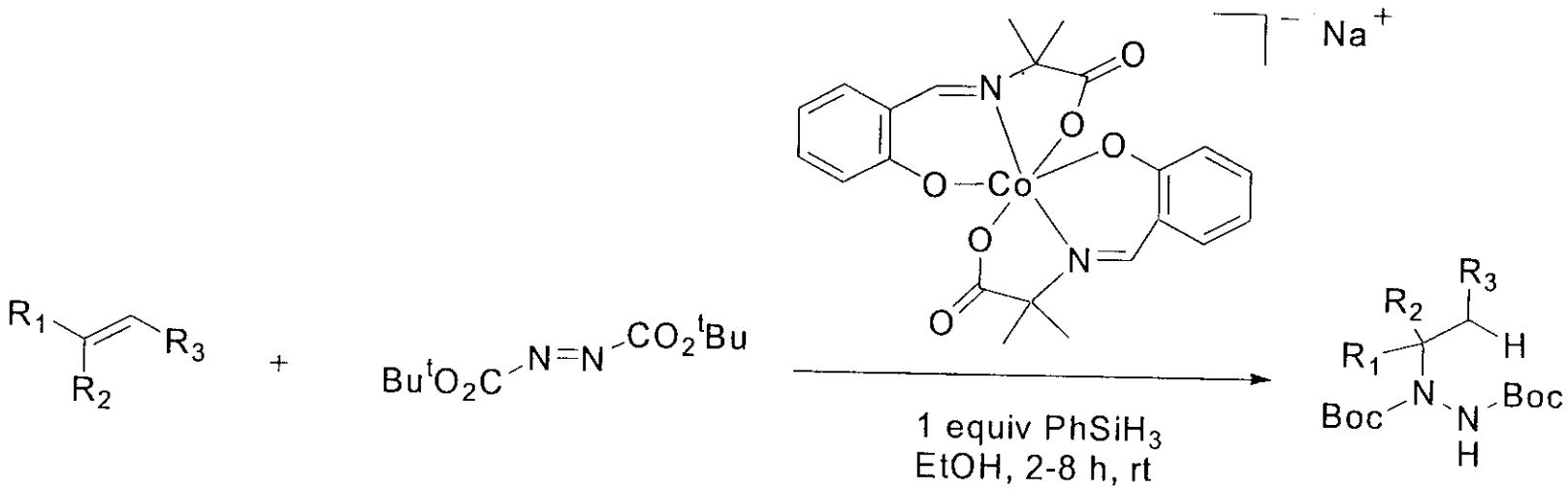
Convenient Synthesis of Alkylhydrazides by the Cobalt-Catalyzed Hydrohyrdazination Reaction of Olefins and Azodicarboxylates

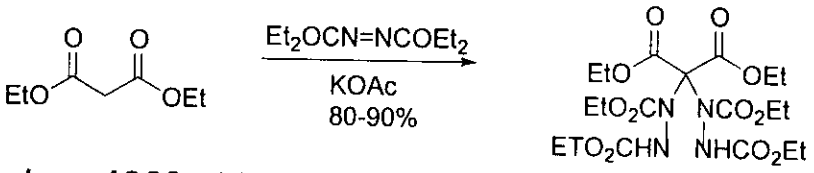
Carreira, E.M.; Waser, J. *J. Am. Chem. Soc.* **2004** ASAP



Current Literature
April 24, 2004
James Mignone

Introduction

First documented example of this process was in 1924



Evans, D.A.; et.al. *Tetrahedron.* **1988**, *44*, 5525

Although the electrophilic reactivity of azodicarboxylate esters has been widely recognized, its application in organic synthesis has remained relatively undeveloped before 1986.

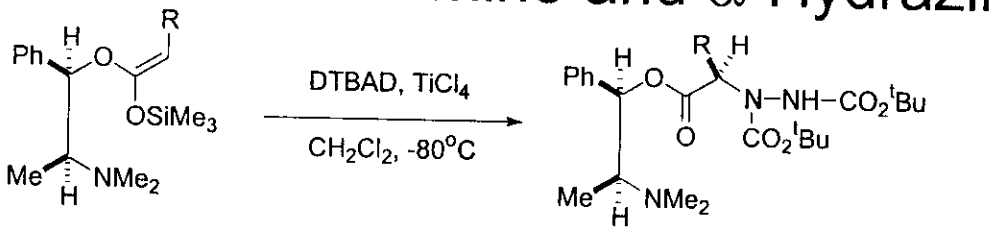
Many groups realized that azodicarboxylates were (+)NH_2 synthons which give rise to α-hydrazino acids and α-amino acids (natural, unnatural and rare)

- displacement reaction of alkyl halides and hydrazides
- nuc. addition to hydrazones or azodicarboxylates
- ene reaction of olefins and azodicarboxylates

