

Axially Chiral Biaryl Diols Catalyze Highly Enantioselective Hetero- Diels-Alder Reactions Through Hydrogen Bonding

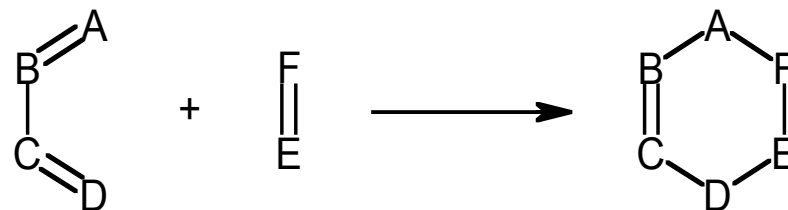
Aditya K. Unni, Norito Takenaka, Hisashi
Yamamoto, and Viresh H. Rawal

J. Am. Chem. Soc. **2005**, *127*, 1336-1337

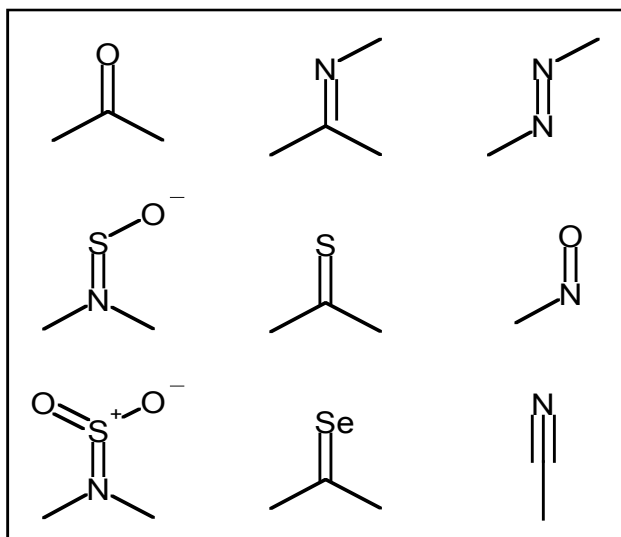
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Background

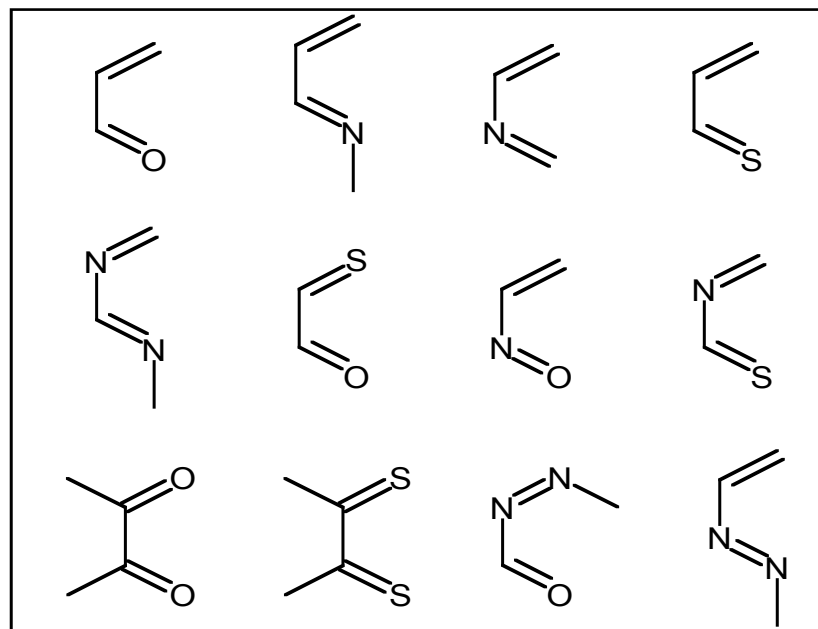
- [4+2] cycloaddition of heterodienophiles with heterodienes.



