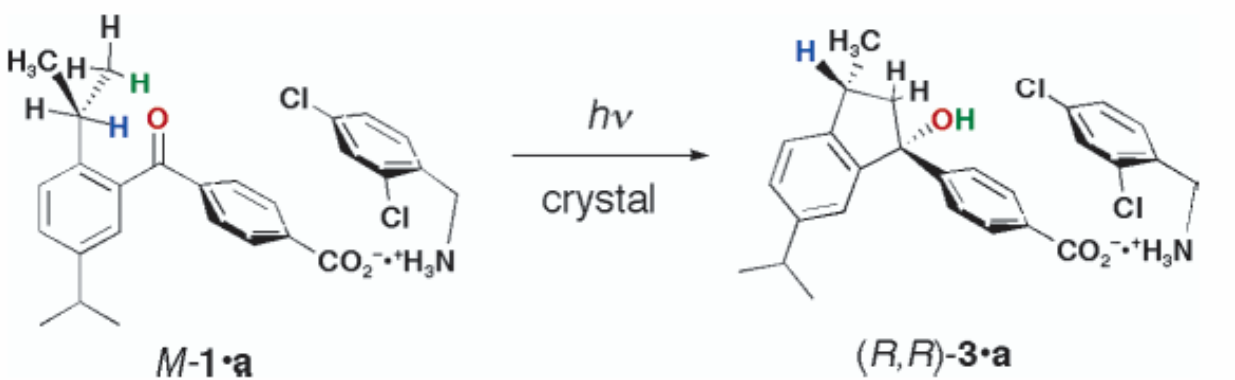
Absolute Asymmetric Photocyclization of Isopropylbenzophenone Derivatives Using a Cocrystal Approach Involving Single-Crystal-to-Single-Crystal Transformation



H. Koshima, H. Kawanishi, M. Nagano, H. Yu, M. Shiro, T. Hosoya, H. Uekusa, Y. Ohashi

Journal of Organic Chemistry, **2005**, *70*, 4490-4497.

Markus Furegati
Current Literature
June 4th 2005

Chiral Solid-State Photochemistry

- Since early 1970s
- Asymmetric photochemistry in solution and in the solid state are still in the area of basic research
- In general: crystalline state photoreactions can lead to high enantio- and diastereodifferentiation

Analytics for solid phase samples

- X-ray crystallography
- Solid state circulardichroism (CD) in Nujol mull or KBr-disc

  Kuroda R., In *Chiral Photochemistry*; Inoue Y., Ramamurthy V., Eds.; Marcel Dekker, Inc.; NY, 2004, p. 385.
- IR, X-ray powder diffractometry, DSC (distinction of polymorphs)

Classification of Solid-State Asymmetric Photoreactions

Reactant Medium	Chiral Source	Optical differentiation	
Chiral crystal from chiral molecule	Chiral molecule	moderate - high	diastereodifferentiation
Supramolecular approach [1]			
Host-guest crystal	Chiral host molecule	moderate - high	enantiodifferentiation
Salt crystal	Chiral acid or base	moderate - high	enantiodifferentiation
Cocrystal	Chiral molecule	moderate - high	enantiodifferentiation
Modified zeolite	Chiral molecule	low - moderate	enantiodifferentiation
Spontaneous chiral crystallization approach [2]			
Chiral crystal from achiral molecule	Chiral crystal lattice	moderate - high	enantiodifferentiation

Table from: Koshima H. In *Chiral Photochemistry*; Inoue Y., Ramamurthy V., Eds.; Marcel Dekker, Inc.; NY, 2004, p. 485.

[1] Toda F. *Acc. Chem. Res.* **1995**, *28*, 480.
[2] Scheffer J. R. *Acc. Chem. Res.* **1996**, *29*, 203.

Absolute Asymmetric Photoreactions by the Spontaneous Chiral Crystallization Approach

The spontaneous chiral crystallization approach is the best methodology for asymmetric synthesis without any external chiral source.
-> Problem: spontaneous chiral crystallization cannot be predicted at present.