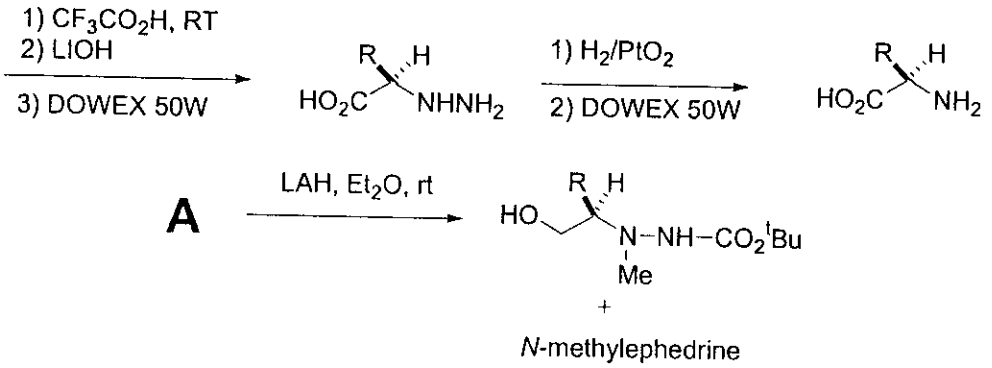
N-alkylhydrazides have never been prepared by direct C=C functionalization of unactivated olefins

Carreira, E.M.; Waser, J. *J. Am. Chem. Soc.* **2004** ASAP

Asymmetric Electrophilic Amination: Synthesis of α-Amino and α-Hydrazino Acids



A



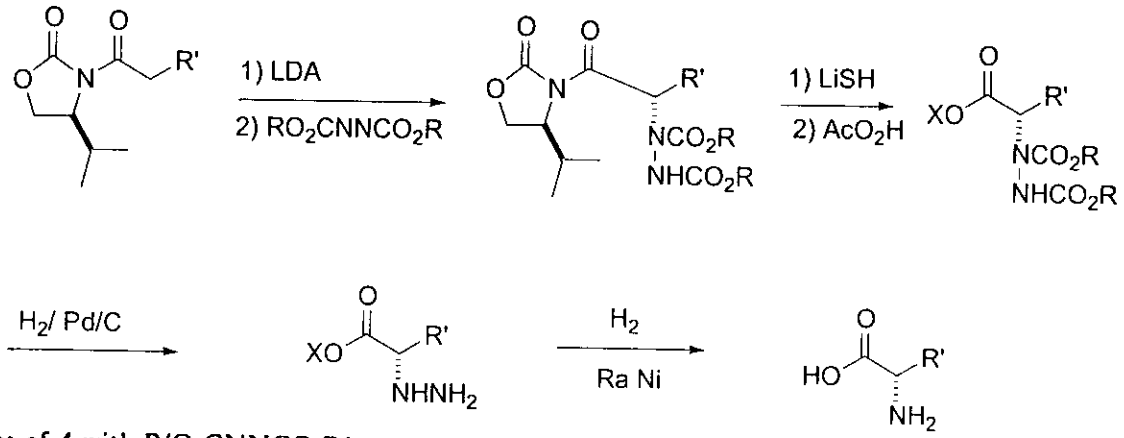
- -ee's 78-91%
- Good chemical yields
- Both enantiomers of auxiliary available and inexpensive
- Auxiliary can be recycled
- Access to natural, unnatural and rare amino acids

Table I. α-Hydrazino and α-Amino Acid Synthesis Using (1*R*,2*S*)-*N*-Methylephedrine

R	2, % yield	3, % yield	4, % yield	4		
				% ee (from crude 3)	% ee (from 3 after crystallization[b])	absolute config
CH_3	70[a]	78[b]	92	90.6[c]	≥98[c]	*R*
CH_2Ph	45[a]	81[b]	89[d]	91.0[d]	≥98[d]	*R*
$CH_2CH(CH_3)_2$	70[a]	81[b]	91	81.5[c]	≥98[c]	*R*
CH_2CH_3	65[a]	80[b]	93	84.0[c]	≥98[c]	*R*
$(CH_2)_3CH_3$	45[a]	78[b]	90	78.0[c]	≥98[c]	*R*

Gennari, C.; Bertolini, A.; Colombo, L. *J. Am. Chem. Soc.* **1986**, *108*, 6394

Amination of Chiral Enolates by Dialkyl Azoformates



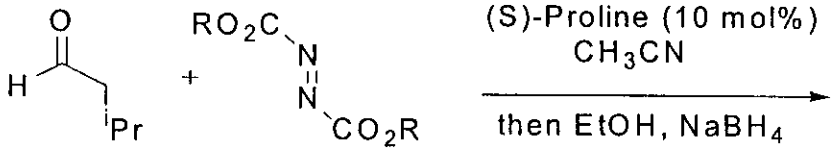
ble I. Amination of Enolates of **4** with $R'O_2CNNCO_2R'$

entry	R	R′	% yield of **5**[a]	diastereomeric ratio of **5**[b]	yield of **6** or **7**[a]	yield of **1**[a]	enantiomeric ratio of **1**[c]
a	Me	CH_2Ph	91	90:10[d]	82[e]	98	88:12
					93[f]	92	72:28[g]
b	CH_2Ph	Me	83	69:31			
c	CH_2Ph	Et	88	75:25			
d	CH_2Ph	CH_2Ph	90	94:6	85[e]	82	94:6
					87[f]	92	88:12
e	CH_2Ph	$C(CH_3)_3$	88	93:7	97[f]	81[h]	83:17[g]
f	$CH(CH_3)_2$	CH_2Ph	85	97:3	86[f]	98	97:3
g	Me	$C(CH_3)_3$	92		74[f]	83[h]	86:14[g]

