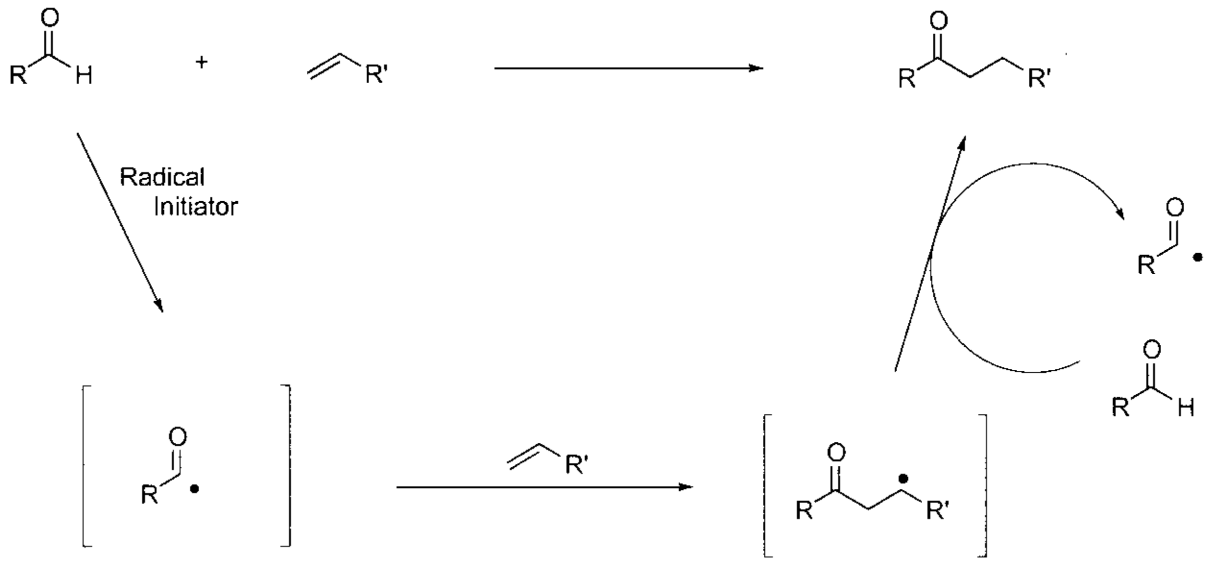
Addition of aldehydes and their equivalents to electron-deficient alkenes using N-Hydroxyphthalimide (NHPI) as a polarity-reversal catalyst

Yasutaka Ishii and Co-workers

Tetrahedron Letters, **2003**, *44*, 5601

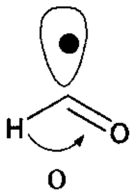


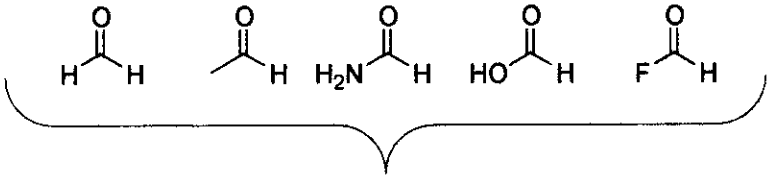
The Acyl Radical

Thermodynamic Data

86.0 **87.4** **87.1** **86.9** kcal mol^{-1}

Structural Data





O = 128°

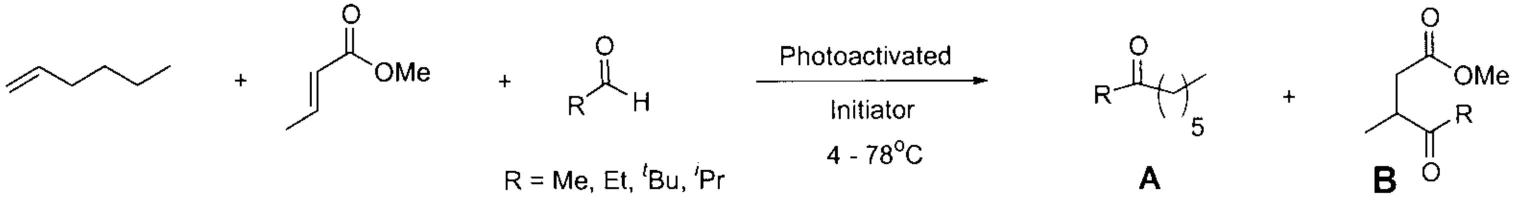
@ UMP2/DZP//UHF/6-311G**
level of theory

SOMO has substantial s character and is relatively unaffected by substituents.

