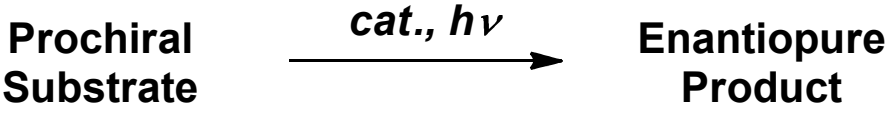
Asymmetric Catalytic Photoreactions in Solution

9th/Sep/2013 (Mon) Ozawa Jun (M2)



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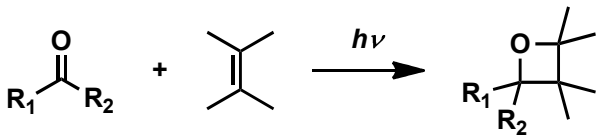
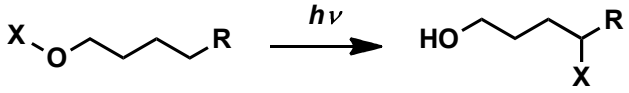
1. Introduction

Photoreaction is a powerful approach to the chemical synthesis that cannot be replaced by thermal reactions.

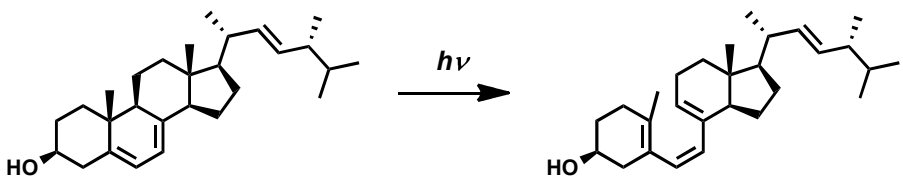
Paternò-Büchi reaction



Barton reaction



photopericyclic reactions

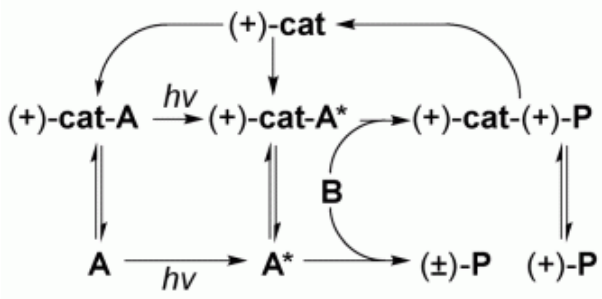


There has been, however, very limited success in developing asymmetric catalytic photoreactions, mainly because of the low-barrier, very rapid process that proceed from short-lived electronic excited states.

→ A chiral catalyst has to have a high ability to bias and organize the molecular architecture of fleetingly excited state of photoreactions.

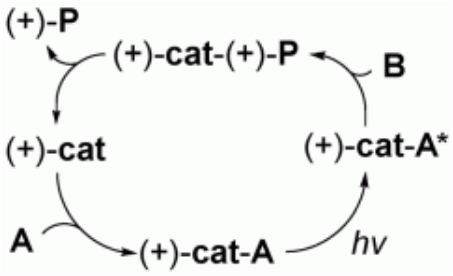
♥ How can the asymmetric reactions be achieved?

(A)



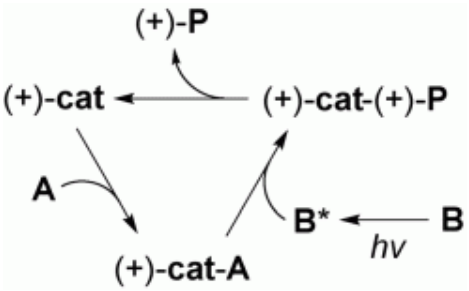
Chiral reagent (+)-cat, which is electronically inert, gives an environment where the photoreaction proceeds enantioselectively.

(B)



Chiral reagent (+)-cat is involved in the photo-activation step of the substrate A to produce (+)-cat-A*, which subsequently reacts with B to produce a chiral product (+)-P.
A alone isn't photoactivated.

(C)



Association of (+)-cat with the substrate A changes the electronic properties , facilitating a reaction with the photoactivated B*.
B* doesn't react with A alone.

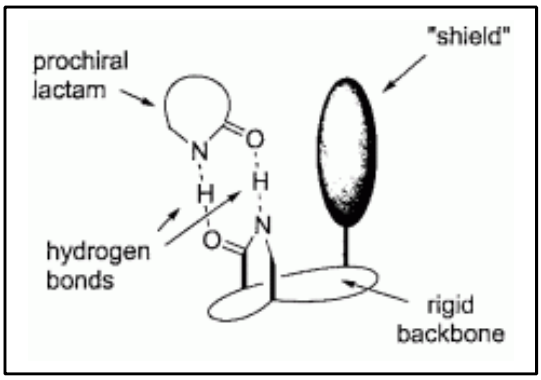
An efficient catalyst must not cause the background or side reactions:
what is necessary is the situation where no reaction proceed without the catalyst, and in the presence of the catalyst the desired reaction then proceeds.