- Substitution of both the dialkyl azoformate and the acyl sidechain influence selectivity

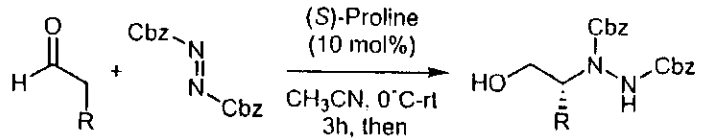
Vederas, J.; Trimble, L. J. *Am. Chem. Soc.* **1986**, 108, 6397

Direct Catalytic Asymmetric α-Amination of Aldehydes



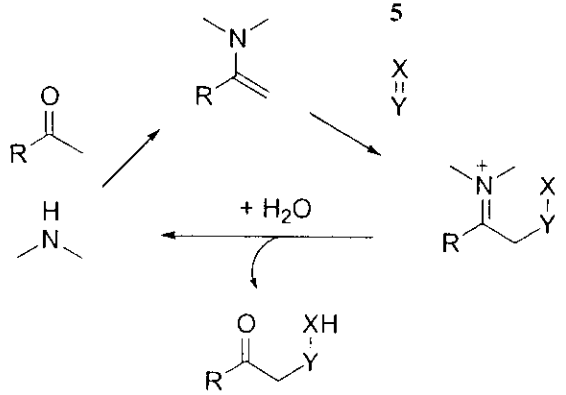
1.5 eq 1 eq

R = t-Bu: 97% yield, 92% ee
R = Bn : 99% yield, 86% ee



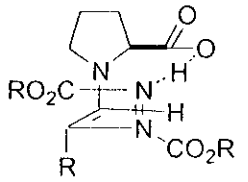
1.5 eq 1 eq

product	R	yield, %	ee, %
1	*i*-Pr	99	96
2	*n*-Pr	93	>95
3	*n*-Bu	94	97
4	Me	97	>95
5	Bn	95	>95

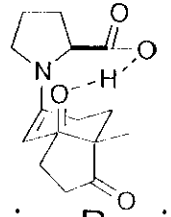


XY = C=O, C=N, C=C, N=N

Proline-enamine involved TS



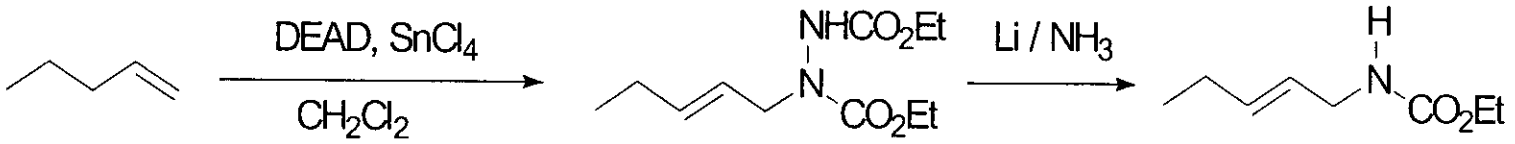
Proposed TS



Hajos-Parrish -Eder-Sauer-Wiechert TS

List, B. *J. Am. Chem. Soc.* **2002**, *124*, 5656

Allylic Amination by the Lewis –Acid- Mediated Ene Reaction of DEAD with Alkenes



Use of DEAD as an electrophile in the "azo-ene" reaction provides a method for the allylic amination of alkenes.

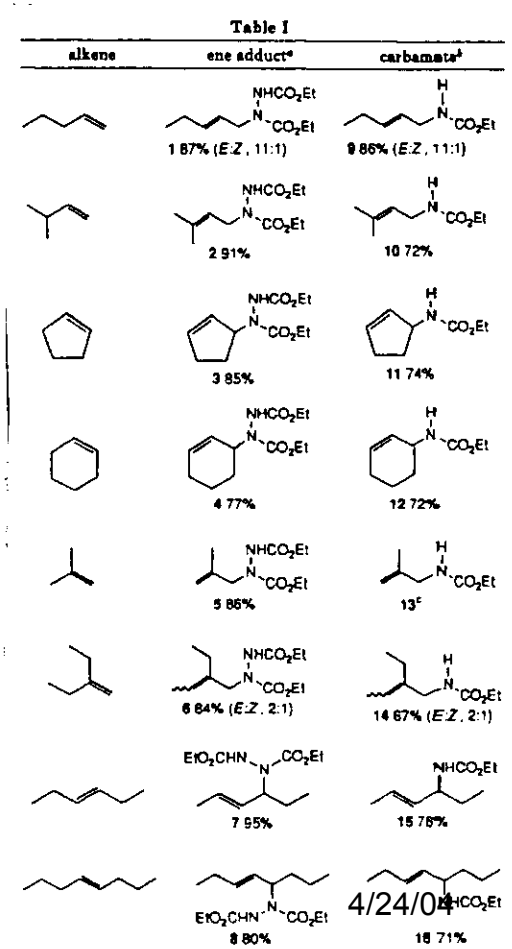
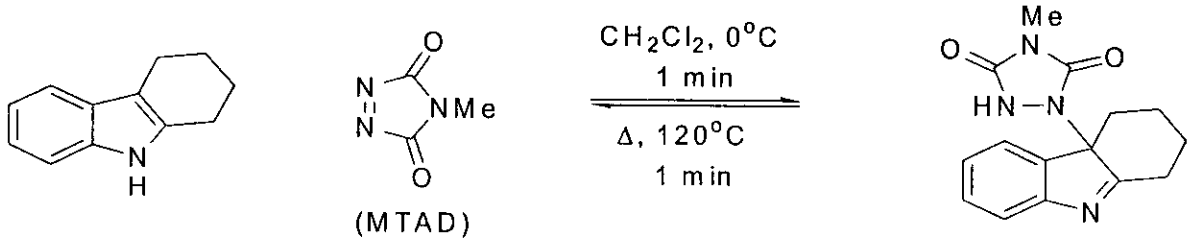