Heterodienophiles



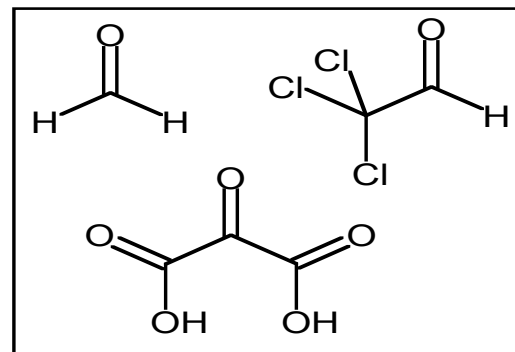
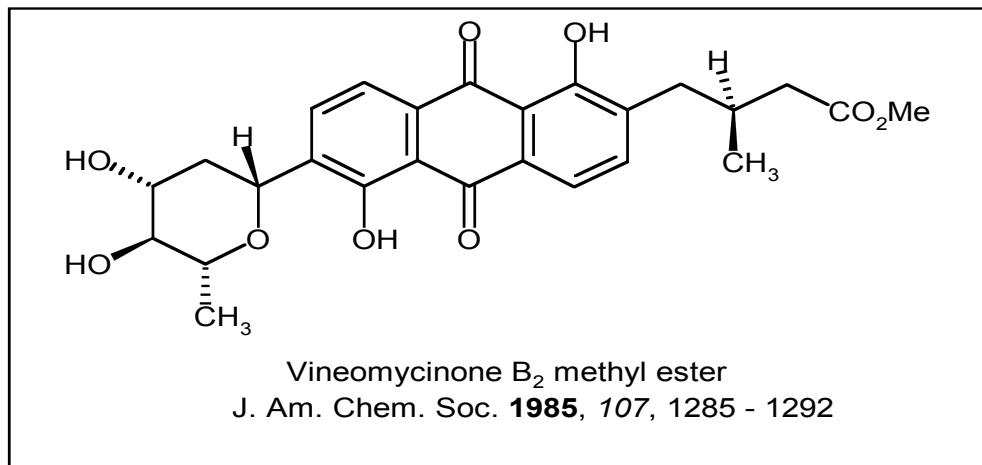
Heterodienes



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HDA Reactions with Aldehydes and Ketones

- **Importance:** Formation of oxygen based heterocycles such as 5,6-dihydropyrans which are important synthetic units found in many natural products.
- **Problem:** Only highly reactive aldehydes and ketones readily undergo HDA reactions with electron rich butadienes.
- **Past solutions:**
 - 1) High temperatures
 - 2) High pressures (15-25 kbar)
 - 3) Lewis acid activation



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Top. Curr. Chem. **1997**, *189*, 1 - 107.

On the Road To Milder Conditions

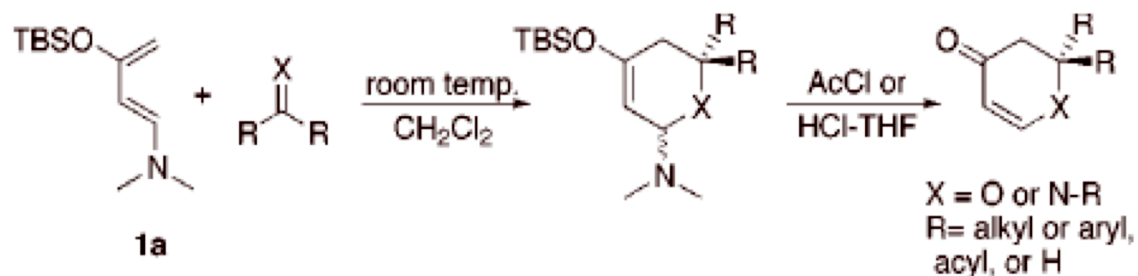


Table 2. Hetero Diels–Alder Reactions of Various Aldehydes

entry	aldehyde (2)	rxn time	product 4	yield ^a
1	2a	1.5 h	7a	86%
2	2b	45 min	7b	81%
3	2c	15 h	7c	71%
4	2d	2.5 h	7d	72%
5	2e	2 h	7e	73%
6	2f	2.5 h	7f	82%
7	2g	8 h	7g	83% ^b
8	2h	6 h	7h	92% ^b
9	2i	2 d	7i	54%

^aYield of chromatographically purified product. ^bObtained as an inseparable mixture of diastereomers.

In 2000, Viresh Rawal discovered that

1-amino-3-siloxy-1,3-butadienes are easily prepared, stable and highly reactive towards unactivated aldehydes at room temp. in CH₂Cl₂ to give dihydro-4-pyrone products, following N-acylation and subsequent β-elimination, in good yields.