The statistical probability for the chiral crystallization of achiral compounds was around 8% (190‘000 structures from Cambridge Structural Database)

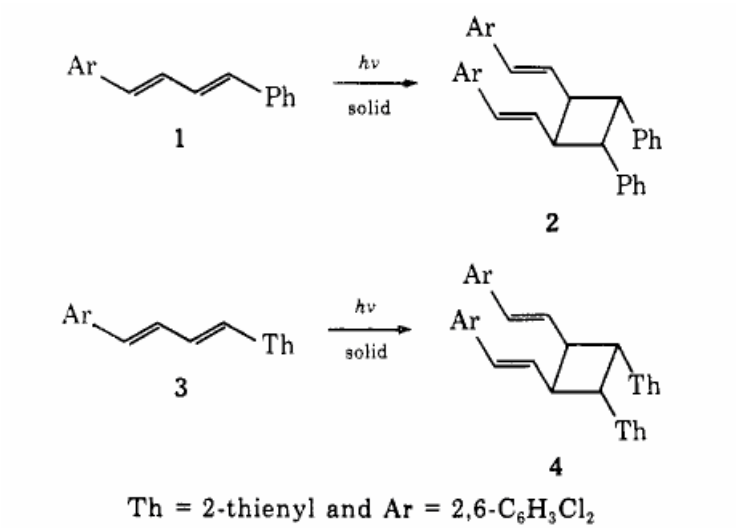
Around 20 absolute asymmetric photoreactions in the solid state have been reported. Most of them are intramolecular and include:

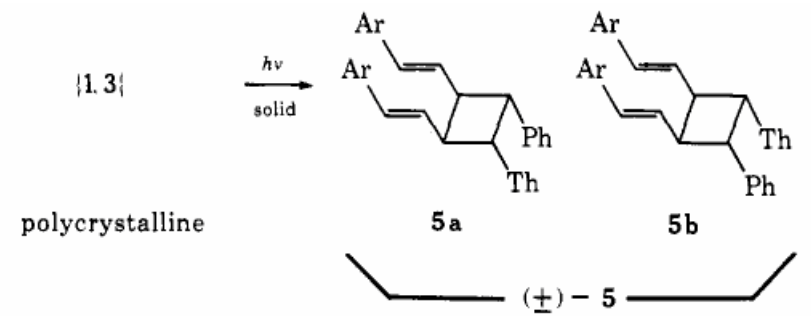
- Photocyclizations [4+2], [2+2]
- Di-π-methane photorearrangement
- Norrish type II photocyclization

Koshima H. In *Chiral Photochemistry*; Inoue Y., Ramamurthy V., Eds.; Marcel Dekker, Inc.; NY, 2004, p. 485.

Examples I

First absolute asymmetric intermolecular [2+2] photodimerization of butadiene derivatives in mixed crystals.





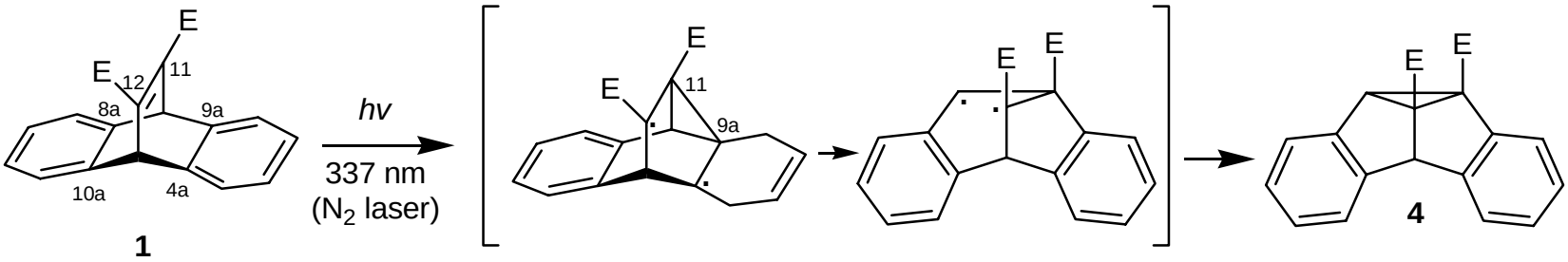
Irradiation of powdered large mixed single crystal gave dextro- or levorotatory material.

