxiliaries

Shinji Yamada has developed two different chiral auxiliaries which achieve high diastereoselectivity. One operates via an unusual π-cation interaction to shield one face of the pyridine from nucleophilic attack:



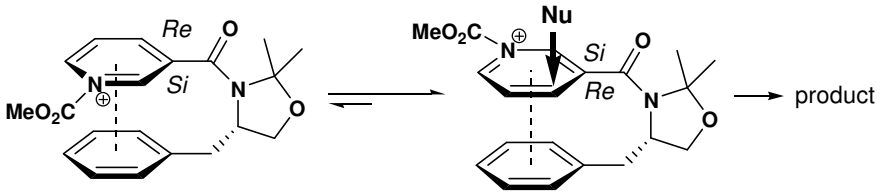
yields = 56-90%, typically 70%
1,4-addn:1,2-addn = ~9:1
de > 99%

Acylation of the pyridine induces π-stacking, due to a π-cation interaction between the benzyl ring and the pyridinium, as seen in X-ray crystal structures:



unacylated pyridine pyridinium salt (N-methyl)

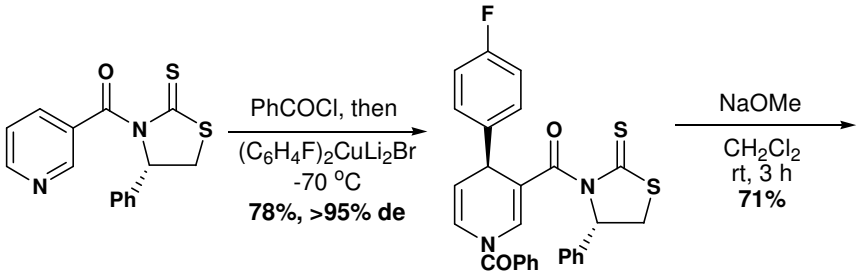
The geometry of the chiral auxiliary is such that one face of the pyridine ring interacts more strongly with with benzyl ring, resulting in a more stable π-stacking intermediate which is then attacked by a nucleophile from the opposite face:

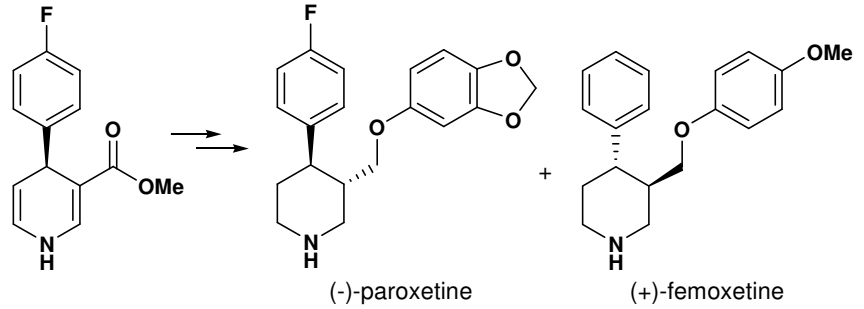


2.1 kcal/mol more stable
by ab initio calculations

S. Yamada, C. Morita. *J. Am. Chem. Soc.* **2002**, *124*, 8184.

Yamada has applied a similar chiral auxiliary to a formal synthesis of the serotonin reuptake inhibitors (-)-paroxetine and (+)-femoxetine.





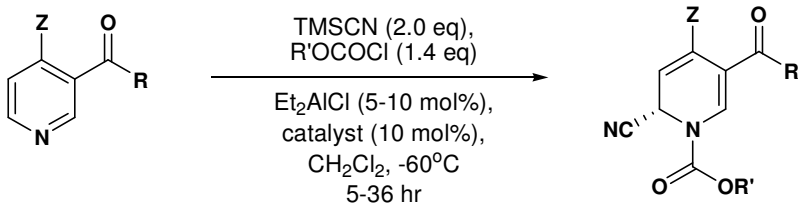
S. Yamada, I. Jahan. *Tet. Lett.* **2005**, *46*, 8673.