→ The catalysts categorized as type (B) or (C) seem to be promising .
(Racemizing backgroun reactions are problematic with type (A) catalysts.)

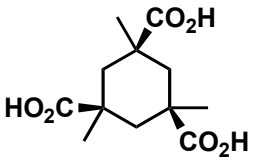
2. Asymmetric Photoreactions

2-1. Chiral Template

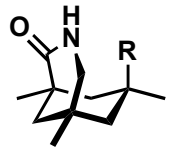
Thorsten Bach's strategy

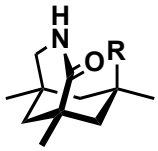


- **The "shield" hinders the substrate from coming from the "shielded" side.**

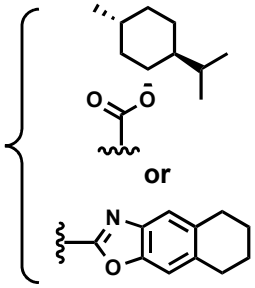


Kemp's triacid





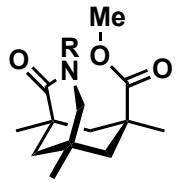
R is mainlyl



or

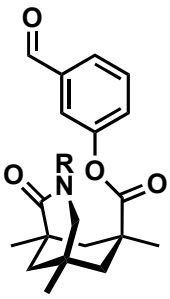
How to synthesize these: T. Bach *Synthesis*, 2001, 1395.

T. Bach *JACS*, 1999, *121*, 10650.



1a R = H
1b R = Me

1. NaOH (DMSO)
2. $SOCl_2$; ArOH,
Et_3N, DMAP (THF)



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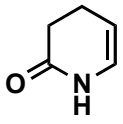
hν,



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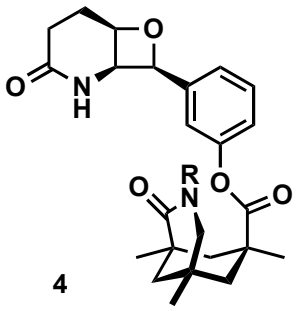

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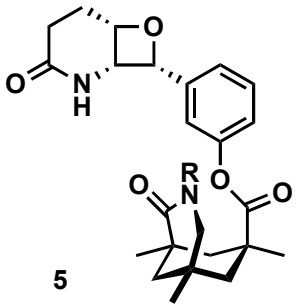

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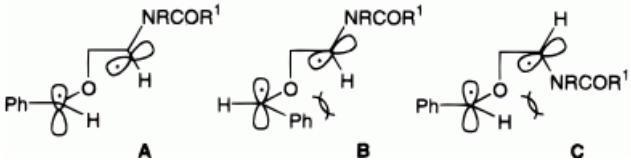
Table 1. Photocycloaddition of the Chiral Amides **2** and the Dihydropyridone **3**

entry	aldehyde	solvent[a]	temp. [°C]	oxetane	yield [%]	dr[b] (**4**/**5**)
1	**2a**	MeCN	65	**4a/5a**	56	50/50
2	**2a**	MeCN	30	**4a/5a**	*c*	50/50
3	**2a**	benzene	30	**4a/5a**	62	83/17
4	**2a**[d]	benzene	30	**4a/5a**	50	89/11
5	**2a**	toluene	−10	**4a/5a**	56	95/5
6	**2b**	benzene	30	**4b/5b**	50	50/50

