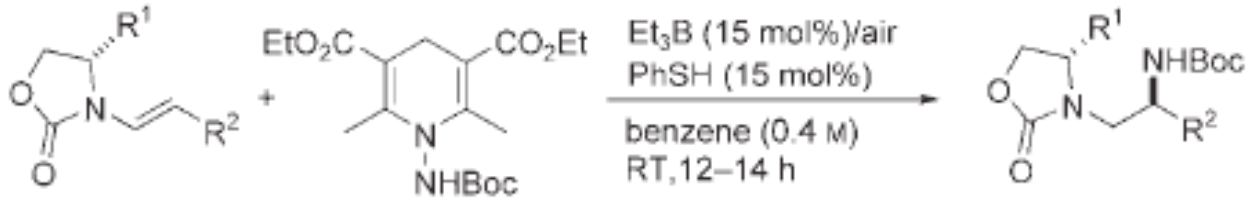
# Thiol-Catalyzed Stereoselective Transfer Hydroamination of Olefins with N-Aminated Dihydropyridines

Joyram Guin, Roland Frohlich, Armido Studer
*Angew. Chem. Int. Ed*., Early View.



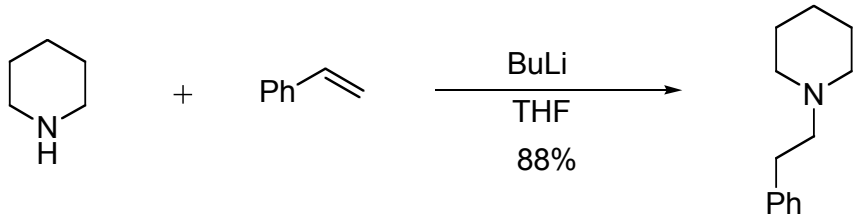

Current Literature

Masafumi Ueda

January 5, 2008

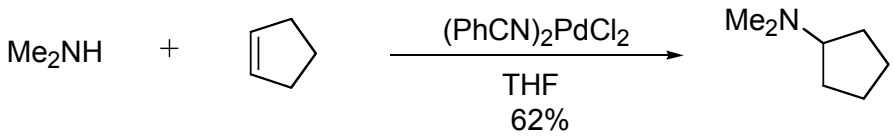
# Hydroaminations of olefins

1. Amination catalyzed by alkali metal




*J. Org. Chem*. **1972**, *37*, 4243.

2. Amination catalyzed by transition metals



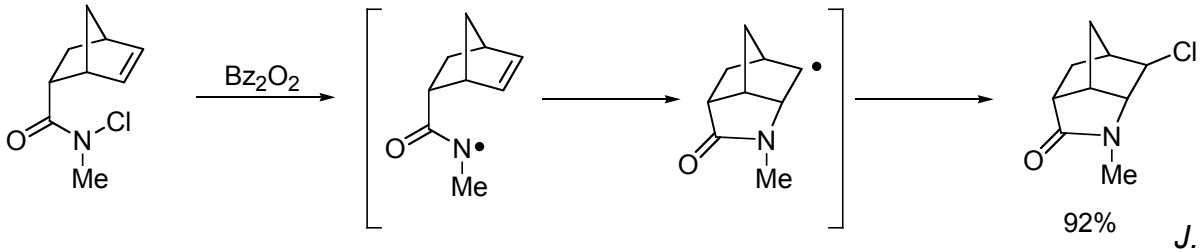

*J. Organometal. Chem*. **1974**, *72*, 127.

Most of the hydroaminations successfully conducted are using transition metals as catalysts. However, many functional groups are not tolerated, therefore these methods lack generality.

*Tetrahedron*. **1983**, *39*, 703.
*Chem. Rev.* **1998**, *98*, 675.