Table I

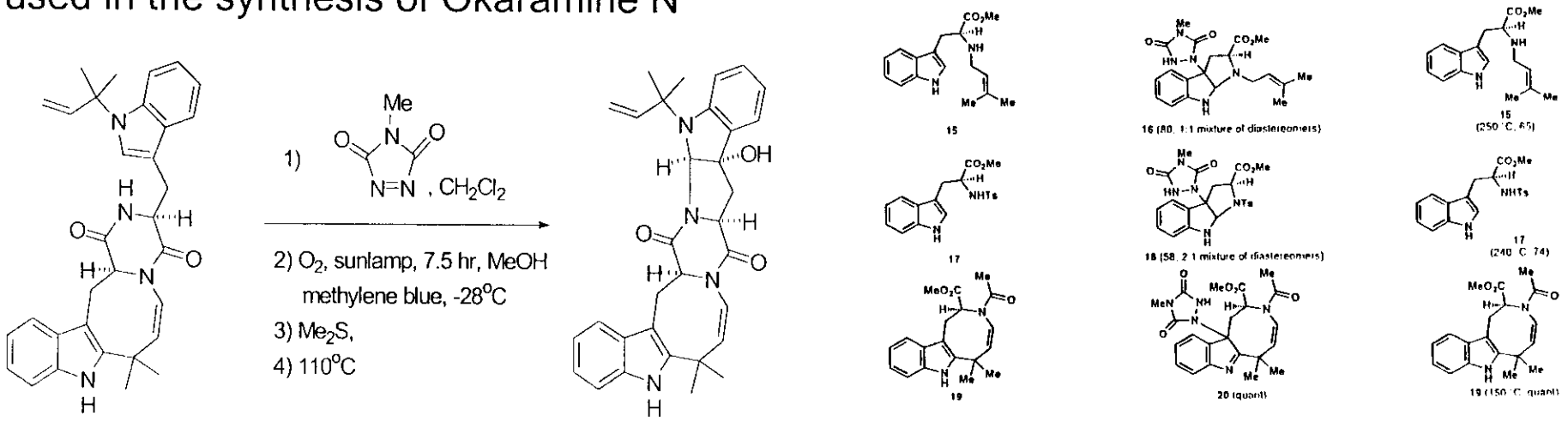
alkene	ene adduct[a]	carbamate[b]
	1 87% (*E*:*Z*, 11:1)	9 86% (*E*:*Z*, 11:1)
	2 91%	10 72%
	3 85%	11 74%
	4 77%	12 72%
	5 86%	13[c]
	6 84% (*E*:*Z*, 2:1)	14 67% (*E*:*Z*, 2:1)
	7 95%	15 78%
	8 80%	16 71%

Heathcock, C.; Brimble, M. *J. Org. Chem.* **1993**, *58*, 5261

Ene-Type reaction of Indoles with MTAD



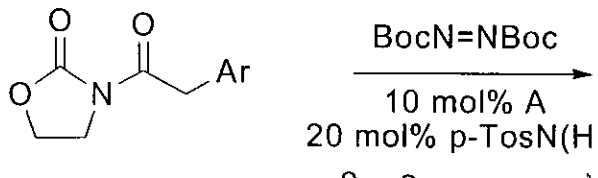
This is the first reported method for the protection-deprotection of the indole 2,3 – π bond, which Corey used in the synthesis of Okaramine N

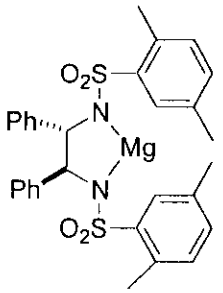


Okaramine N

Corey, E.J.; Guerrero, C.; Baran, P. *Org. Lett.* **2003**, *5*, 1999

Chiral Mg-Bis(sulfonamide) Complexes as Catalysts for the Merged Enolization and Enantioselective Annulation of *N*-Acyloxazolidinones





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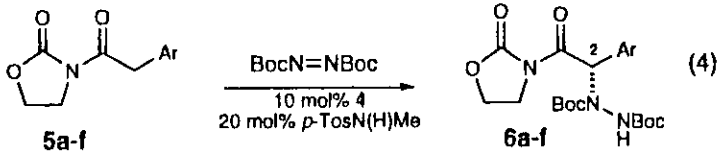
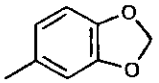
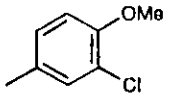
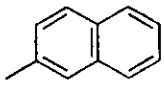
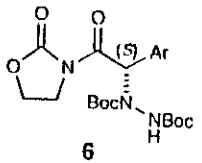