Chem. Rev. **1999**, *99*, 1991

Some Acyl Radical Additions to Olefins

- *A competition experiment*



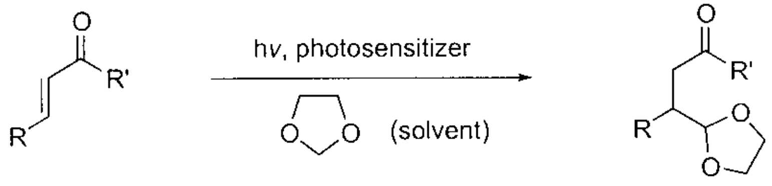
Yields : 10 - 35%

Selectivity (A:B) : 1:10

-Acyl radical is nucleophilic in nature.
-Yields are low, selectivities better at low temperature.

J. Org. Chem. **1985**, *50*, 3498.

-Acyl equivalent addition to enones

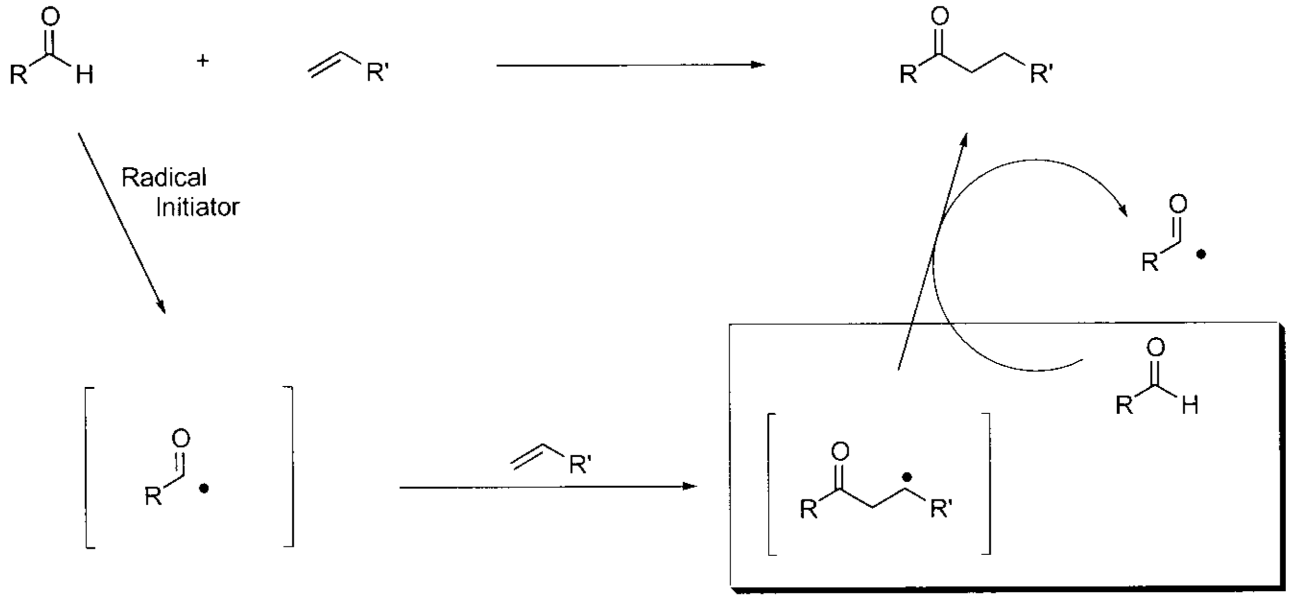


Yields: 35 - 65 %

-Yields spotty, photlytic conditions make sensitizer choice crucial.

J. Org. Chem. **1999**, *64*, 5024.

The problem with acyl radical chain reactions



Chain Transfer Is Slow!

-The solution is to by-pass this step.

Hydrogen atom transfer from silane

$$R\bullet + Et_3SiH \xrightarrow{\text{Very Slow}} RH + Et_3Si\bullet$$

(90.1 kcal)

Nucleophilic radical abstracting electron rich hydrogen atom.