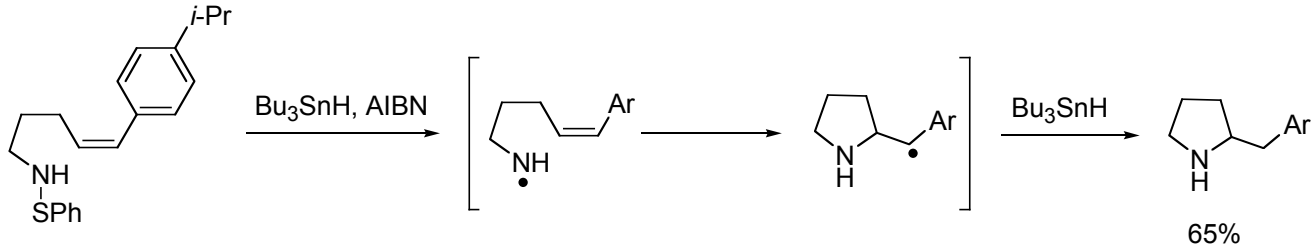
# Addition of N-centered radical to olefins

Peroxide-initiated cyclization of N-chloro amide: Cl atom transfer reaction




*J. Org. Chem*. **1978**, *43*, 3746.

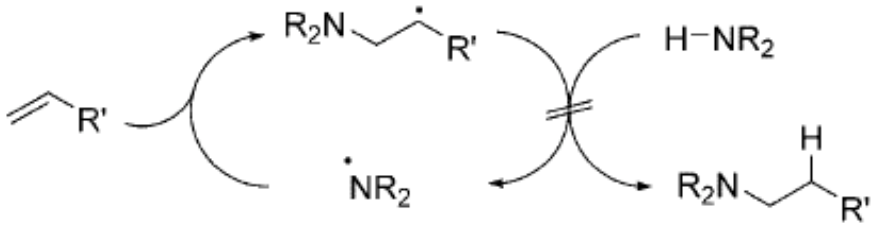
Stannyl radical-mediated cyclization of sulfenamide




*Tetrahedron*. **1994**, *50*, 1275.

The addition of N-centered radical to alkenes is well established.
However, radical additions of amines or amine derivatives to olefins by H-transfer processes are not known to date.

# Addition of N-centered radical to olefins via H transfer reaction using NH compounds

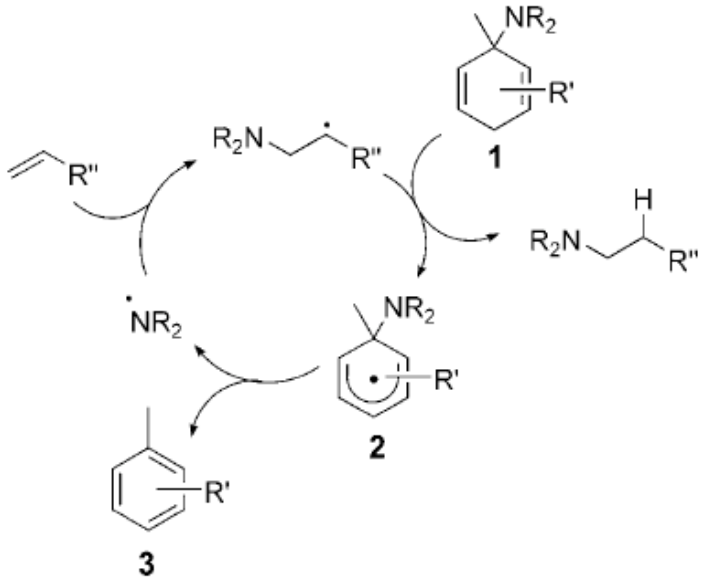



H transfer from N to C radical is not an efficient step.
The reverse reaction, H transfer from C to N radical, is favored process.
Therefore, the direct radical hydroamination via H transfer reaction using NH compounds is not feasible.

*Angew. Chem. Int. Ed.* **2005**, *44*, 4914.
*J. Am. Chem. Soc.* **2007**, *129*, 4498.

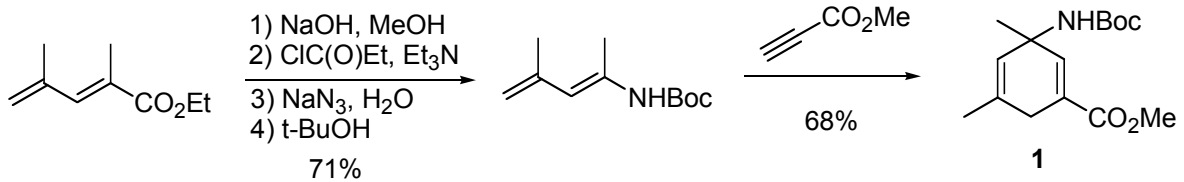
# Studer's previous study – the Concept

Amino cyclohexadiene **1** was used as a N-radical precursor and a reducing reagent.