90% of dimeric material, no optical yield given

Schmidt G. M. J. *et al. JACS* **1973**, *95*, 2058.
racemic [2+2] photoreaction:
Schmidt G. M. J. *et al. J. Chem Soc.* **1964**, 1996.
Schmidt G. M. J. *et al. ACIEE* **1969**, *8*, 608.

Examples II

Stereospecific di-π-methane photorearrangement of dibenzobarrelene diisopropylester **1** to the dibenzosemibullvalene derivative **4**.

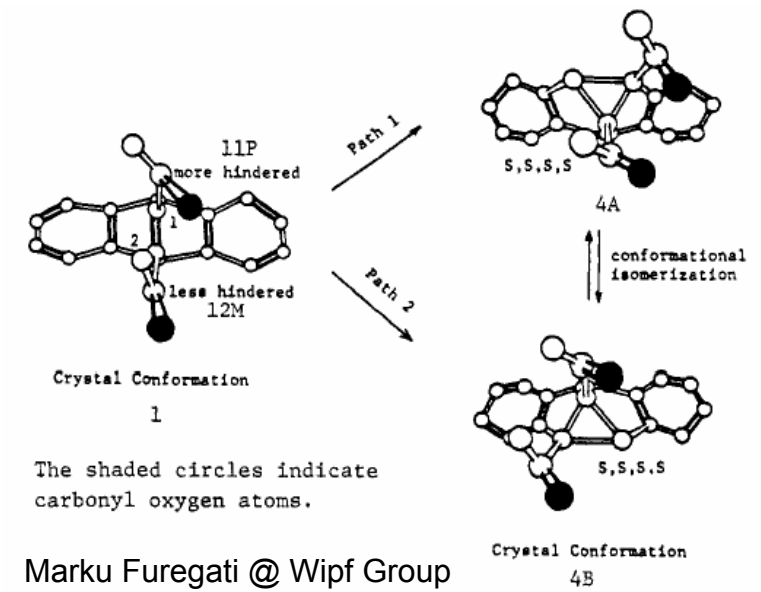


1

E = $CO_2{}^iPr$

Path I : initial 9a-11 bonding
Path II : 10a-12
Path III: 4a-12
Path IV: 8a-11

up to 25% yield
100% *ee* (determined with NMR shift reagents)

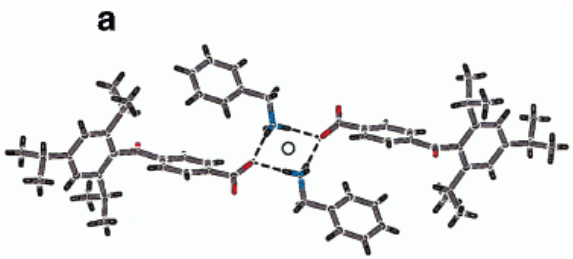


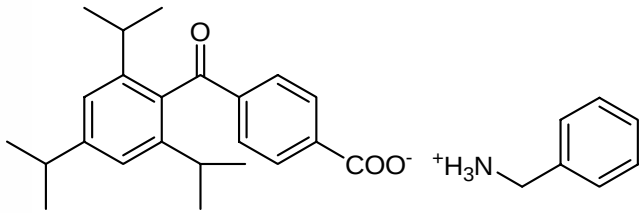
Paths I + II lead to one enantiomer of **4**, paths III + IV lead to the other.

Di-π-methane rearrangement:
H. E. Zimmermann, G. L. Grunewald, *JACS* **1966**, *88*, 183.
example taken from:
Garcia-Garibay M. Omkaram N. Scheffer J. R. Trotter J. Wirenko F. *JACS* **1989**, *111*, 4985.