Chem. Commun. **1989**, 1387.

Add a thiol to cycle radical around slow step

$$R\bullet + XSH \xrightarrow{\text{Fast}} RH + XS\bullet$$

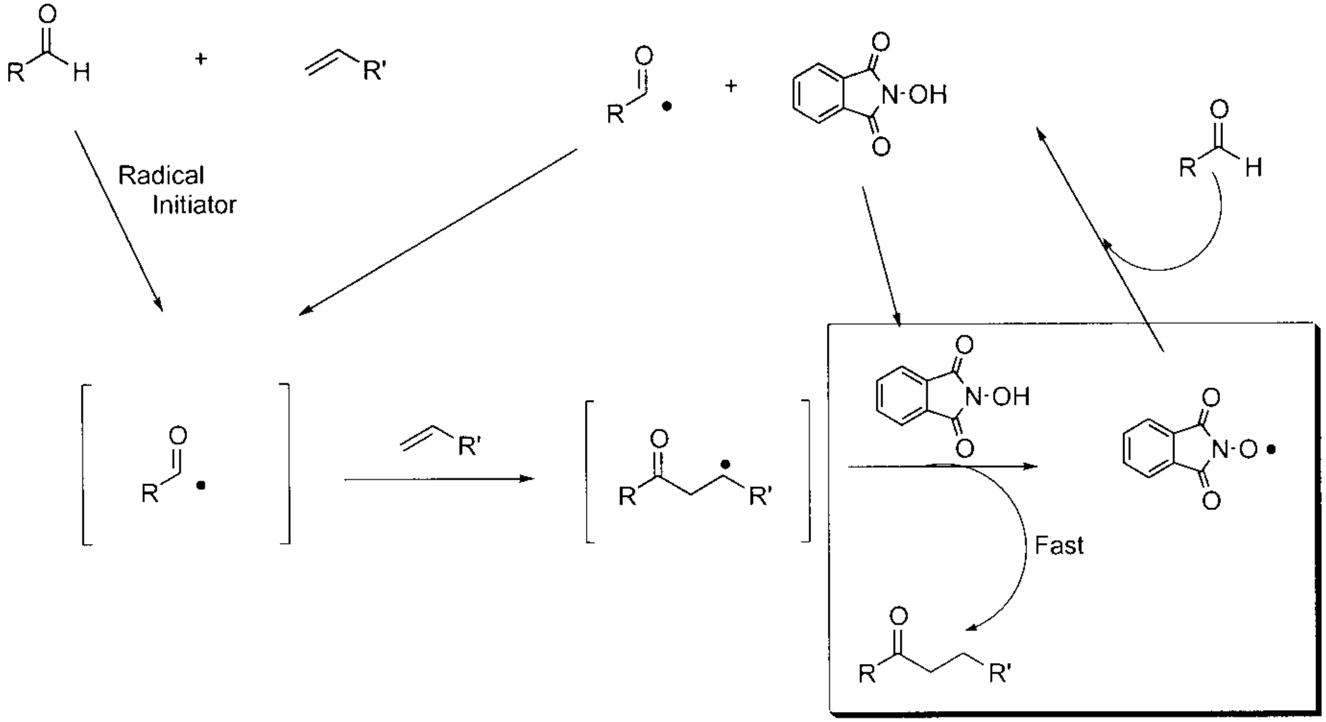
(91.8 kcal)

$$XS\bullet + Et_3SiH \xrightarrow{\text{Fast}} XSH + Et_3Si\bullet$$

Nucleophilic radical easily generates electrophilic radical which can easily abstract electron rich hydrogen.

Bond polarity is dictating reaction kinetics! Thiols are a polarity reversal catalysts.