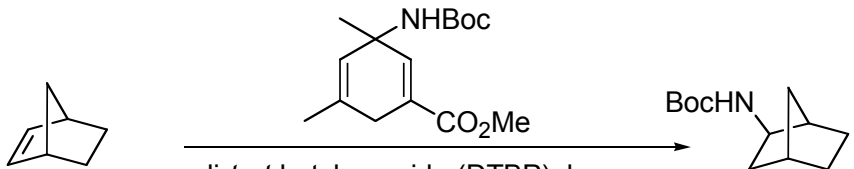

1. Addition of aminyl radical to an alkene afforded the corresponding C radical.
2. C radical reduced with **1** to provide **2** and the desired hydroamination product.
3. Chain propagating occurred through aromatization of **2** to deliver an aminyl radical and **3**

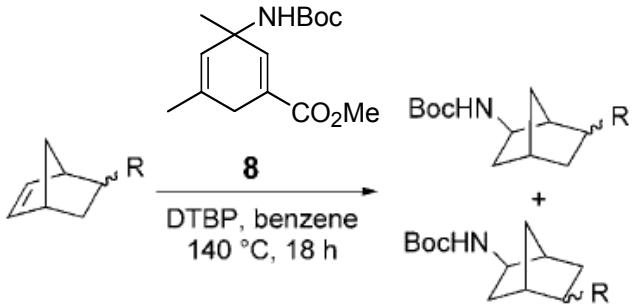
Preparation of amino cyclohexadiene **1**



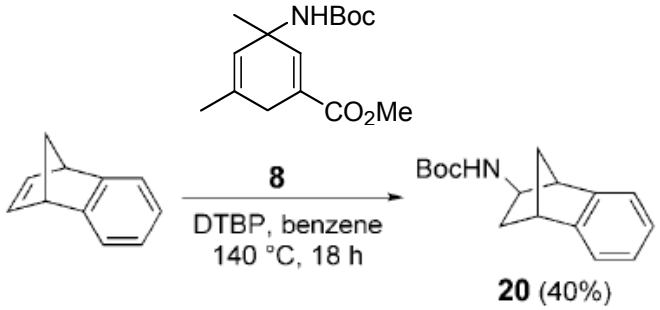

*Angew. Chem. Int. Ed.* **2005**, *44*, 4914.
*J. Am. Chem. Soc.* **2007**, *129*, 4498.

# Studer's previous study



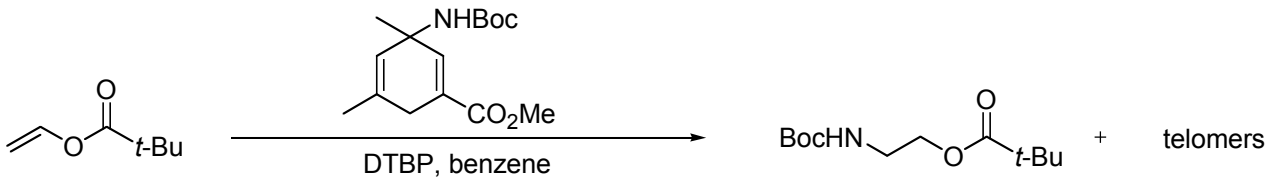

**15** (43%, R = $CH_2CH_2Ph$)
**16** (42%, R = $(CH_2)_5CH_3$)
**17** (56%, R = $(CH_2)_8CO_2Et$)
**18** (53%, R = $CO_2Bu$)
**19** (42%, R = $SiMe_3$)