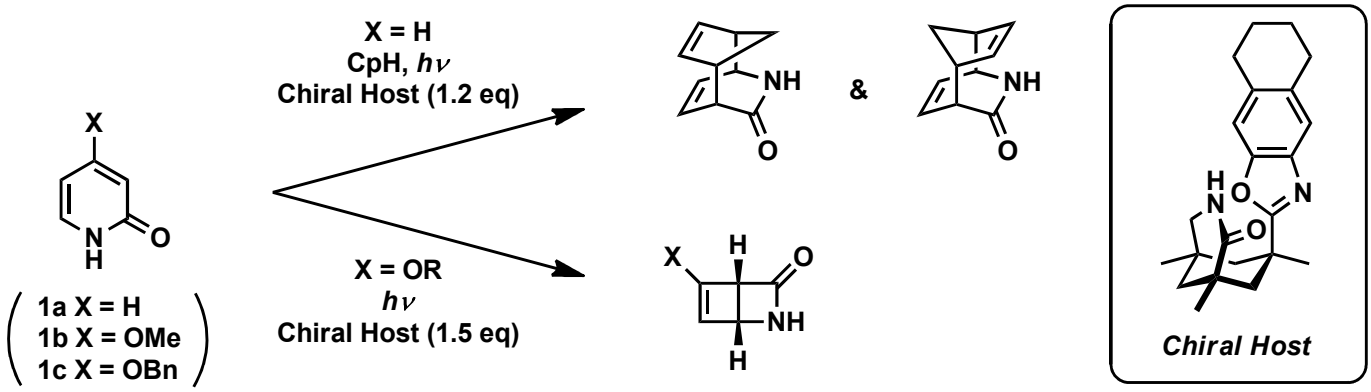
[a] The reaction was conducted at 65 °C and 30 °C in a merry-go-round apparatus Rayonet RPR-100 (λ = 300 nm; light source: Rayonet RPR 3000) and at −10 °C in an immerison apparatus (Duran filter; light source: Original Hanau TQ 150). [b] The diastereomeric ratio of oxetanes in the crude product was determined by integration of appropriate ^{1}H NMR signals. [c] The yield of isolated product was not determined in this case. [d] An excess of the chiral aldehyde **2a** was employed (3 equiv).

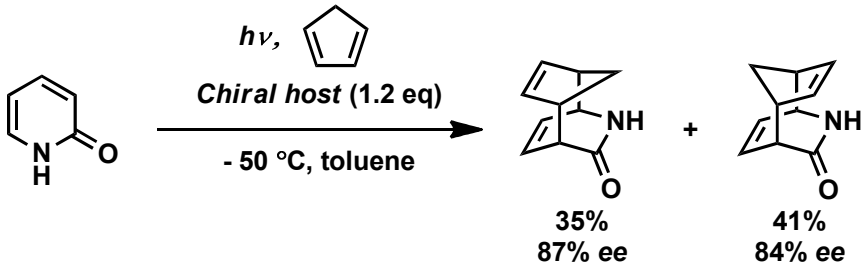
- **90% *ee* is obtained (entry 5).**
- **In entry 6 the *ee* is 0%, which indicates the two H-bonings between 2 and 3 are essential for this asymmetric reaction.**



T. Bach *ACIE*, 1999, *64*, 1265.

T. Bach *Org. Lett.*, 2001, *3*, 601.





High yields (total 76%) and high *ee*s (> 80%) are obtained.
(only one example for an intermolecular reaction)

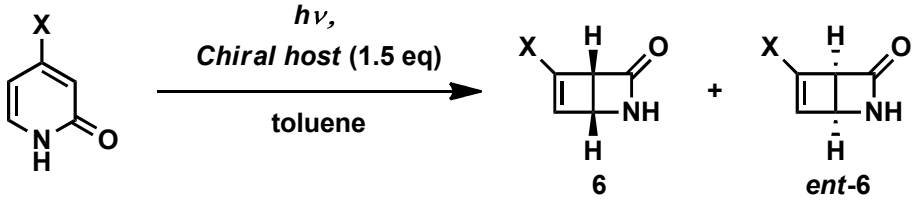
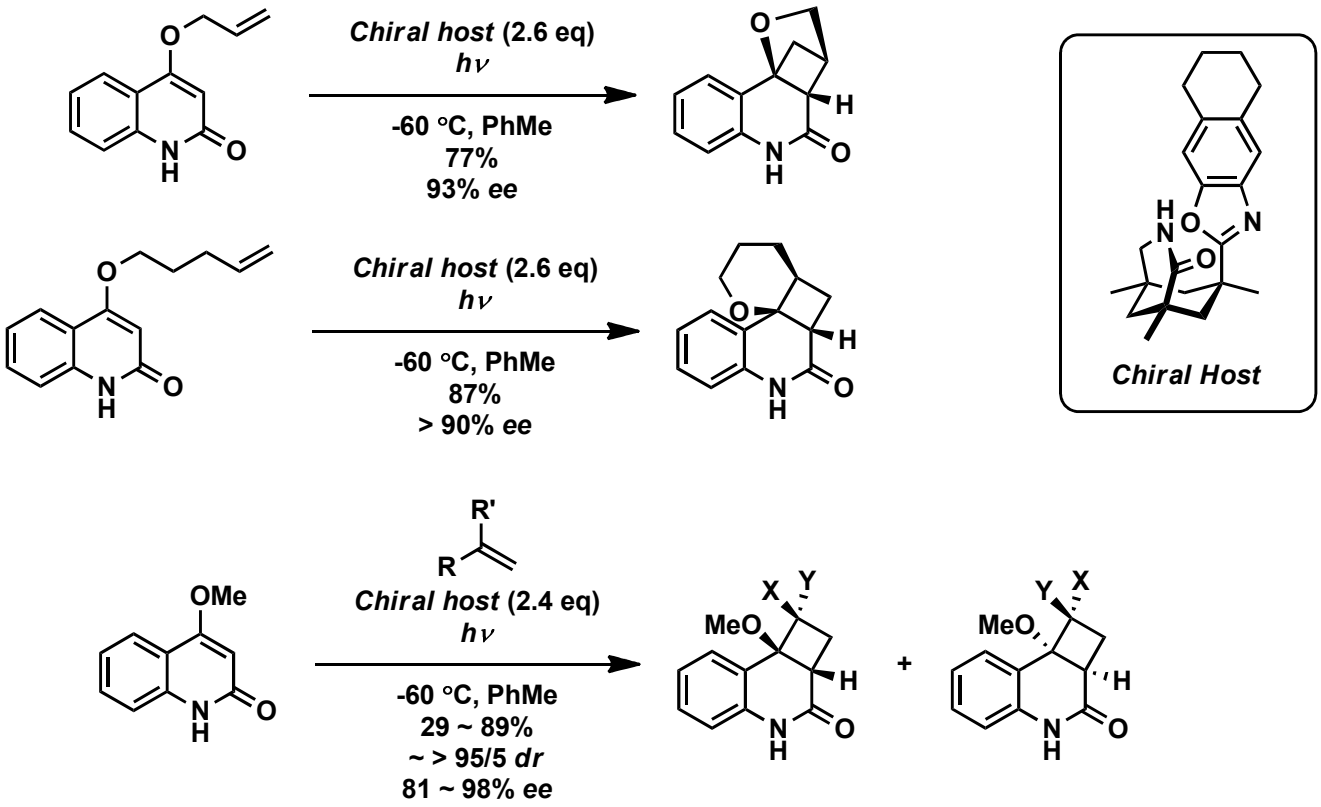