N-hydroxyphthalimide (NHPI) as a polarity reversal catalyst



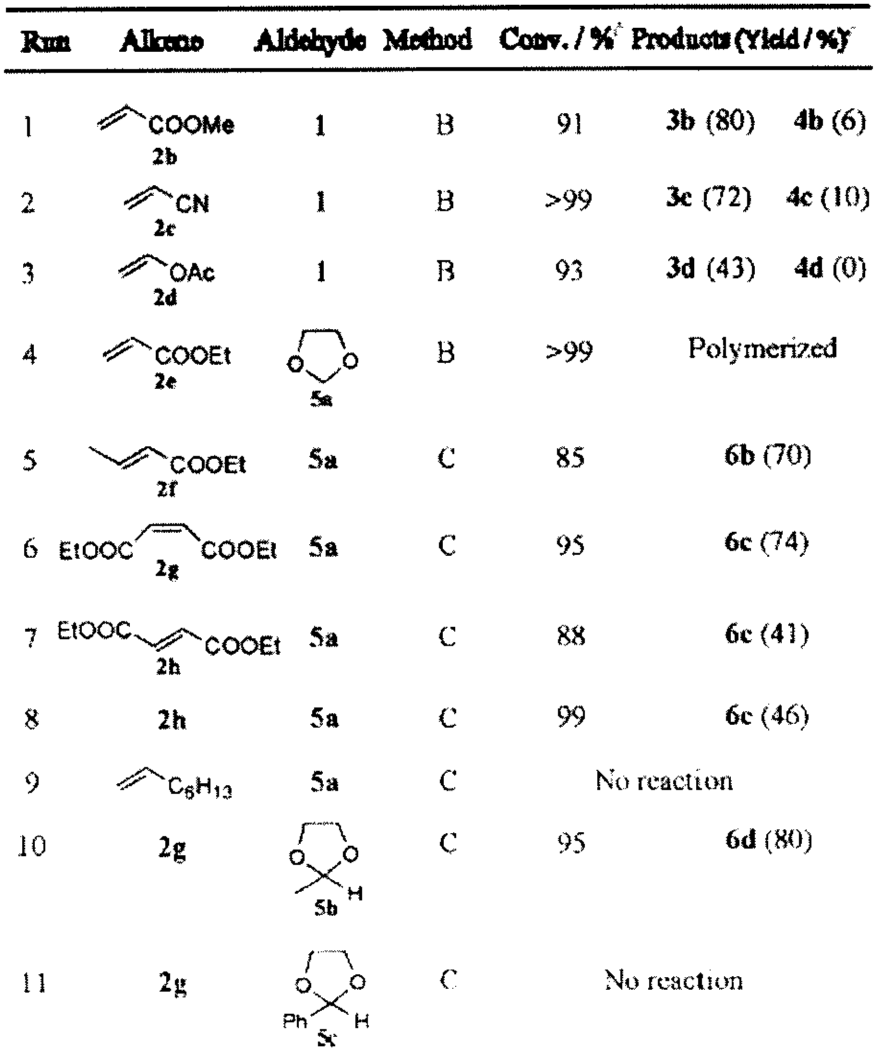
Slow step is by-passed by NHPI propogation

General Conditions:

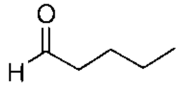
8 :1 Aldehyde : Olefin
20% NHPI
20% Peroxide Initiator
Toluene @ 80°C, 12 hr

Reaction also works with oxolanes

N-hydroxyphthalimide (NHPI) as a polarity reversal catalyst



Run	Alkene	Aldehyde	Method	Conv. / %[a]	Products (Yield / %)[b]
1	COOMe **2b**	**1**	B	91	**3b** (80) **4b** (6)
2	CN **2c**	**1**	B	>99	**3c** (72) **4c** (10)
3	OAc **2d**	**1**	B	93	**3d** (43) **4d** (0)
4	COOEt **2e**	O O **5a**	B	>99	Polymerized
5	COOEt **2f**	**5a**	C	85	**6b** (70)
6	EtOOC COOEt **2g**	**5a**	C	95	**6c** (74)
7	EtOOC COOEt **2h**	**5a**	C	88	**6c** (41)
8	**2h**	**5a**	C	99	**6c** (46)
9	C_6H_{13}	**5a**	C	No reaction	
10	**2g**	O O H **5b**	C	95	**6d** (80)
11	**2g**	O O Ph H **5c**	C	No reaction	