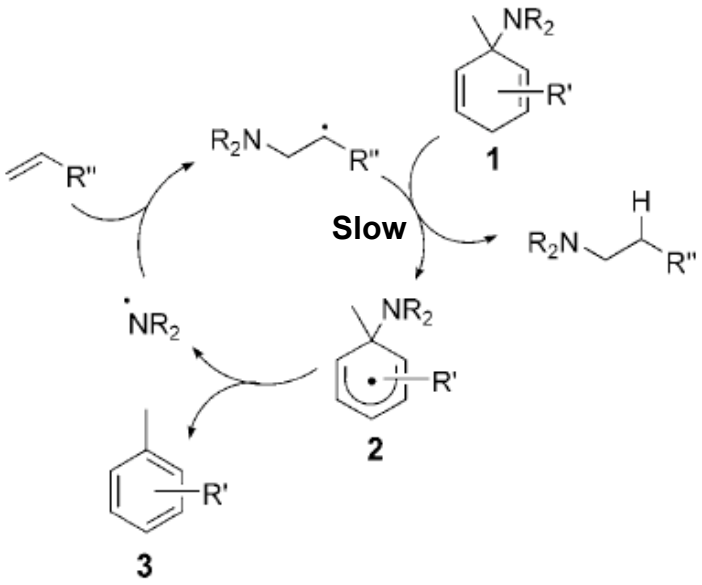



**20** (40%)

*Angew. Chem. Int. Ed.* **2005**, *44*, 4914.
*J. Am. Chem. Soc.* **2007**, *129*, 4498.

# Studer's previous study



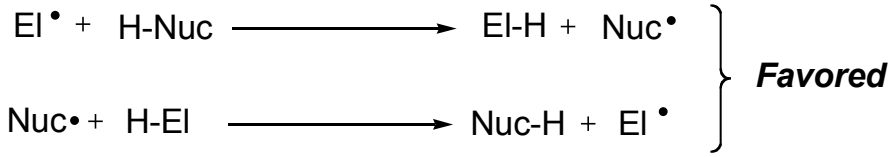

The reduction of C radical with cyclohexadiene is slow. Therefore, reduction of α-oxy radical cannot efficiently complete with telomerization.

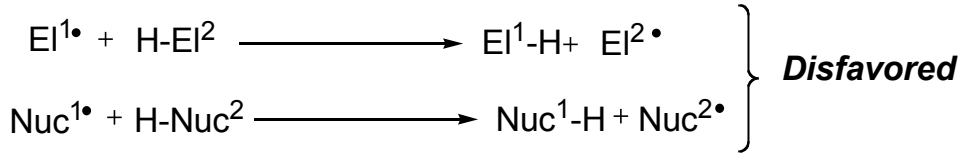
This problem can be solved by using polarity reversal catalysis.

*Angew. Chem. Int. Ed.* **2005**, *44*, 4914.
*J. Am. Chem. Soc.* **2007**, *129*, 4498.