Table 1. Electrocyclic [4π]-Ring Closure of Pyridones **1** in the Presence of the Chiral Lactam **2** (cf. Scheme 2)

entry	pyridone	X	time[a] (h)	temp[b] (°C)	product	yield (%)	ee[c] (%)
1	**1a**	H	4	30	**6a**	18	10
2	**1b**	OMe	2.5	30	**6b**	75	17
3	**1b**	OMe	96	−20	**6b**	44	20
4	**1c**	OBn	3.5	30	**6c**	75	19
5	**1c**	OBn	96	−20	**6c**	51	23

[a] Time after which the irradiation was stopped. [b] Irradiation temperature. Irradiation source: Original Hanau TQ 150. [c] The ee values {ee = [(+)-**6** − (−)-*ent*-**6**]/[(+)-**6** + (−)-*ent*-**6**]} were determined by chiral HPLC (column, chiracel OD; eluent, *n*-hexane/2-propanol 92/8).

Poor *ee*s are obtained (max 23%);
according to Bach, it's probably because
a) the steric differences of the two cyclization mode are marginally, or
b) the transition states are located very early on the reaction coordinate.



Cyclization : T. Bach *ACIE*, 2000, *39*, 2302.
Annulation : T. Bach *JACS*, 2000, *122*, 11525.
Full paper : T. Bach *JACS*, 2002, *124*, 7982.

This Bach's Chiral templates enable highly efficient enantioselective photoreactions, but there are some disadvantages:

1. the stoichiometric use of the chiral hosts
In this system *ee* cannot exceed the amount of the chiral host.

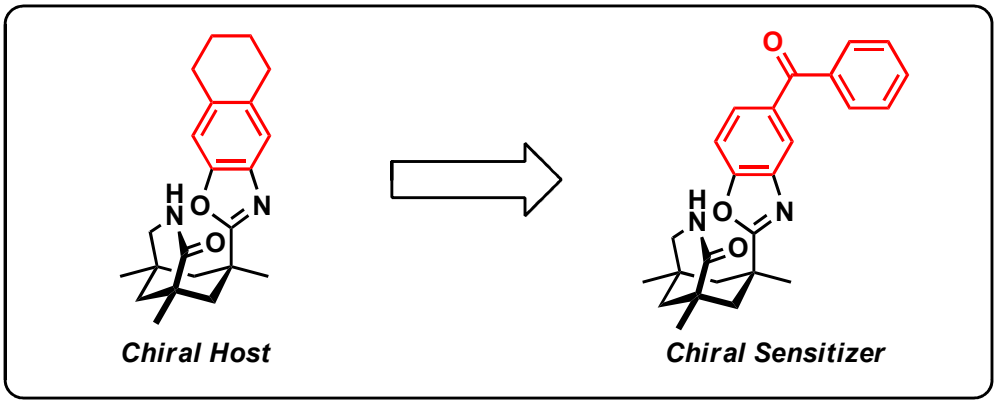
2. limited substrate scope
a) The substrates have to contain cyclic amide structure.
b) The reaction site has to be close to the cyclic amide enough to be "shielded".