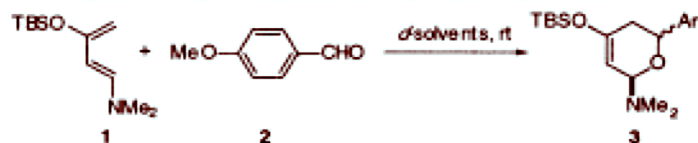
- 1) Aromatic aldehyde reaction rates corresponded to their respective carbonyl electrophilicities.
- 2) Primary aliphatic aldehydes reacted within 2-3 hrs.
- 3) Secondary aliphatic aldehydes reacted within 6-8 hrs.
- 4) The tertiary aldehyde reacted in 71 hrs.

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Org. Lett., **2000**, 2, 3321 – 3323.

H-Bond Rate Acceleration of HDA Reactions of Unactivated Ketones: Viresh Rawal 2002

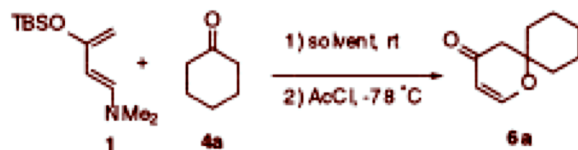
Table 1. Rates of HDA Reactions in Different Solvents



entry	solvent	dielectric constant ^a	rate constant (k) ^b	relative rate
1	THF- <i>d</i> ₃	7.6	1.0 × 10 ⁻⁵	1
2	benzene- <i>d</i> ₆	2.3	1.3 × 10 ⁻⁵	1.3
3	acetonitrile- <i>d</i> ₃	37.5	3.0 × 10 ⁻⁵	3.0
4	chloroform- <i>d</i>	4.8	3.0 × 10 ⁻⁴	30
5	<i>tert</i> -butyl alcohol- <i>d</i> ₁₀	10.9	2.8 × 10 ⁻³	280
6	isopropyl alcohol- <i>d</i> ₈	18.3	6.3 × 10 ⁻³	630

^a For the corresponding undeuterated solvent, at 25 ± 5 °C. ^b Kinetics measured by NMR integration using internal standard.

Table 2. Reactions of Cyclohexanone and 1 in H-Bonding Solvents



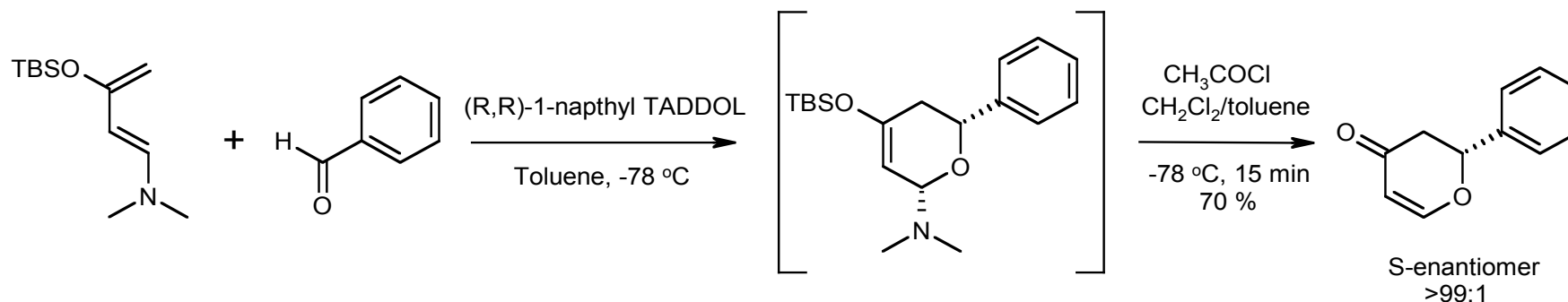
entry	solvent	time (h)	solvolysis (%) ^a	yield (%) ^b
1	chloroform	48	20–25	45
2	<i>tert</i> -butyl alcohol	24	<5	71
3	isopropyl alcohol	3	10–15	60
4	ethanol	0.5	~50 ^b	30
5	methanol	0.5	~40 ^b	0
6	2-butanol	5	<5	78