1

5a

Three component coupling with NHPI

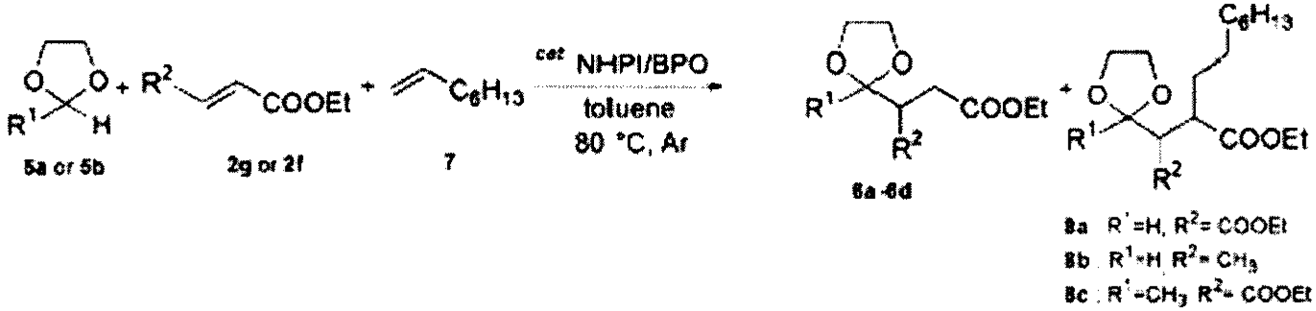
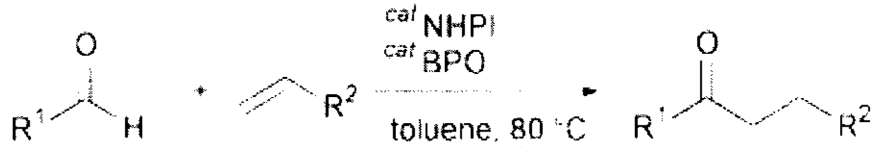


Table 3. Three-component coupling of oxolane. **2g** or **2f** and alkene or alkyne in the presence of NHPI and BPO[a]

Run	Oxolane (mmol)	**2g** or **2f**	Alkene or alkyne	Conv. (%)[b]	Product (Yield %)[c]	
1	**5a** (15)	**2g**	1-Octene (**7**)	58	**8a** (40)	**6c** (6)
2[d]	**5a** (15)	**2g**	**7**	75	**8a** (4)	**6c** (6)
3	**5a** (30)	**2g**	**7**	81	**8a** (67)	**6c** (3)
4	**5a** (30)	**2g**	Norbornene (**9**)	90	**8d** (57)	**6c** (12)
5	**5a** (15)	**2g**	1-Octyne (**10**)	37	**8e** (39)	**6c** (5)
6[e]	**5a** (30)	**2f**	**7**	47	**8b** (30)	**6b** (5)
7	**5b** (15)	**2g**	**7**	90	**8c** (44)	**6d** (10)
8[e]	**5b** (30)	**2g**	**9**	99	**8f** (77)	**6d** (12)
9	**5b** (15)	**2g**	**10**	50	**8g** (52)	**6d** (20)

[a] A mixture of oxolane (15 mmol), **2g** or **2f** (2 mmol), and alkene or alkyne (10 mmol) in toluene (1 mL) was reacted in the presence of NHPI (0.2 mmol) and BPO (0.2 mmol) under Ar (1 atm) at 80°C for 15 h.

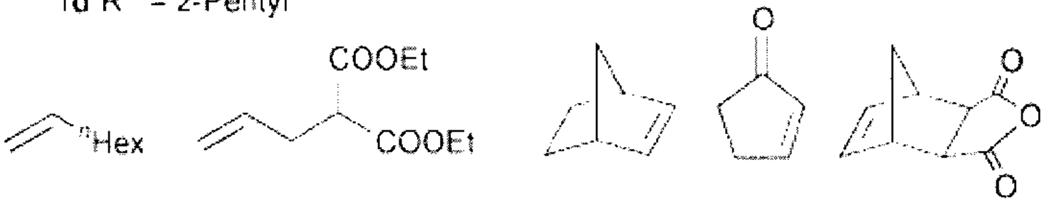
Hydroacylation of electron-rich alkenes with NHPI



1a-d **2a-e** **3**

1a R^1 = ^{n}Bu
1b R^1 = Et
1c R^1 = Ph
1d R^1 = 2-Pentyl

(1)



2a **2b** **2c** **2d** **2e**

Table 2 Hydroacylation of alkenes with aldehydes catalyzed by NHPI[a]