3. The reaction temperature has to be low enough for the H-bonds to facilitate the tight binding between the substrate and the host.

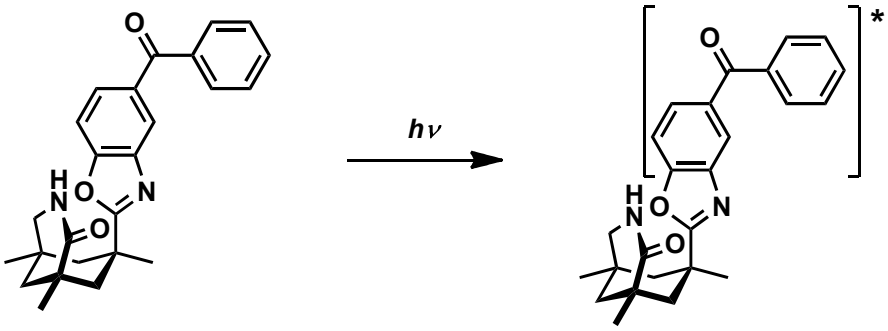
→ To overcome these problems, another strategies are necessary.

2-2. Chiral Catalyst Involved in Photoactivation

- **Thorsten Bach's strategy 1**



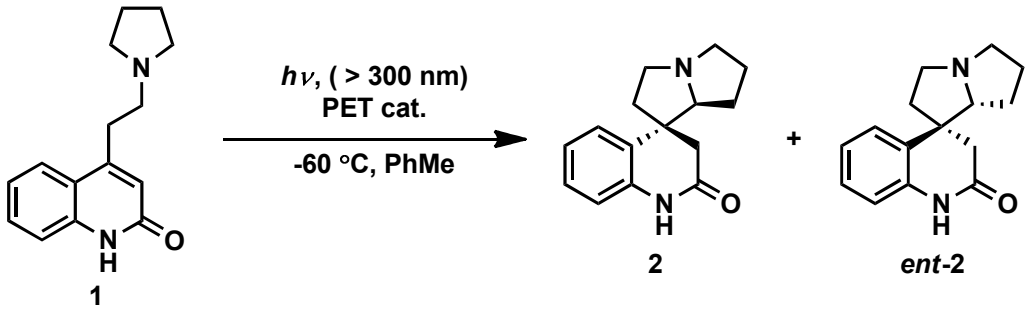
The "shield" plays another role of photosensitization.



This initiates some photoreactions.

Substrates have to be close to the catalyst to be activated by the photoexited chiral sensitizer.
→ It is possible that asymmetric photoreaction is achieved under catalytic amount of the catalyst.

T. Bach *Nature*, 2005, *436*, 1139.



70% *ee* is obtained with a catalytic amount of the catalyst 4.

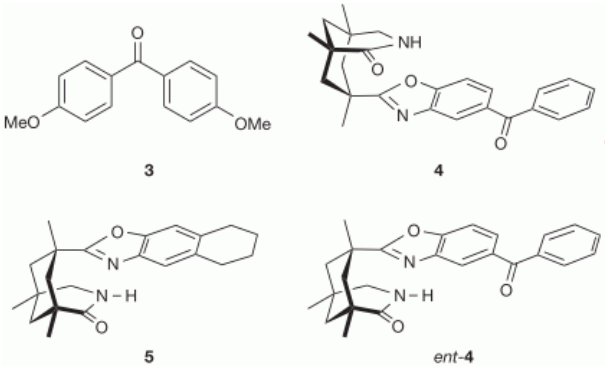
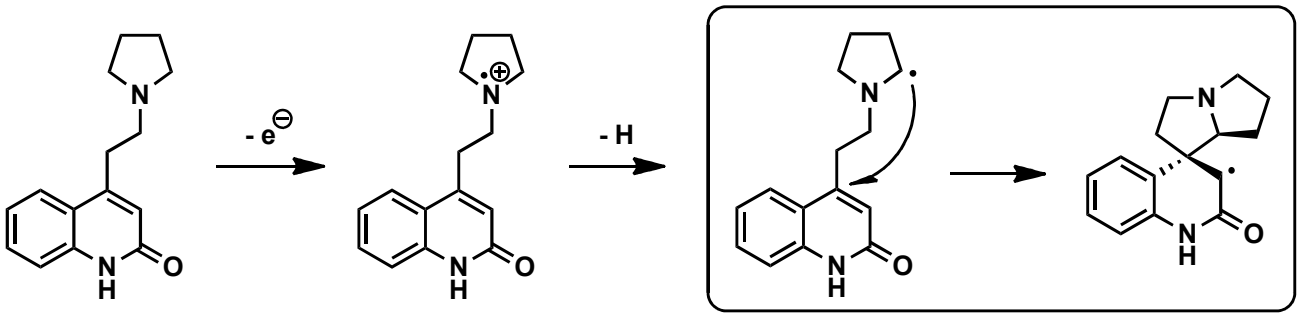