# Polarity reversal catalysis

H atom transfer reaction

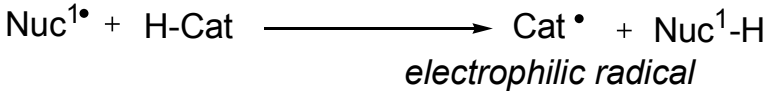


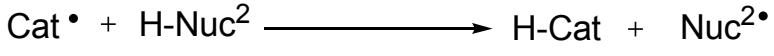

El• ; electrophilic radical

Nuc• ; nucleophilic radical

Polarity reversal catalysis




*electrophilic radical*

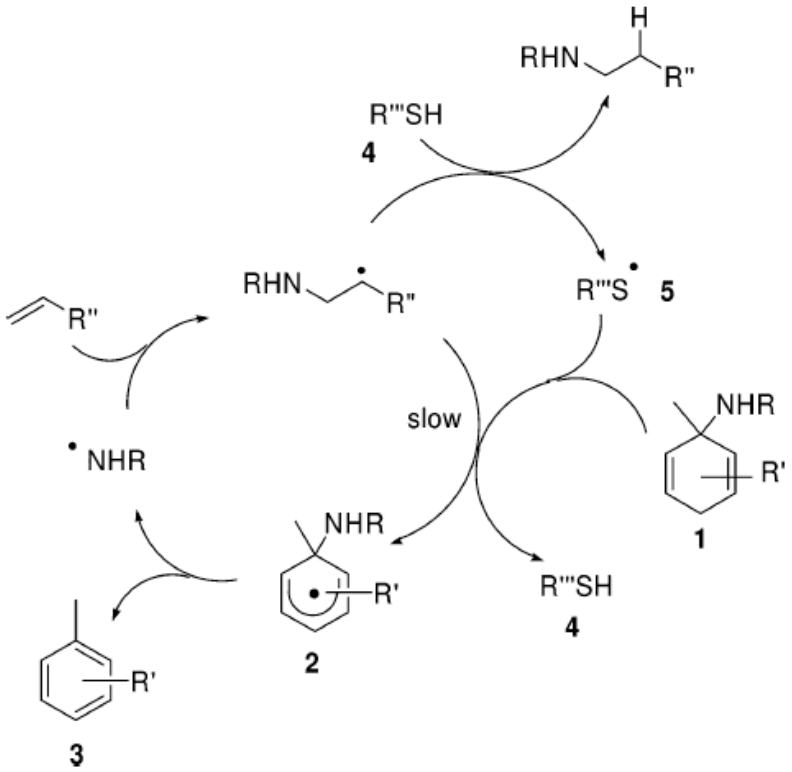


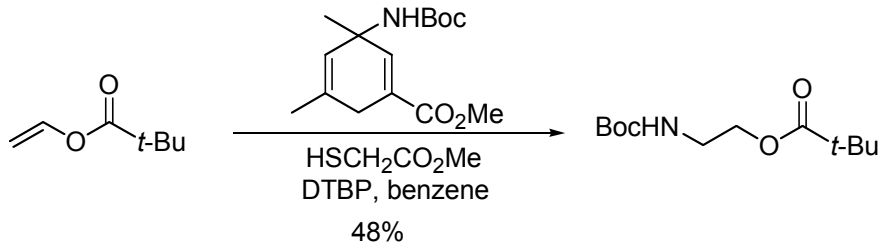

H-Cat ; polarity reversal catalyst

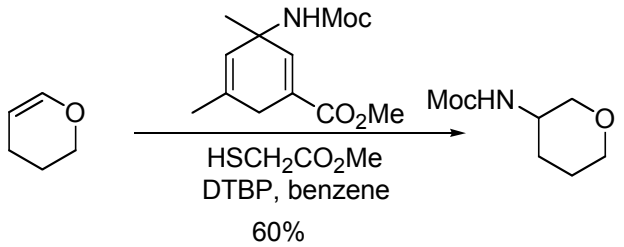
*Chem. Soc. Rev*. **1999**, *28*, 25.

# Studer's previous study

More efficient chain reaction using thiol as a polarity reversal catalyst



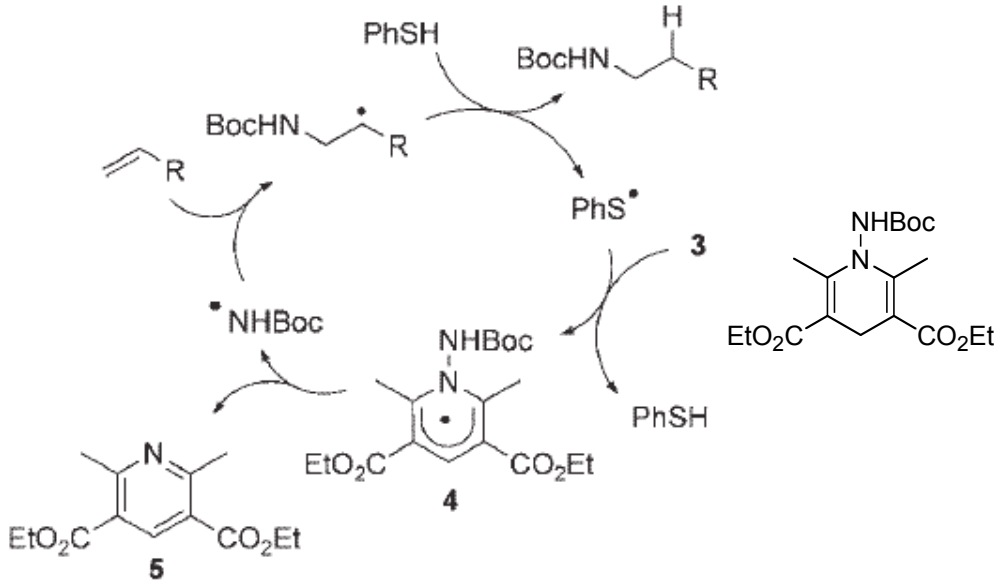

## Drawbacks

1) Large-scale synthesis of amino cyclohexadiene **1** is rather tedious.
2) compound **1** readily decomposes under acidic conditions.
3) Stereoselective hydroaminations are highly unlikely since reactions have to be conducted at 140 °C.