The Chemistry of 1-Acylpyridiniums

D. W. Lin

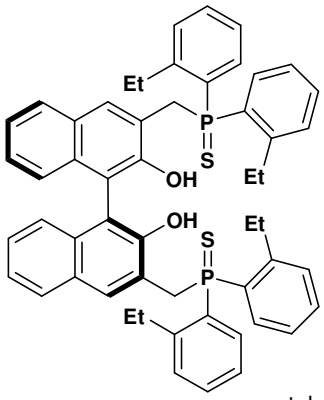
Shibasaki's Chiral Catalyst

Shibasaki and coworkers have developed an aluminum-based catalyst with BINOL-like chiral ligands for the enantioselective 1,2-addition of cyano groups to quinolines, isoquinolines, and pyridines.

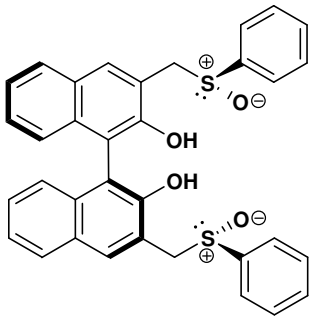


substrate	ligand	R′ (R′OCOCl)	product	yield (%)	ee (%)
7:R = NMe_2, Z = H	6	Me	**8b**	98	91[d]
7:R = NMe_2, Z = H	6	Fm[c]	**8c**	89	93
10:R = N^iPr_2, Z = H	6	Fm[c]	**11a**	98	96
10:R = N^iPr_2, Z = H	6	neopentyl	**11b**	98	93
12:R = OMe, Z = H	6	Fm[c]	**13**	85 (42)[e]	57 (>99)[e]
14:R = N^iPr_2, Z = Cl	3	neopentyl	**15**	92	91
16:R = N^iPr_2, Z = Br	3	neopentyl	**17**	89	86

E. Ichikawa, et al. *J. Am. Chem. Soc.* **2004**, *126*, 11808.

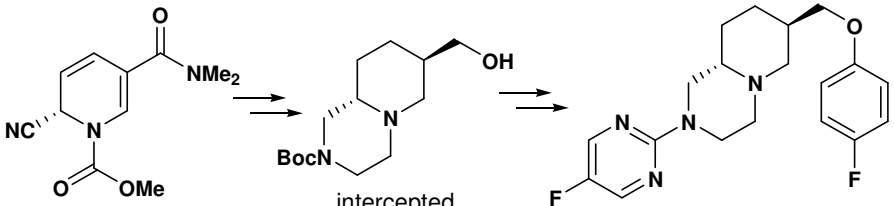


catalyst **3**



catalyst **6**

Shibasaki has elaborated one of these substrates asymmetrically into CP-293,019:



CP-293,019

Shibasaki's group has also applied this method to quinolines and isoquinolines, which are unfortunately beyond the scope of this review. Interested readers may find a discussion of Shibasaki's work with these systems here: M. Takamura, et al, *J. Am. Chem. Soc.* **2000**, *122*, 6327; K. Funabashi, et al., *J. Am. Chem. Soc.* **2001**, *123*, 10784; M. Takamura, et al., *J. Am. Chem. Soc.* **2001**, *123*, 6801.

Interested readers may also find a recent report from Eric Jacobsen's laboratory describing another catalyst for enantioselective additions into isoquinolines: M.S. Taylor, N. Tokunaga, E.N. Jacobsen. *Angew. Chem. Intl. Ed. Eng.* **2005**, *44*, 6700.

The Chemistry of 1-Acylpyridiniums

D. W. Lin

ACTIVATION OF ACYL GROUPS BY PYRIDINE SPECIES

Pyridines, of course, are excellent activating agents for nucleophilic addition into acyl groups, particularly the venerable catalysts 4-(dimethylamino)pyridine (DMAP) and 4-pyrrolidinopyridine (4-PPY). Their utility in organic synthesis has already been detailed in a number of comprehensive reviews and will not be discussed here.