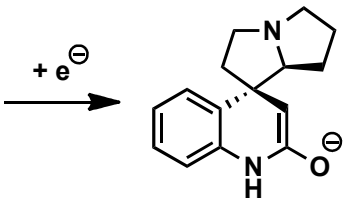
Table 1 | Enantioselective catalytic PET reactions of substrate 1 (see Figs 1 and 2)

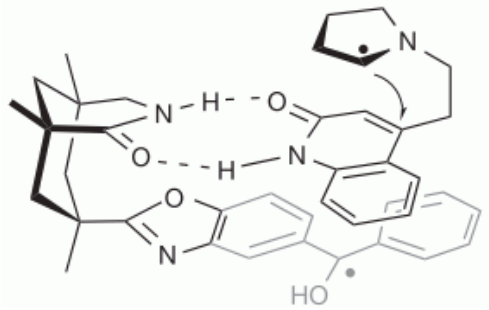
Entry no	Catalyst	Equiv.*	Time (h)	Product	e.r.†	e.e.‡ (%)	Yield§ (%)
1	3	0.1	3.5	2/*ent*-2	50/50	–	71
2	4	0.05	5	2	60/40	20	61
3	4	0.1	2.5	2	69/31	38	55
4	*ent*-4	0.1	3	*ent*-2	31/69	38	52
5	4	0.2	2	2	77/23	54	57
6	4	0.3	1	2	85/15	70	64
7	3/5‖	0.1/1.2	2	*ent*-2	14/86	72	39

*The reactions were carried out in deaerated toluene as the solvent at −60 °C (irradiation source: Orginal Hanau TQ 150) and with a substrate concentration of 4 mM (see Supplementary Information page SI 5).
†The enantiomeric ratio (e.r.) was determined by ^{1}H-NMR shift experiments (see Supplementary Information page SI 9)[15].
‡The enantiomeric excess (e.e.) was calculated from the e.r. based on the uncertainty of the ^{1}H-NMR integration, the variance of e.e. data are estimated as ±2%.
§Yield of isolated product.
‖A stoichiometric amount (1.2 equiv.) of the chiral complexing agent 5 was added to the reaction mixture.



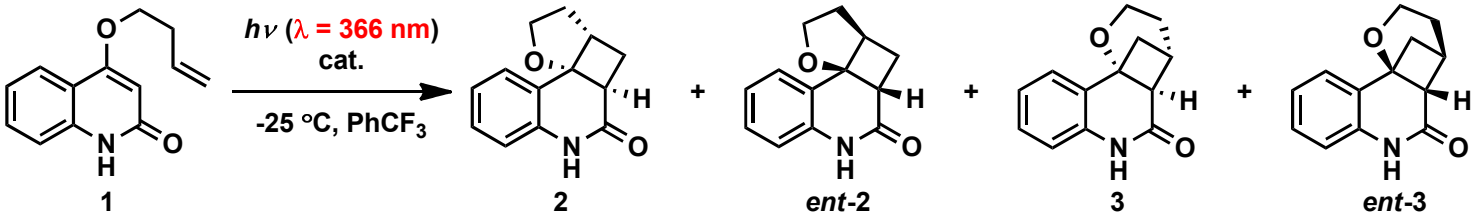
facial differentiation step

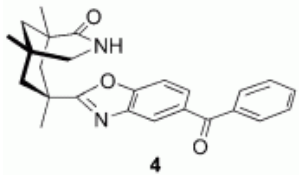




You can control the photosensitizing ability by exchanging the benzophenone unit for other ones.