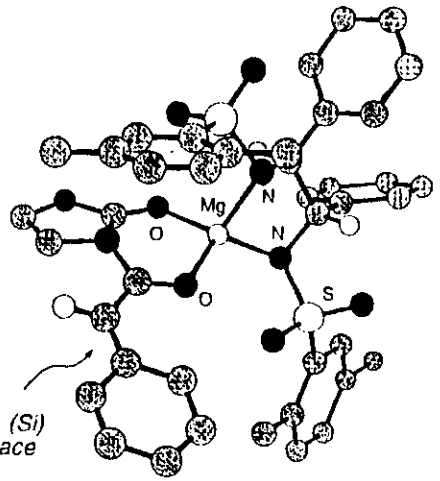
5a-f **6a-f** (4)

entry	aryl group	reaction time, h (temp, °C)	2(*S*):2(*R*) (% yield)[c, d]	% ee (mp °C)[e]
a	C_6H_5–	48 (–75)	93:7 (92)	>99 (185-7)
b	*p*-F-C_6H_4–	48 (–65)	95:5 (97)	>99 (207-8)
c	*p*-CH_3O-C_6H_4–	48 (–65)	93:7 (93)	99 (201-2)
d		72 (–75)	91:9 (85)	>99 (182-3)
e		60 (–75)	90:10 (84)	97 (191-3)
f		48 (–65)	91:9 (87)	96 (201-2)



6

BocN=NBoc



Accessible (Si) Diastereoface

This methodology employs a catalytic chiral metal complex which acts as the base and source of enantioselectivity.

Evans, D.A.; Nelson, S.G. *J. Am. Chem. Soc.* **1997**, *119*, 6452

Asymmetric Synthesis of α-Hydrazino and α-Amino Acids via Stereoselective Amination of Chiral Enolates

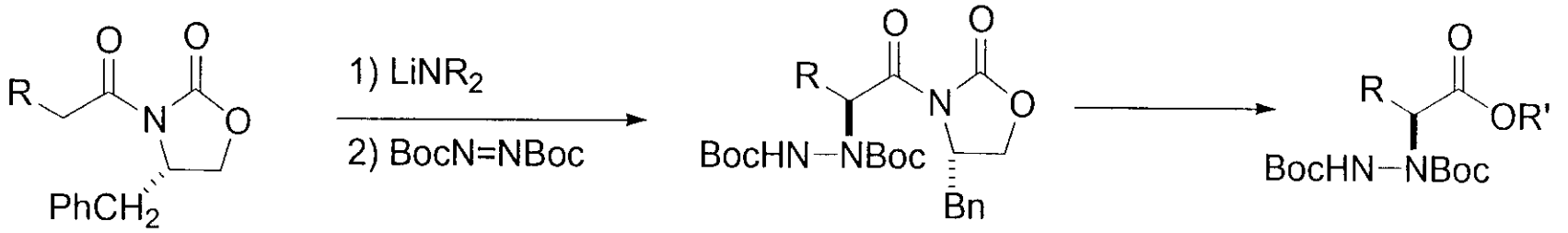


Table II. Transesterification (Hydrolysis) of Hydrazide Adducts (eq 4)

entry	substrate **2**	product[a]	yield, %	ee, %[b]
A	**2c**, R = CH_2Ph	**3c**	82	>99
B	**2c**	**4c**	89	>99
C	**2c**	**5c**	96	>99
D	**2d**, R = Ph	**3d**	84	98
E	**2d**	**4d**	71	93
F	**2d**	**5d**	89	22
G	**2e**, R = $CHMe_2$	**4e**	12	>99
H	**2e**	**5e**	82	>99
I	**2f**, R = CMe_3	**5f**	51	>99

[a] Specific reaction conditions for hydrolysis, methanolysis, and benzyl alcohol transesterification are reported in text. [b] The ee values were determined by gas chromatographic analysis of the derived MTPA amides **7**.

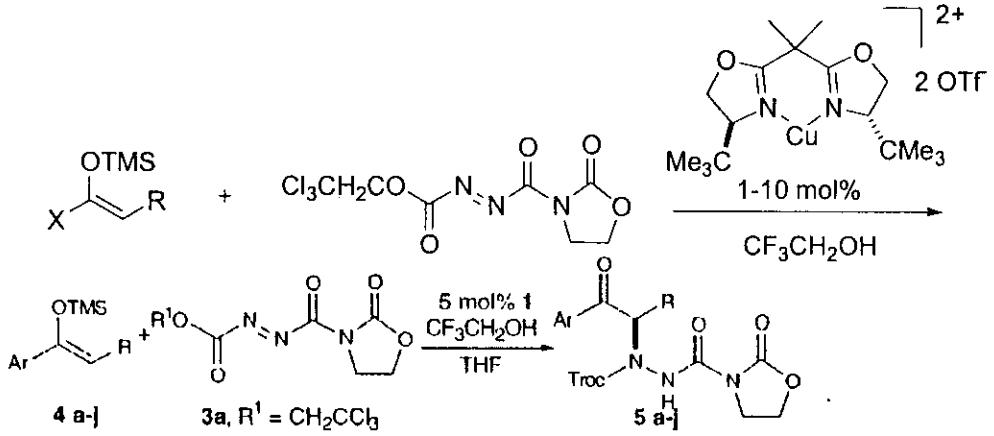
Table I. Stereoselective "Amination" of *N*-Acyloxazolidones (eq 3)

entry	imide **1** R	kinetic ratio[a] (2*S*:2*R*)	yield, %[b] **2**
A	Me	98:2	92[c]
B	$CH_2CH{=}CH_2$	98:2	94
C	CH_2Ph	97:3	91
D	Ph	97:3	96
E	$CHMe_2$	98:2	95
F	CMe_3	>99:1	96