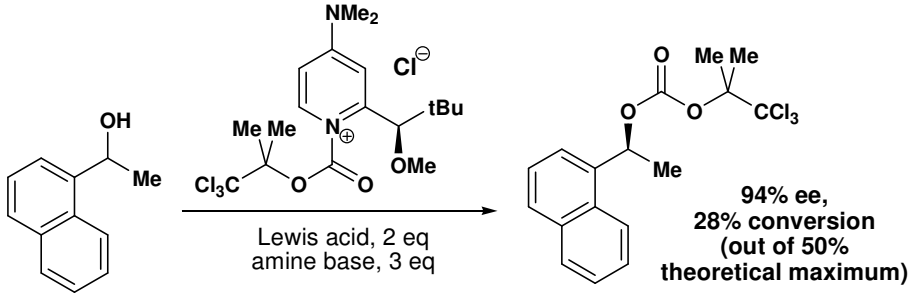
For representative reviews of DMAP and 4-PPY chemistry, see:

R. Murugan, E.F.V. Scriven. *Aldrichimica Acta* **2003**, *36* (1), 21.
D.J. Berry, et al. *ARKIVOC* **2001** (i), 201, or at http://www.arkat-usa.org/ark/journal/ 2001/I01_General/401/review.pdf
U. Ragnarsson, L. Grehn. *Acc. Chem. Res.* **1998**, *31*, 494.

In recent years there has been a growing interest in developing chiral pyridine analogs of DMAP and 4-PPY for enantioselective transformations. A few of these transformations are discussed below.

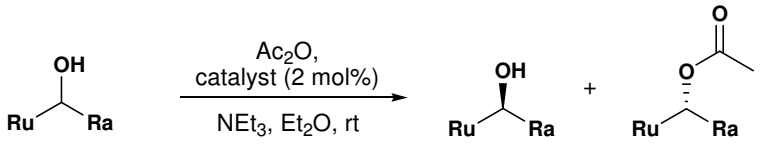
Nonenzymatic Kinetic Resolution of Racemic Secondary Alcohols

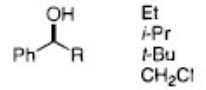
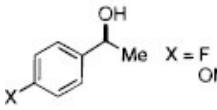
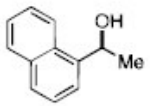
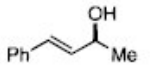
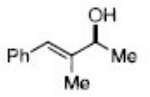
A number of groups have developed pyridine-based catalysts for the kinetic resolution of racemic secondary alcohols. Perhaps the first truly successful strategy, the first to match the enantioselectivities of the esterases, was a stoichiometric acylpyridinium species developed by Vedejs and Chen:

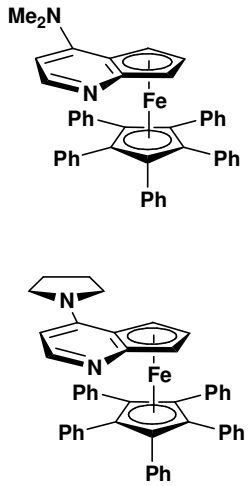


E. Vedejs, X. Chen. *J. Am. Chem. Soc.* **1996**, *118*, 1809.

Greg Fu and colleagues took this work a step further, deploying his planar chiral pyridine catalysts in the kinetic resolution of alcohols and amines, to excellent effect:



unreacted alcohol, major enantiomer		% ee of unreacted alcohol (% conversion)	s[a] (selectivity)
	R = Me	95.2 (62)	14
	Et	98.8 (62)	20
	i-Pr	97.7 (55)	36
	t-Bu	92.2 (51)	52
	CH_2Cl	98.9 (69)	12
	X = F	99.2 (64)	18
	OMe	94.5 (60)	15
		99.7 (63)	22
		99.1 (67)	14
		99.0 (61)	22

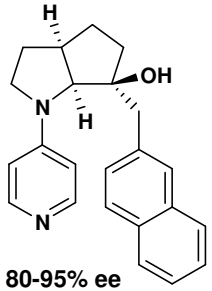


Fu's chiral planar catalysts

J.C. Ruble, H.A. Latham, G.C. Fu. *J. Am. Chem. Soc.* **1997**, *119*, 1492 (*sec*-alcohols);
B. Tao, et al. *J. Am. Chem. Soc.* **1999**, *121*, 5091 (propargylic alcohols);
S. Arai, S. Bellemin-Laponnaz, G.C. Fu. *Angew. Chem. Intl. Ed. Eng.* **2001**, *40*, 234 (amines).