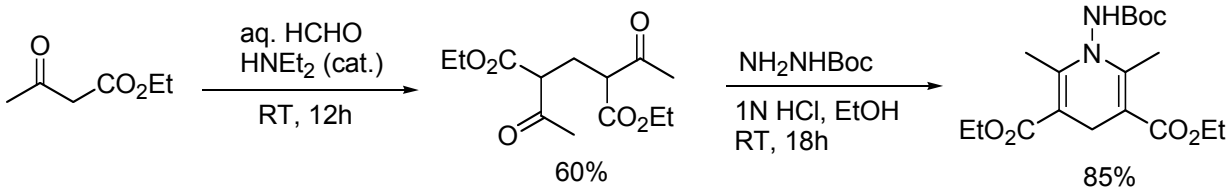
*Angew. Chem. Int. Ed*. **2005**, *44*, 4914.
*J. Am. Chem. Soc.* **2007**, *129*, 4498.

# This work

Radical transfer hydroamination with N-aminated Hantzsch ester

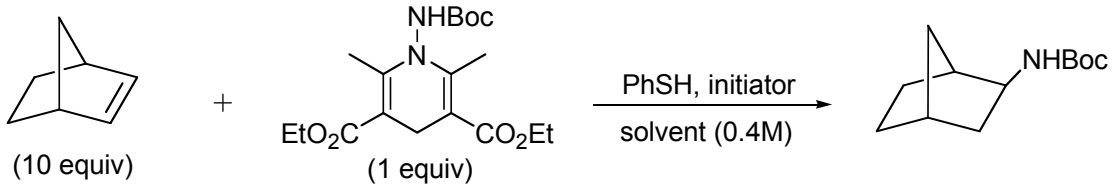



Synthesis of N-aminated Hantzsch ester




N-Aminated Hantzsch ester was readily prepared on a large scale in two steps.

# Hydroamination of norbornene with N-aminated Hantzsch ester under different conditions



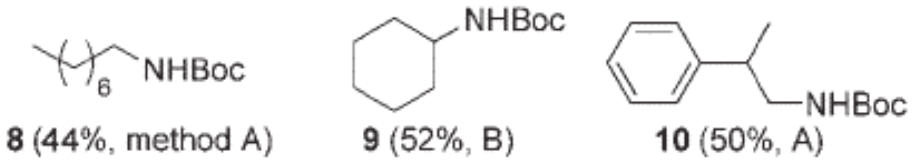

(10 equiv) + (1 equiv)

| Entry | Solv. | *T* [°C] | PhSH [equiv] | Init.[a] | Yield [%][b] |
|---|---|---|---|---|---|
| 1 | $C_6H_6$ | 80 | 0.15 | AIBN | 54 |
| 2 | $C_6H_6$ | 20 | 0.15 | air | 57 |
| 3 | $C_6H_6$ | 20 | 0.15 | $Et_3B/O_2$[c] | 60 |
| 4 | $C_6H_6$ | 0 | 0.15 | $Et_3B/O_2$[c] | 51 |
| 5 | $C_6H_5CH_3$ | 20 | 0.15 | $Et_3B/O_2$[c] | 42 |
| 6 | $CH_2Cl_2$ | 20 | 0.15 | $Et_3B/O_2$[c] | 46 |
| 7 | $ClCH_2CH_2Cl$ | 20 | 0.15 | $Et_3B/O_2$[c] | 54 |
| 8 | $ClCH_2CH_2Cl$ | −30 | 0.15 | $Et_3B/O_2$[c] | 53 |
| 9 | $CH_2Cl_2$ | −80 | 0.15 | $Et_3B/O_2$[c] | 46 |
| 10 | $C_6H_6$ | 20 | – | AIBN | 40 |
| 11 | $C_6H_6$ | 20 | 0.20 | $Et_3B/O_2$[c] | 56 |
| 12 | $C_6H_6$ | 20 | 0.10 | $Et_3B/O_2$[c] | 51 |
| 13 | $C_6H_6$ | 20 | 0.05 | $Et_3B/O_2$[c] | 44 |

[a] Initiator: 0.1 equiv of $Et_3B$ or 0.3 equiv of AIBN were used. [b] Yields of isolated products. [c] Air was used as $O_2$ source.