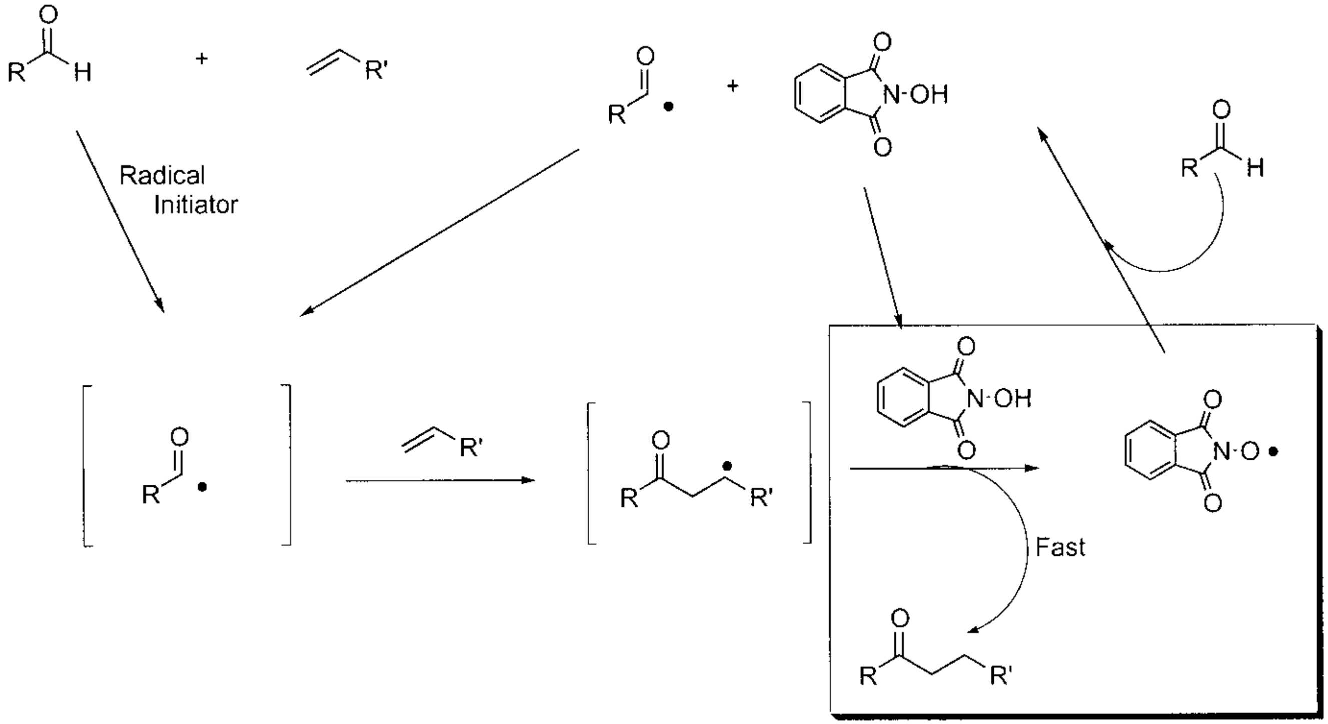
Run	Aldehyde	Alkene	Conv. (%)	Product	Yield (%)
1	**1a**	**2b**	91	**3ab**	67
2[b]	**1a**	**2b**	91	**3ab**	80
3	**1a**	**2c**	90	**3ac**	73
4	**1a**	**2d**	>99	**3ad**	53
5	**1a**	**2e**	>99	**3ae**	92
6	**1b**	**2a**	58	**3ba**	73
7	**1c**	**2a**	30	**3ca**	90
8[c]	**1c**	**2a**	33	**3ca**	83

[a] See Table 1a. [b] Chlorobenzene was used as a solvent. [c] Reaction condition was 90 °C.

-Addition of acyl radical into electron rich alkenes more difficult.
-Conditions relatively mild.

Chem. Commun., **2001**, 2352

Summary



Slow step is by-passed by NHPI propogation

- ***NHPI mediated acyl radical addition to alkenes proceeds in good yields with modest generality.***
- ***Mild conditions which do not require photolysis.***
- ***Addition to electron-rich alkenes substantially improved with NHPI as cataýst.***