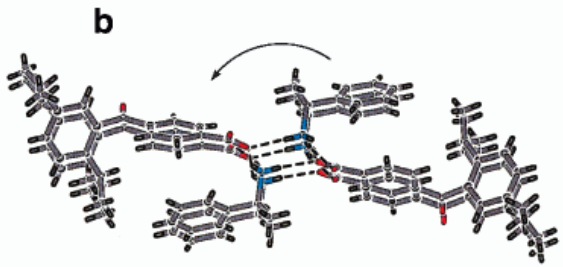
Examples III

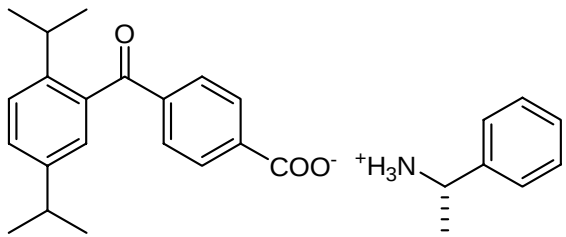
Absolute Asymmetric Photocyclization of Isopropylbenzophenone Derivatives Using a Cocrystal Approach Involving Single-Crystal-to-Single-Crystal Transformation.



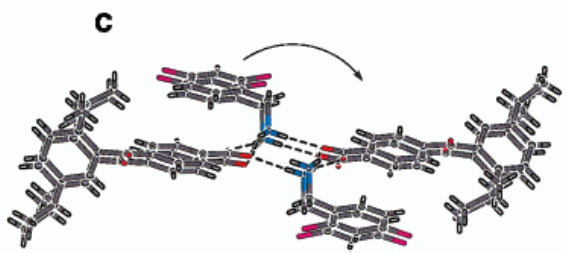


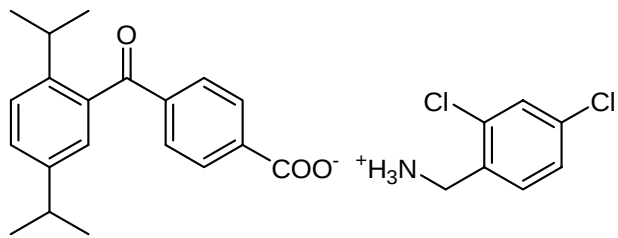
achiral





chiral

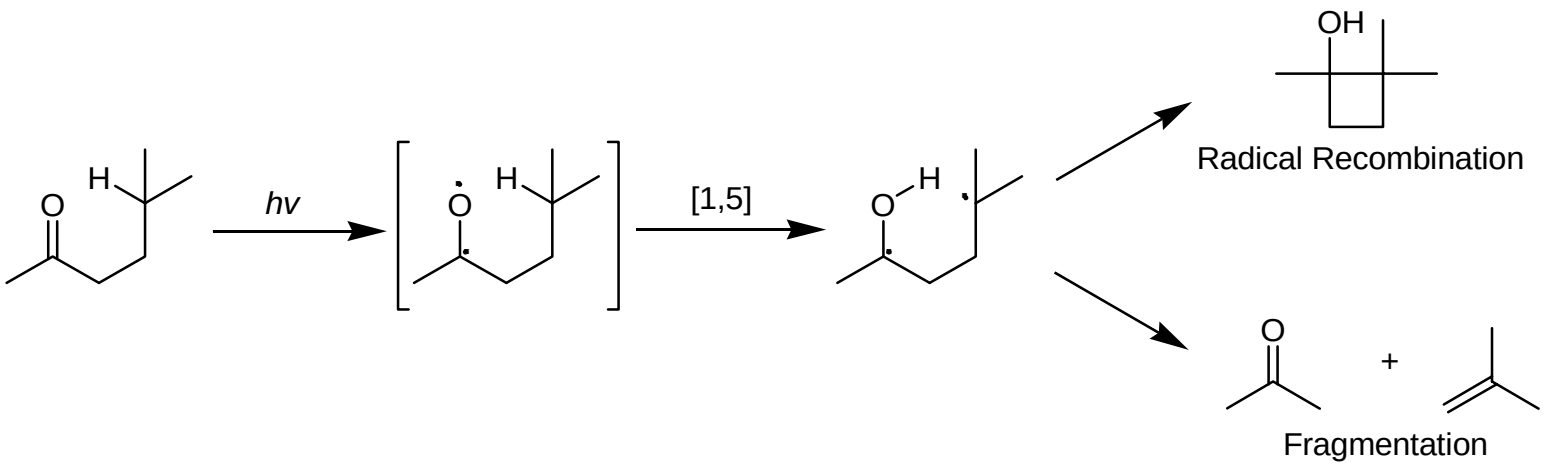




chiral

H. Koshima *et al*. *JOC* **2005**, *70*, 4490-4497.
H. Koshima *et al. CrystEngComm* **2001**, *33*, 1 (p. 141!)

Norrish Type II Reaction

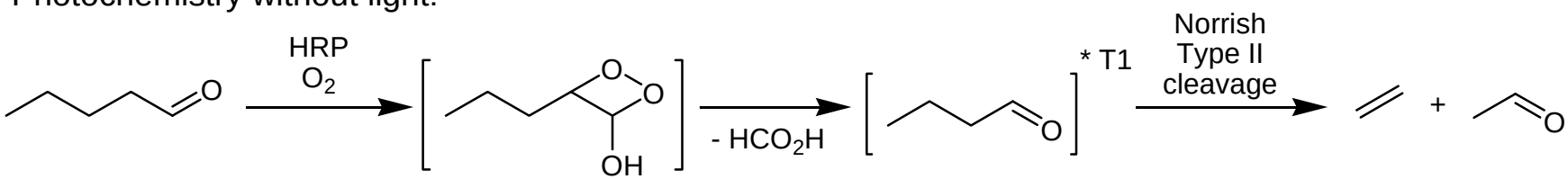