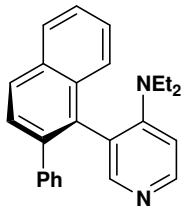
Fu has demonstrated the enantioselective powers of these catalysts in a number of contexts. For reviews and other references, consult his two recent accounts of his research: *Acc. Chem. Res.* **2000**, *33*, 412; *Acc. Chem. Res.* **2004**, *37*, 542.

Other catalysts have been developed in recent years, with variable results and enantioselectivities:



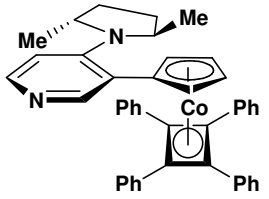
80-95% ee

T. Kawabata, et al. *J. Am. Chem. Soc.* **1997**, *119*, 3169.



30-85% ee

A.C. Spivey, et al. *J. Chem. Soc. Perkin Trans. 1* **2001,** 1785.



75% ee

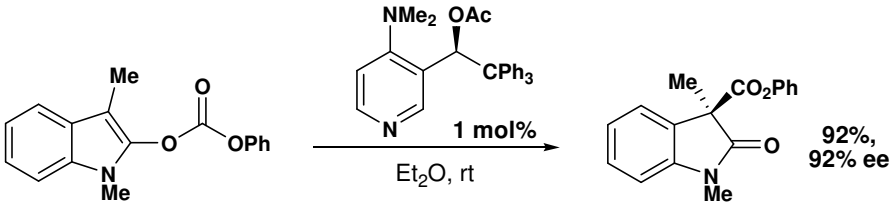
H.V. Nguyen, D.C.D. Butler, C.J. Richards. *Org. Lett.* **2006**, *8*, 769.

The Chemistry of 1-Acylpyridiniums

D. W. Lin

C-Acylation and Asymmetric Synthesis of Quaternary Centers

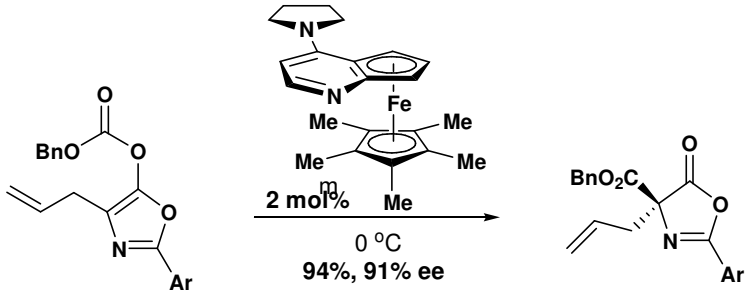
Several groups have exploited activated acylpyridiniums for use in forming new quaternary centers asymmetrically. Vedejs and coworkers have extended their pyridine catalysts in such a way with oxindole substrates:



S.A. Shaw, P. Aleman, E. Vedejs. *J. Am. Chem. Soc.* **2003**, *125*, 13368.

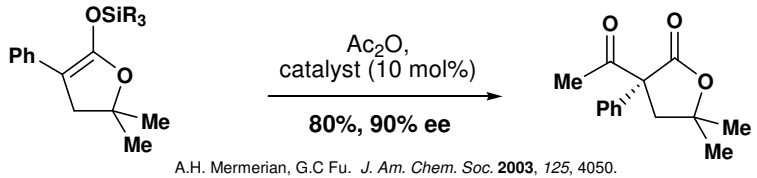
Fu's Asymmetric Method for 1,3-Dicarbonyl Compounds

Fu and coworkers have also applied his planar chiral pyridine catalysts to a bewildering array of reactions, based on addition of the pyridine catalyst into either a ketene or an acyl ester or anhydride.



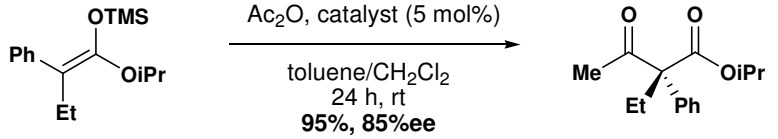
J.C. Ruble, G.C. Fu. *J. Am. Chem. Soc.* **1998**, *120*, 11532.