[a] Ratios determined by HPLC analysis. [b] Values refer to isolated yields of isomerically pure (2*S*:2*R* > 300:1) adduct. [c] Isolated yield of the diastereomeric mixture.

Evans, D.A.; et.al. *J.Am. Chem. Soc.* **1986**, *108*, 6395

Catalytic Enantioselective Amination of Enolsilanes Using C_2-Symmetric Cu(II) Complexes as Chiral Lewis Acids



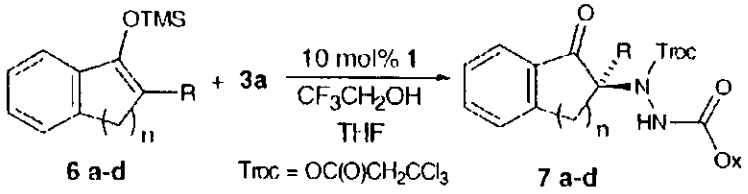
entry	4[b]	Ar	R	T (°C)	% yield[c]	% ee[d]	time[e]
1	**4a**	Ph	Me	-20	95	99	2 min
2	**4b**	4'-MeOPh	Me	-20	96	99	<1 min
3	**4c**	6'-MeONap[a]	Me	-20	96	99	1 min
4	**4d**	Ph	Et	-20	93	98	0.5 h
5	**4e**	Ph	Allyl	-20	92	97	2 h
6	**4f**	Ph	^{t}Bu	-20	92	98	2 h
7	**4g**	Ph	^{i}Pr	-20	86	99	3h
8	**4h**	4'-MeOPh	^{t}Bu	-20	84[f]	98	(6 h)
9	**4i**	4'-MeOPh	Bn	-20	88	91	3 min
10	**4i**	4'-MeOPh	Bn	-78	94	99	(12 h)
11	**4j**	4'-MeOPh	Ph	-20	95	91	(2 h)
12	**4j**	4'-MeOPh	Ph	-50	94	97	(13 h)

- Reaction is completely selective on the azo component
- Provides an enantioselective catalytic route to differentially protected α-hydrazino carbonyl compounds

Evans, D.A.; Johnson, D.S. *Org. Lett.* **1999**, *1*, 595

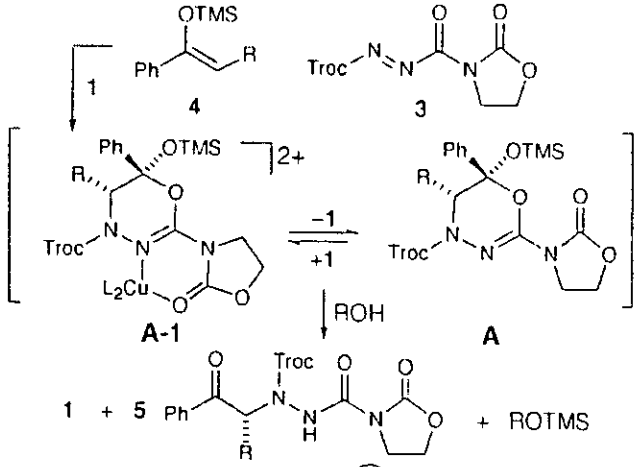
Catalytic Enantioselective Amination of Enolsilanes Using C_2-Symmetric Cu(II) Complexes as Chiral Lewis Acids

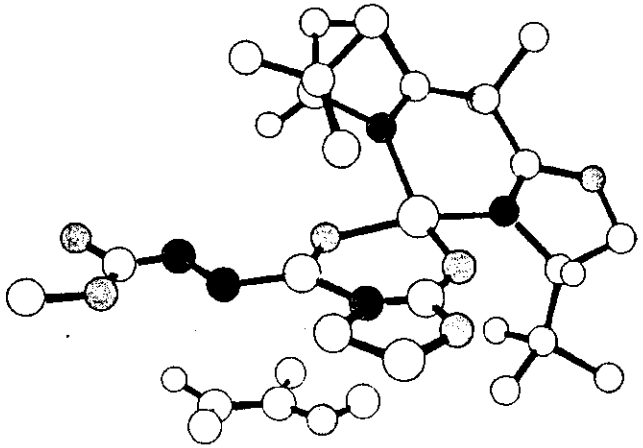
Table 3. Amination of Cyclic Enolsilanes (6)



6 a-d — Troc = $OC(O)CH_2CCl_3$ — 7 a-d

entry	6	R	n	T (°C)	% yield[a]	% ee[b]
1	6a	H	1	-78	90	21
2	6b	Me	1	-20	90	86
3	6b	Me	1	-78	88	96
4	6c[c]	H	2	-20	51[d]	90
5	6d	H	3	-78	94	99