- R. G. W. Norrish *Trans. Faraday Soc.* **1937**, *33*, 1521.
- *Norrish Type II Cleavage:* Reaction originating from the nπ* excited state of aldehydes and ketones that involves intramolecular γ-hydrogen abstraction via 6-membered transition state followed by cleavage of the resulting diradical to an olefin and an enol.
- Only a few applications, mostly of mechanistic interest.

Norrish Type II Reaction – Occurrence and Applications

- Analogy in mass spectrometry: *McLafferty* fragmentation (F. W. McLafferty, *Anal. Chem.* **1959**, *31*, 82)

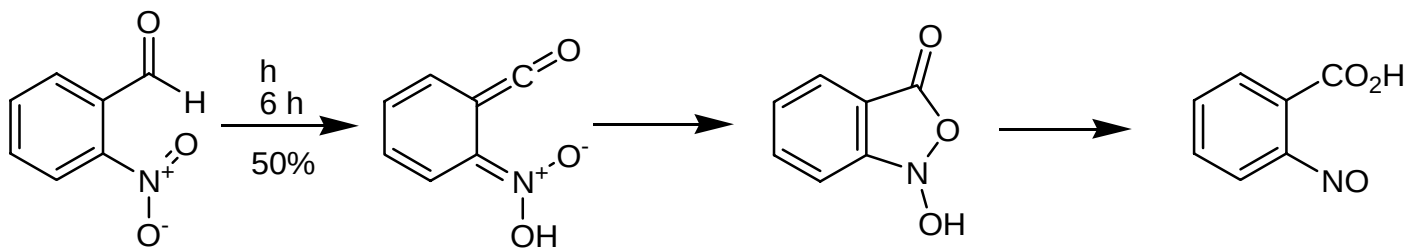
- Photochemistry without light:



G. Cilento *et al. Proc. Natl. Acad. Sci. USA* **1994**, *91*, 410.

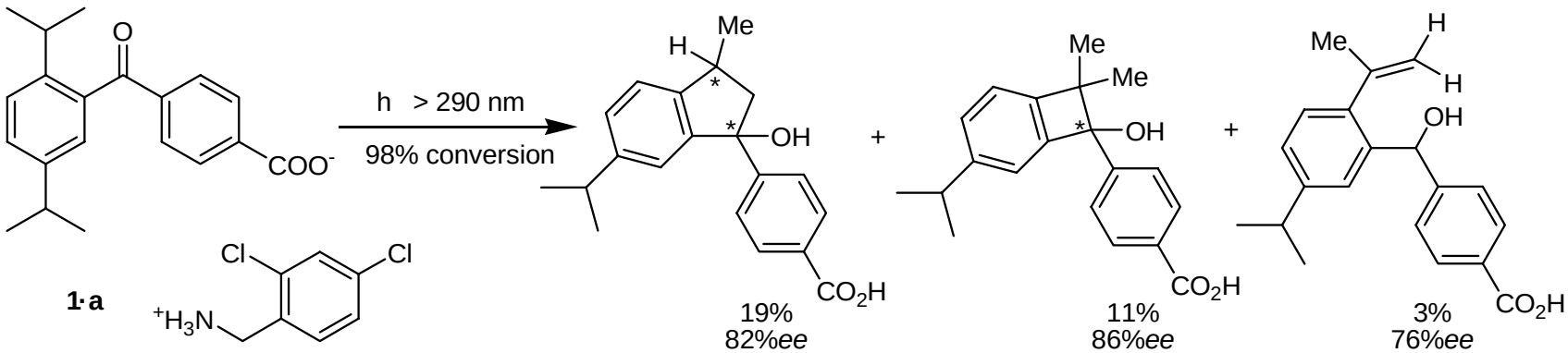
- Photodegradation of polymers -> Insertion of carbonyls into the polymer molecule leads to fragmentation
  a) J. E. Guillet, Y. Amerik *Macromolecules* **1971**, *4*, 375.
  b) P. Hrdlovic, I. Lukac *Dev. Polym. Degrad.* **1982**, *4*, 101.

- Photoisomerization of *o*-nitrobenzaldehyde to *o*-nitrosobenzoic acid
  Journal of Antibiotics **1986**, *39* 864.



Experimental

Irradiation of pulverized crystals using high-pressure mercury lamp at r.t. under Ar.
Treatment of the mixture with CH_2N_2, analysis by HPLC.