Table 3. Cycloaddition Reactions of Diene 1 and Unactivated Ketones

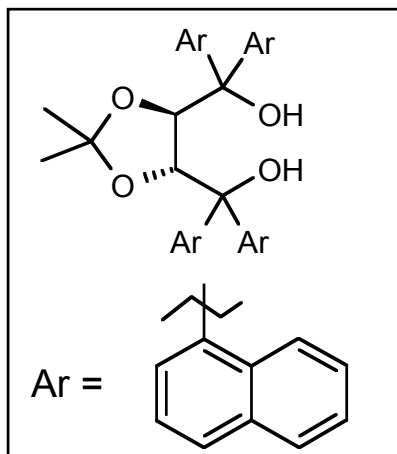
entry	ketone	time ^a	product	ratio	yield (%) ^c	
1		5 h		6a	78	
2		4 d		6b	35	
3		5.5 h		6c	4.2:1	75
4		5.5 h		6d	2.8:1	74
5		5.5 h		6e	3:1	76
6 ^b		8 h		6f	1.5:1	81
7		3 h		6g		82
8		19 h		6h		41
9		30 h		6i		40
10		6 h		6j		33 ^d
11		1.5 h		6k		77

David Arnold 5/6/06 J. Am. Chem. Soc. 2002, 124, 9662-9663.

Chiral-Alcohol Catalysts: Viresh Rawal 2003



Chiral Catalyst



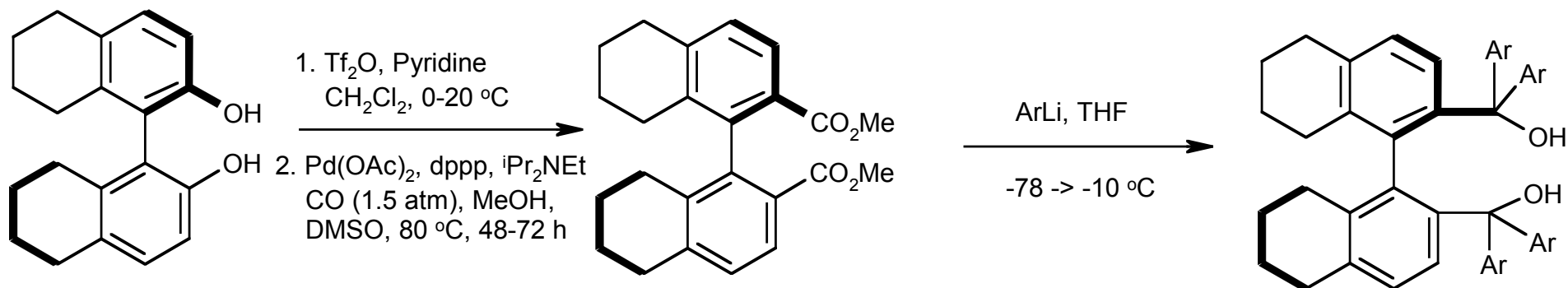
- Novel example of a hydrogen bonding chiral catalyst, catalyzing an HDA reaction.
- Good yields and enantioselectivities
- Uncatalyzed HDA reaction does not proceed in toluene under identical conditions.

Nature **2003**, 424, 146.

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A Natural Extension: Axially Chiral Biaryl Diols: Viresh Rawal and Hisashi Yamamoto 2005

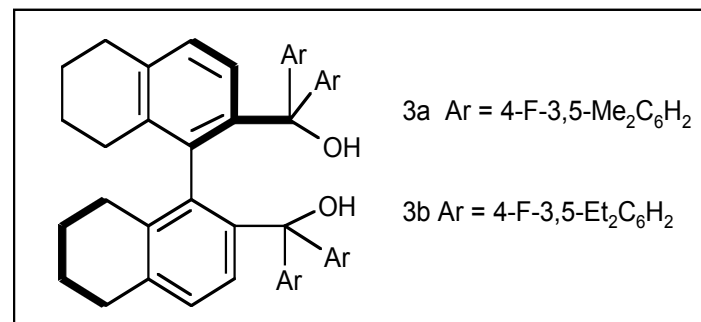
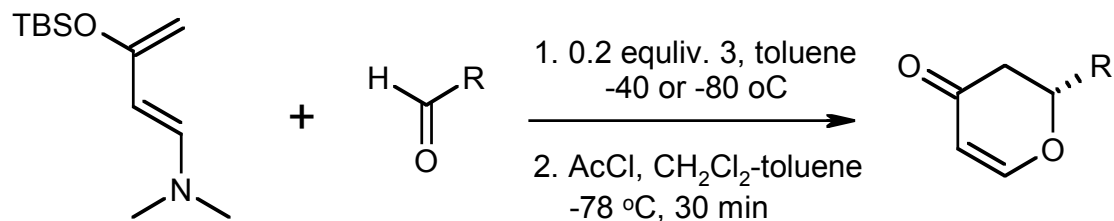
Synthesis of Axially Chiral BAMOLs