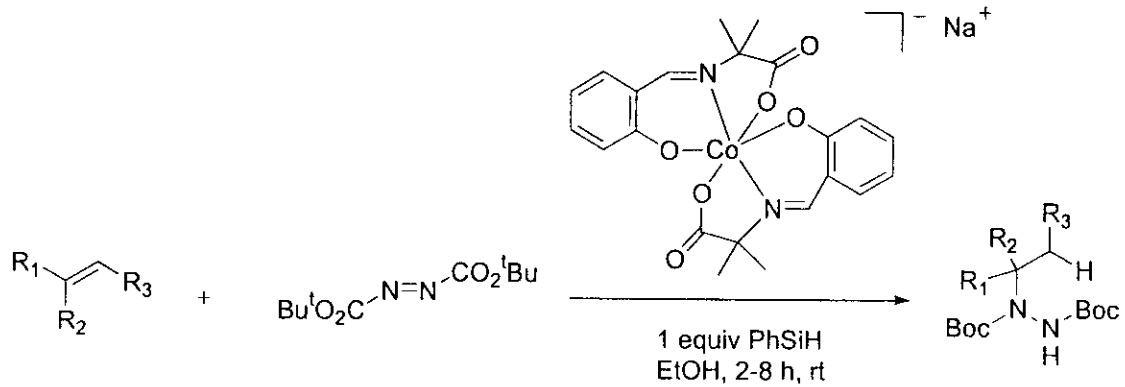




Hetero Diels-Alder TS

Evans, D.A.; Johnson, D.S. *Org. Lett.* **1999**, *1*, 595

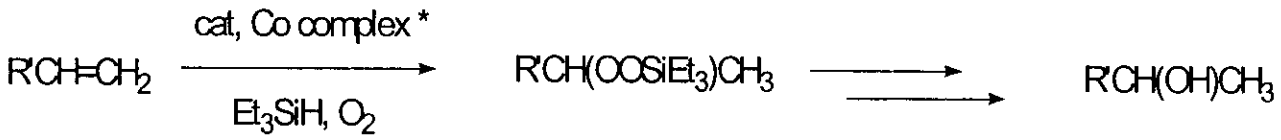
Convenient Synthesis of Alkylhydrazides by the Cobalt-Catalyzed Hydrohyrdazination Reaction of Olefins and Azodicarboxylates



The use of cobalt complexs and silanes in the presence of oxygen for the oxyfunctionalization of alkenes has received extensive investigation by Mukaiyama and Isayama

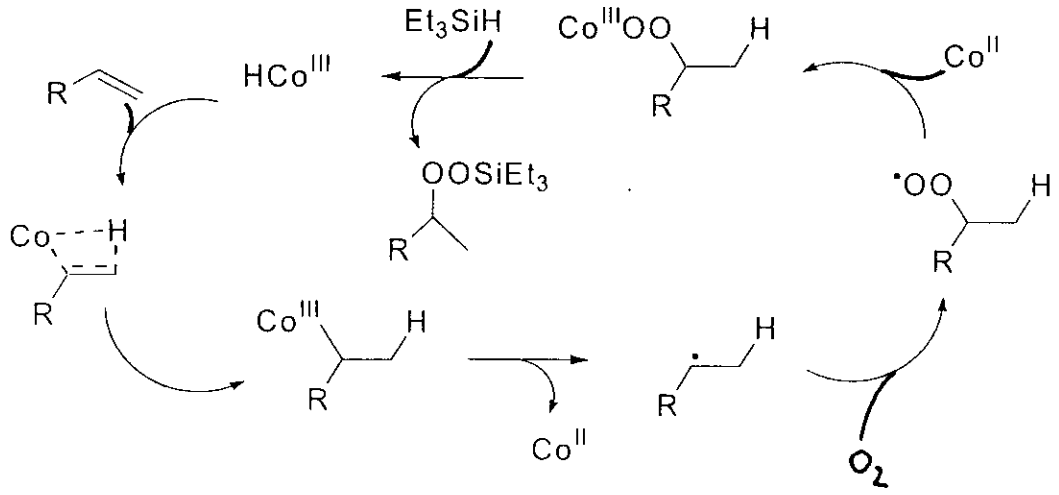
Carriera believed that this process would work with a N=N acceptor substituted for O_2

Carreira, E.M.; Waser, J. *J. Am. Chem. Soc.* **2004** ASAP



* = $Co(modp)_2$, $Co(acac)_2$, Co(SB)

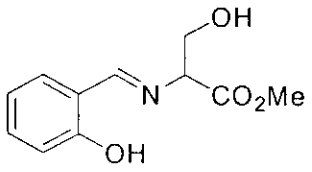
Proposed catalytic Cycle



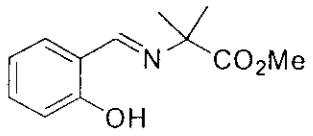
Nojima, N.; et.al. *Org. Lett.* **2002**, *4*, 3595