T. Bach *ACIE*, 2009, *48*, 6640.

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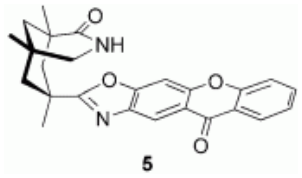
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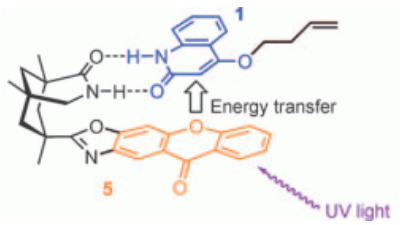
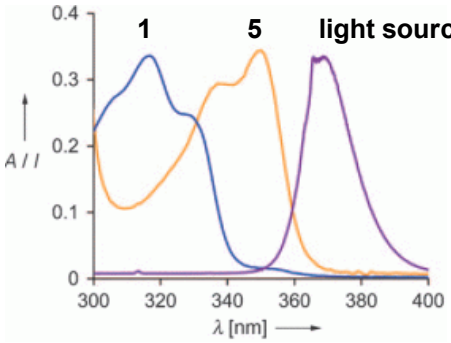
Table 1: Intramolecular [2+2] photocycloaddition of substrate **1** to form products **2** and **3** (Scheme 1): Influence of catalysts on conversion and enantioselectivity.

Entry	Catalyst	Mol %[a]	*t* [h]	Conv. [%][b]	Yield [%][b]	r.r.[c]	*ee* (**2**) [%][d]	*ee* (**3**) [%][d]
1	–	–	1	14	–	86/14	–	–
2	**4**	10	1	57	90	75/25	39	17
3	**5**	10	1	64	90	78/22	92	90
4	**5**	10	2	78	89	77/23	91	91
5	**5**	10	4	90	55	>99/1	91	–
6	**5**	5	1	50	95	78/22	90	n.d.[e]
7	**5**	20	1	73	78	79/21	94	94
8	xanthone	10	1	39	77	79/21	–	–

[a] Reactions were carried out under argon in deaerated trifluorotoluene as solvent at −25 °C (irradiation at 366 nm) and with a substrate concentration of 5 mM (see Supporting Information). [b] The conversion and yield were determined gravimetrically after separation of substrate (**1**) and products (**2**,**3**). Conversion and yield are calculated based on recovered starting material. [c] The **2**/**3** regiomeric ratio (r.r.) was determined by HPLC. [d] The enantiomeric excess (*ee*) was determined by HPLC. [e] The *ee* value could not be determined in this case.

The light (λ = 366 nm) doesn't activate the starting olefins.
→ The reaction is very slow when 1 is far from 5.





normalized absorption spectra (1,5)
normalized emission spectra (light source)

• **Thorsten Bach's strategy 2**

Lewis acids can form a complex with coumarin and are able to promote [2 + 2] photocycloadditions by increasing a) the absorption at longer wavelengths, b) the singlet-state lifetime, and c) the electrophilicity.

F. D. Lewis *JASC*, 1989, *111*, 8653.

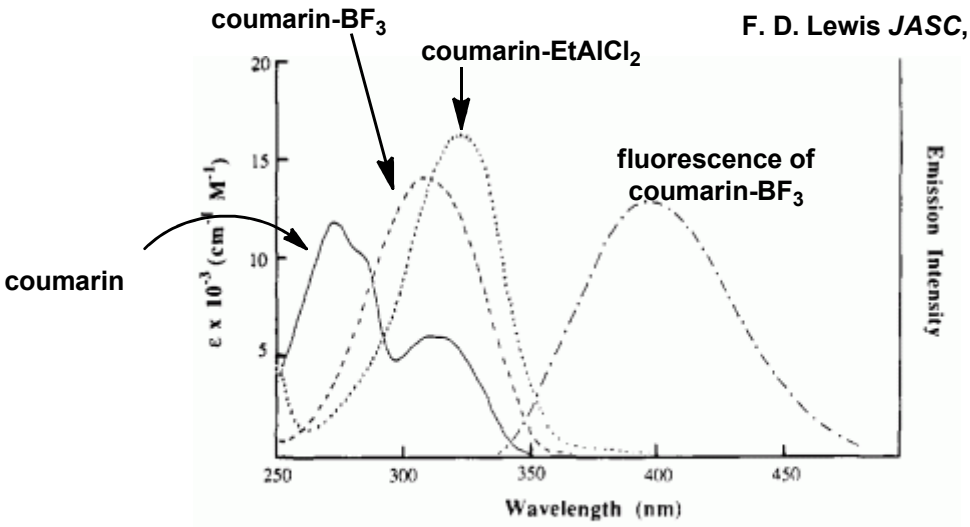
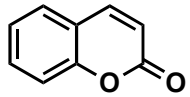
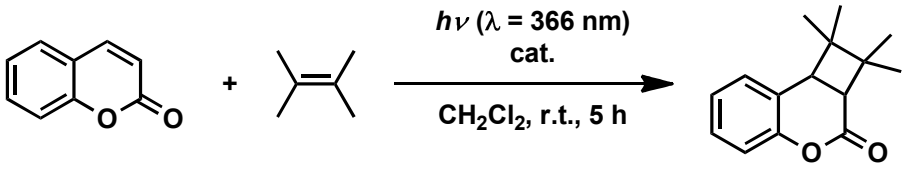


Figure 1. UV absorption spectra of coumarin (—), coumarin–BF_3 (- - -), coumarin–$EtAlCl_2$ (···), and fluorescence spectrum of coumarin–BF_3 (–·–) in dichloromethane solution.