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A Natural Extension Continued...



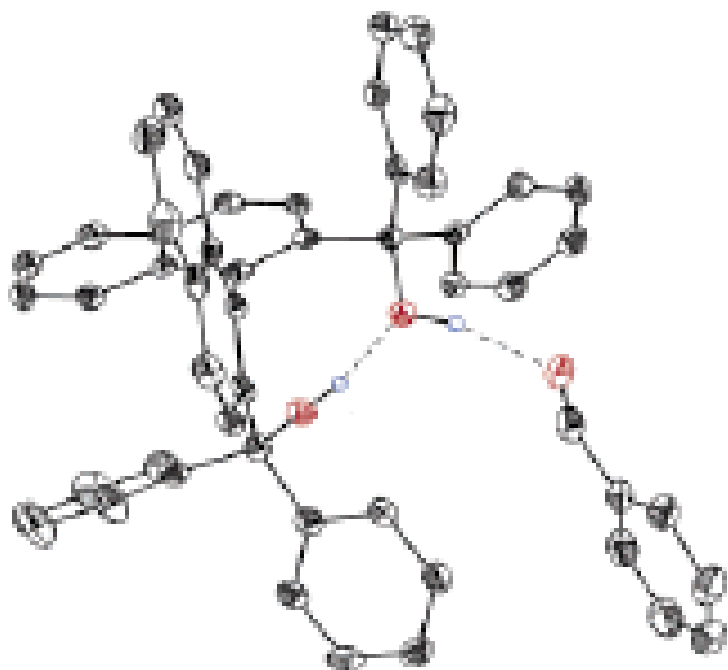
entry	product	R	catalyst ^b	yield (%) ^c	ee (%) ^d
1	4a	Me	3b	75	97 ^e
2	4b	<i>n</i> -propyl	3a	76	94
3	4c	Ph(CH ₂) ₂	3a	95	95
4	4d	PhS(CH ₂) ₂	3a	76	94 ^e
5	4e	Phth(CH ₂) ₃ ^f	3a	67	92 ^e
6	4f	1-propynyl	3a	42	98 ^e
7	4g	<i>i</i> -butyl	3a	79	90 ^e
8	4h	<i>c</i> -hexyl	3a	99	84
9	4i	Ph	3b	84	98
10	4j	3-(MeO)-C ₆ H ₄	3b	86	98 ^e
11	4k	2-(NO ₂)-C ₆ H ₄	3b	93	98 ^e
12	4l	1-naphthyl	3b	67	97 ^e
13	4m	2-furyl	3b	96	>99

- Straight-chain aliphatic aldehydes: good yields excellent ee's
- Branch-chain aldehydes: lower ee's
- Lewis basic heteroatoms are well tolerated
- Electron rich and electron poor aromatic aldehydes give comparable ee's.

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Crystal Structure of the Inclusion Complex of 2,2'-bis-(diphenylhydroxymethyl)binaphthylene and benzaldehyde



- 1:1 complex
- Intramolecular hydrogen bond between hydroxyls
- Intermolecular hydrogen bond to carbonyl of benzaldehyde
- Carbonyl activation through a single-point hydrogen bond

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Conclusion

- The use of hydrogen bonding solvents and chiral hydrogen bonding catalysts as carbonyl activators has proved to be an efficient method for both accelerating the hetero Diels-Alder reaction and controlling the stereochemical outcome.
- Chiral alcohol catalysis offers a potentially very useful alternative to traditional metal based Lewis acid catalysis and may possibly be extended successfully to many other asymmetric reactions requiring carbonyl activation.

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