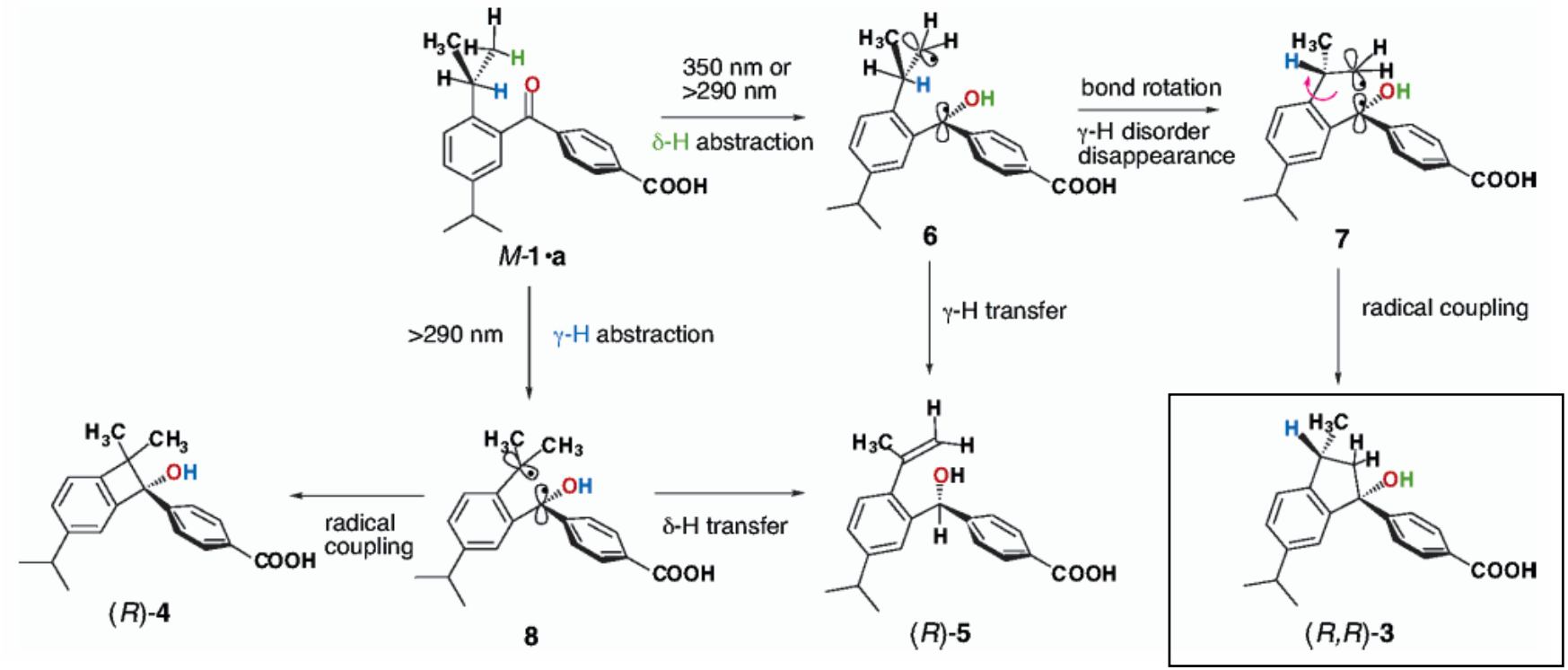


entry	crystal	irradiation time (min)	conversion (%)	3 yield (%)	3 ee (%)	4 yield (%)	4 ee (%)	5 yield (%)	5 ee (%)
1	*P*-1·a	45	28	18	(*S*,*S*) 86	7	(*S*) 80	2	(*S*) 79
2	*P*-1·a	90	81	46	(*S*,*S*) 87	23	(*S*) 82	7	(*S*) 85
3	*P*-1·a	180	91	56	(*S*,*S*) 86	27	(*S*) 80	8	(*S*) 83
4	*M*-1·a	45	28	17	(*R*,*R*) 80	7	(*R*) 78	4	(*R*) 80
5	*M*-1·a	90	75	43	(*R*,*R*) 83	21	(*R*) 84	8	(*R*) 83
6	*M*-1·a	180	85	52	(*R*,*R*) 86	25	(*R*) 85	7	(*R*) 81

H. Koshima *et al*. *JOC* **2005**, *70*, 4490-4497.

Experimental

Irradiation of a single crystal at 350 nm for 1 month at r.t. 1.86% increase in volume of the unit cell. Analysis: **3** : **1** = 7 : 3, no **4** or **5** detected by HPLC.



- The Xray structure could not be resolved properly to determine the position of the γ-H. (both H's are shown)
- Slow conversion by the excitation of the absorption edge keeps the crystal from deteriorating due to the irradiation.

H. Koshima *et al*. *JOC* **2005**, *70*, 4490-4497.

Summary

Absolute asymmetric solid-state photoreactions:

The only chiral element is the enantiomorphic space group of the crystal. Ideally, the solid-state reaction should transfer the crystal chirality to the product permanently in the form of new chemical bonds.

moderate to high enantioselectivities, especially for intramolecular reactions

promising methodology even if spontaneous chiral crystallization cannot be predicted at present

Title paper:

Synthesis of 3 chiral crystals derived from achiral acids/bases.

Irradiation at 350 nm gave mainly the cyclopentenol **3** in high enantioselectivities.

The selectivity for the formation of **3**, **4** and **5** at >290 nm and only **3** at 350 nm cannot be explained at the present time.