Fu has also found this catalyst useful for *intermolecular* couplings of acyl groups and silyl enol ethers to produce 1,3-dicarbonyl compounds.



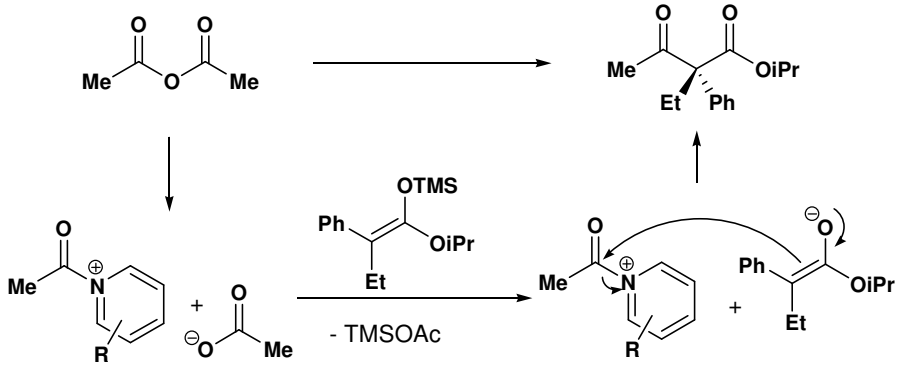
A.H. Mermerian, G.C Fu. *J. Am. Chem. Soc.* **2003**, *125*, 4050.

This also works on acyclic enol ether substrates:



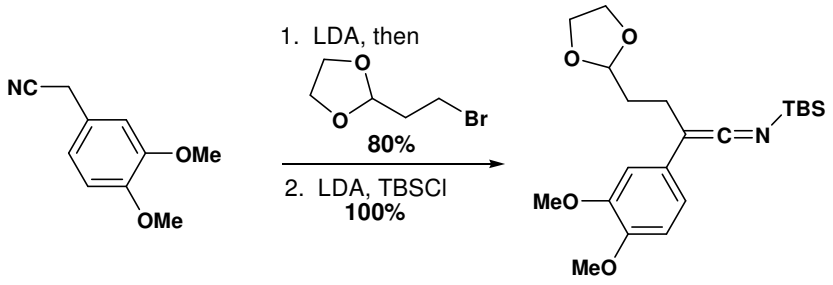
A.H. Mermerian, G.C. Fu. *J. Am. Chem. Soc.* **2005**, *127*, 5604.

The mechanism proceeds through an N-acetylpyridinium intermediate which is then attacked by the unmasked enolate to form the 1,3-dicarbonyl compound.



A.H. Mermerian, G.C Fu. *J. Am. Chem. Soc.* **2003**, *125*, 4050.