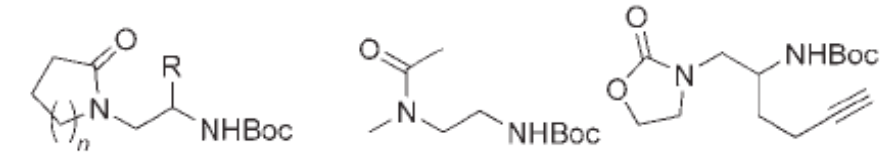
# Hydroamination of various alkenes

Method A: $Et_3B/O_2$
Method B: AIBN




**8** (44%, method A) **9** (52%, B) **10** (50%, A)

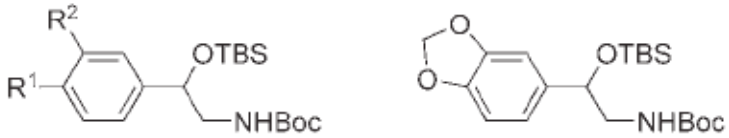
6% of regioisomeric Markovnikov product was also obtained.




**11** (58%, *n* = 1, R = H; A)
**12** (55%, *n* = 3, R = H; A)
**13** (52%, *n* = 1, R = Et; A)

**14** (55%, A)

**15** (33%, A)

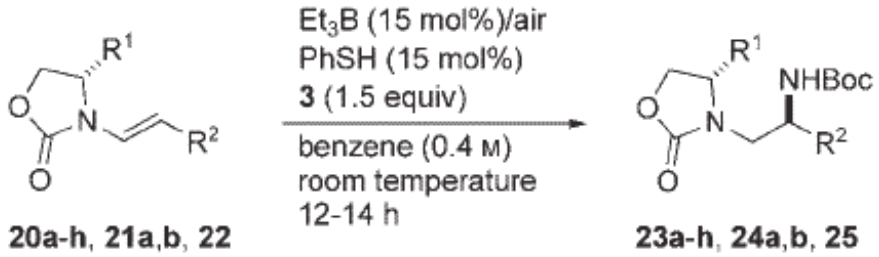



**16** (59%, $R^1 = R^2 = H$; B)
**17** (42%, $R^1$ = Br, $R^2$ = H; B)
**18** (62%, $R^1 = R^2$ = OMe; B)

**19** (59%, B)

Highly regioselectivity to give anti-Markovnikov product

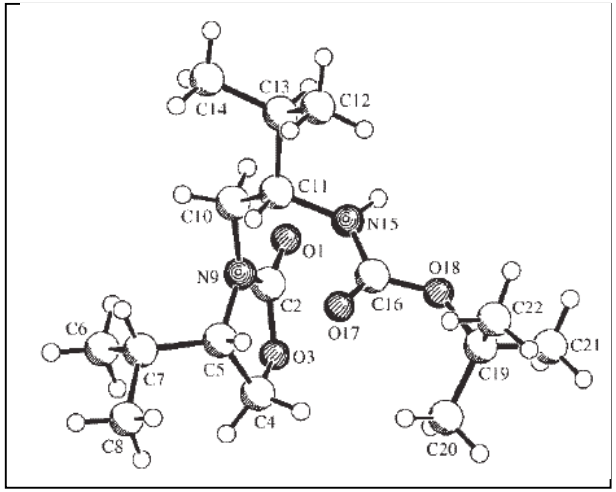
# Stereoselective radical transfer hydroamination