- Following Nojima's methodology, Carreira failed to observe olefin hydrohydrazination with $Co(acac)_2$, $Co(modp)_2$, $Co(dpm)_2$, $Co(OAc)_2$, $CoCl_2$-$6H_20$, $Co(NO_3)$-$6H_2O$ and $PhSiH_3$ or Et_3SiH along with DEAD in EtOH, THF or 1,2-dichlorethane at 23°C

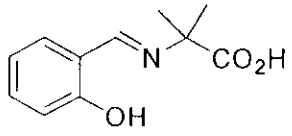
- Cobalt complexes known to mediate epoxidation and peroxidation were next investigated



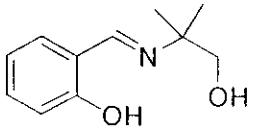
1



2



3



4

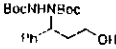
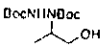
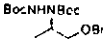
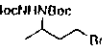
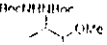
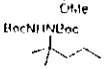
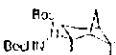
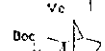
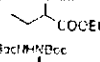
- Cobalt complex derived from 2 gave the desired alkylhydrazide in 85% yield

Carreira, E.M.; Waser, J. *J. Am. Chem. Soc.* **2004** ASAP

Under optimized conditions cyclic and acyclic (mono, 1,1-and 1,2-di and trisubtituted) olefins were hydrohydrazinated

- 1,2-disubstituted olefin selectivity is governed by electronic effects
- Only limitations involve unactivated 1,2-disubstituted olefins (crotyl alcohol, cyclohexene

Table 1. Hydrohydrazination Reaction of Olefins (Eq 1)

Entry	Alkene	Product	Yield[a]
1			86%[b]
2			88%[b]
3			88%
4			91%
5			94%[c]
6			80%[c]
7			78%[b]
8			76%
9			73% (d.r. 1:1)
10			76%
11			90%
12			82%[b]
13			70%[b]
14			88%[c]
15			84% dr 2:1-3:1
16			69% dr 5:1
17			90%[b]
18			66%[c]
19			70%
20			66%
21			62%[c]
22			74%[c]

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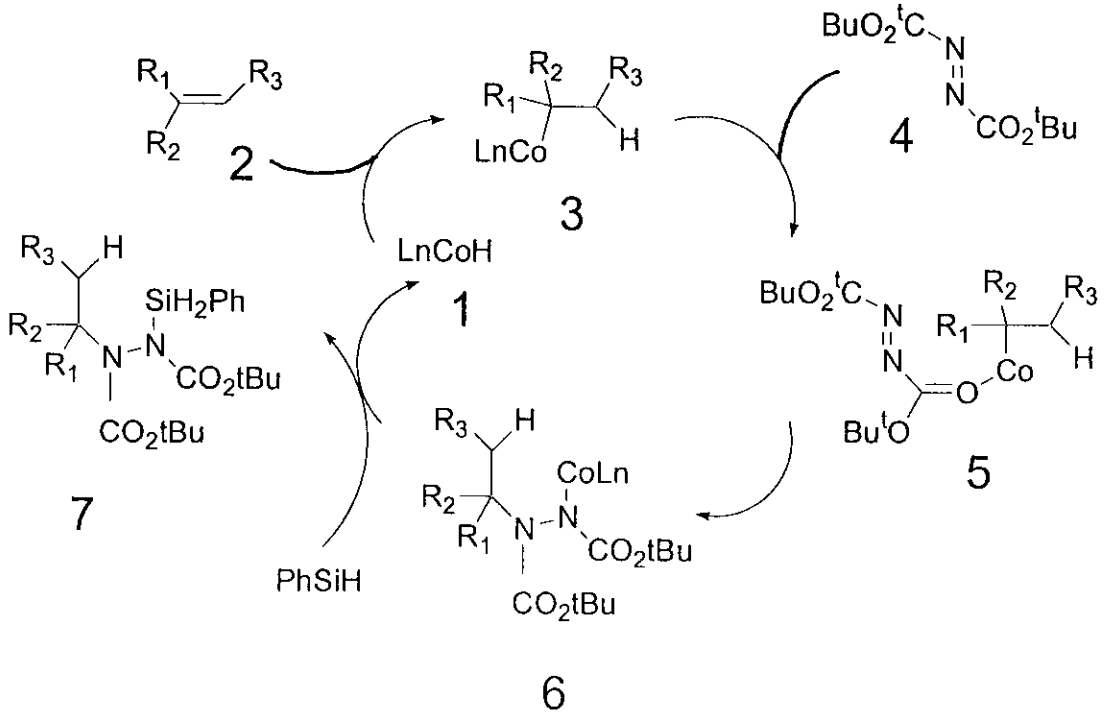
Proposed Mechanism



1

Carreira, E.M.; Waser, J. *J. Am. Chem. Soc.* **2004** ASAP

Conclusion

Azodicarboxylates are:

1) Highly reactive toward nucleophiles
2) (+) NH_2 synthons
3) Simple and commercially available
4) Have good shelf-life and stability

Carreira reported the first synthesis of a N-alhylhydrazides by the direct C=C functionalization of unactivated olefins.

N-alkylhydrazides can serve as precursors to a broad range of amines

The reaction is easy to perform - using unpurified solvents, done at room temperature, all starting material is commercially available.

Currently, studies are being conducted to fully understand the mechanism and develop a more efficient catalytic system