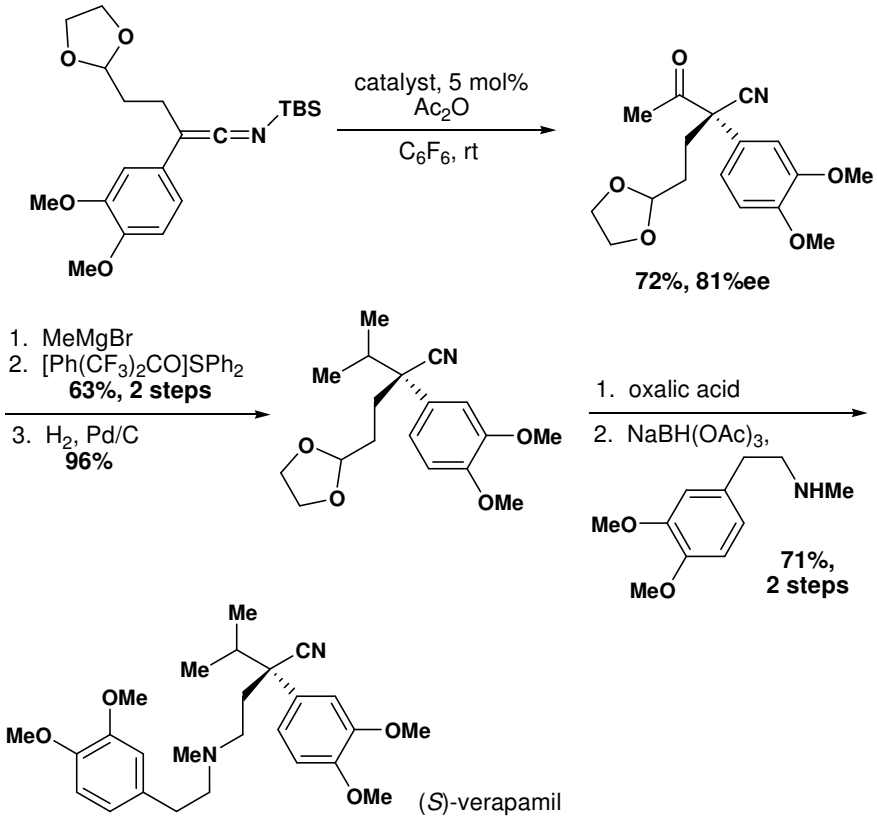
Fu has demonstrated that silyl ketene imines are also are substrates of this reaction, as seen in a brief enantioselective total synthesis of the drug verapamil:



A.H. Mermerian, G.C. Fu. *Angew. Chem. Intl. Ed. Eng.* **2005**, *44*, 949.

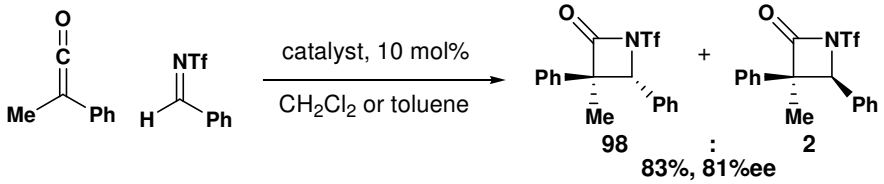
The Chemistry of 1-Acylpyridiniums

D. W. Lin

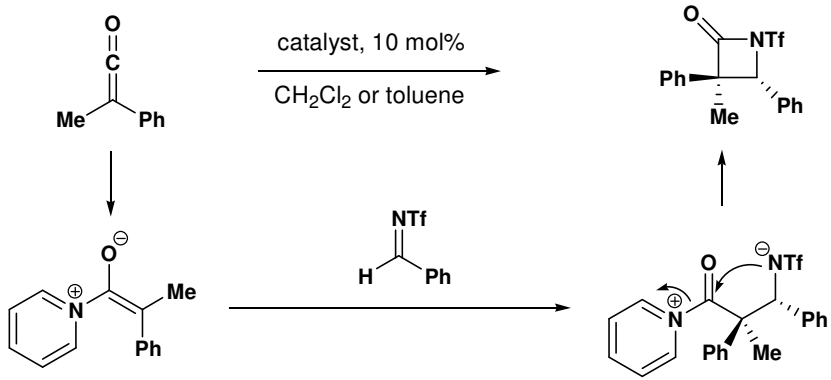


A.H. Mermerian, G.C. Fu. *Angew. Chem. Intl. Ed. Eng.* **2005**, *44*, 949.

Fu's pyridine catalyst will also induce the following transformation of ketenes:

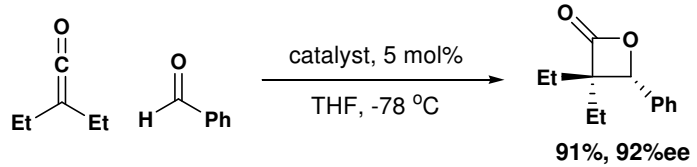


The mechanism apparently proceeds through an N-acylpyridinium zwitterion:



E.C. Lee, et al. *J. Am. Chem. Soc.* **2005**, *127*, 11586.

This method has also been extended to aldehydes:



J.E. Wilson, G.C. Fu. *Angew. Chem. Intl. Ed.* **2004**, *43*, 6358.