**20a-h, 21a,b, 22** → **23a-h, 24a,b, 25**

| Entry | Olefin | $R^1$ | $R^2$ | Yield [%] (product) | d.r. |
|---|---|---|---|---|---|
| 1 | **20a** | *i*Pr | Et | 47 (**23a**) | 13:1[a] |
| 2 | **20b** | *i*Pr | Bu | 48 (**23b**) | 13:1[a] |
| 3 | **20c** | *i*Pr | *i*Pr | 33 (**23c**) | 13:1[a] |
| 4 | **20d** | *i*Pr | *t*Bu | 30 (**23d**) | 20:1[a] |
| 5 | **20e** | *i*Pr | PMB[c] | 40 (**23e**) | 13:1[b] |
| 6 | **20f** | *i*Pr | $(CH_2)_3Ph$ | 44 (**23f**) | 13:1[b] |
| 7 | **20g** | *i*Pr | $(CH_2)_3CO_2Et$ | 41 (**23g**) | 13:1[b] |
| 8 | **20h** | *i*Pr | $(CH_2)_2OAc$ | 48 (**23h**) | 13:1[b] |
| 9 | *ent*-**21a** | Ph | Et | 48 (*ent*-**24a**) | 11:1[b] |
| 10 | *ent*-**21b** | Ph | *i*Pr | 34 (*ent*-**24b**) | 11:1[b] |
| 11 | **22** | *t*Bu | Et | 48 (**25**) | 14:1[a] |

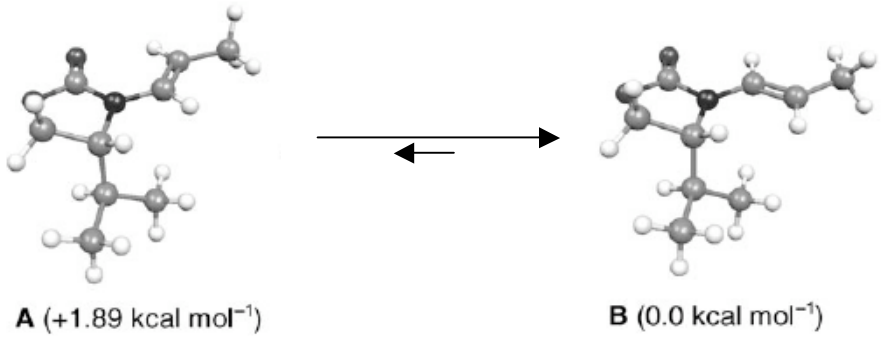
[a] Diastereomeric ratio (d.r.) determined by gas chromatography. [b] d.r. determined by $^1$H NMR spectroscopy. [c] PMB = *para*-methoxybenzyl.



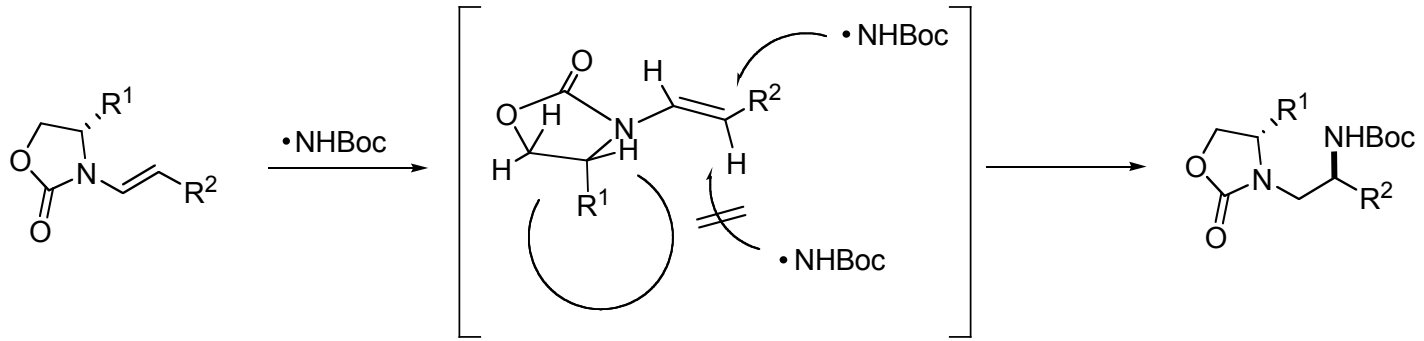

Molecular structure of the major isomer of the protected 1,2-diamine **23c**.

# Stereochemistry

Energy difference between the two conformers




The energy difference mainly results from dipole interactions of C=O and C=C bonds.



# Summary

1) The synthesis of N-aminated dihydropyridine as a novel precursor for the generation of carbamoyl radical.

2) Radical anti-Markovnikov hydroaminations on various olefins were performed.

3) Protected vicinal diamines were prepared with good stereoselectivities by hydroamination of chiral enecarbamates.