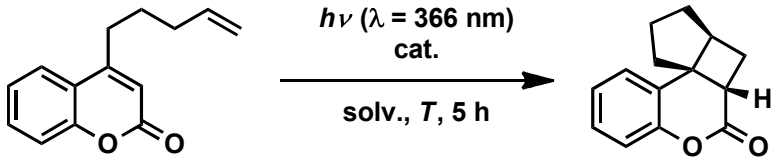
coumarin

T. Bach *ACIE*, 2010, *49*, 7782.



no cat.: N.R.
BF_3·OEt_2: 33%
$AlBr_3$: 97%

→ **Chiral Lewis acids can promote enantioselective photoreactions?**



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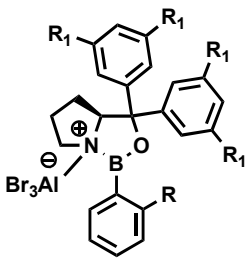


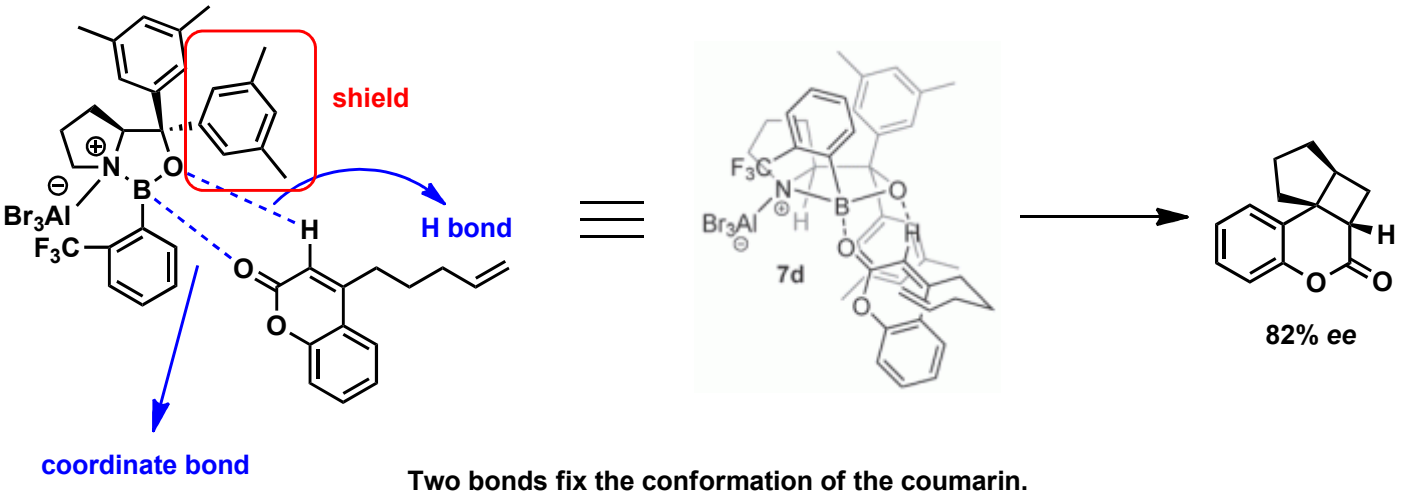
Table 1: Enantioselective catalytic [2+2] photocycloaddition reactions of coumarin **5** (cf. Scheme 2).

Entry	Catalyst	R	R[1]	mol %[a]	Solvent	*T* [°C]	Yield [%][b]	e.r.[c]	*ee* [%]
1	–	–	–	–	CH_2Cl_2	30	28	50:50	–
2	**7a**	Me	H	50	CH_2Cl_2	30	88	60:40	20
3	**7b**	H	H	50	CH_2Cl_2	30	77	66:34	32
4	**7b**	H	H	20	CH_2Cl_2	30	77	65:35	30
5	**7b**	H	H	20	Et_2O	30	74	50:50	–
6	**7c**	CF_3	H	50	CH_2Cl_2	30	83	72:28	44
7	**7d**	CF_3	Me	50	CH_2Cl_2	30	88	81:19	62
8	**7e**	CF_3	*t*Bu	50	CH_2Cl_2	30	82	63:37	26
9	**7d**	CF_3	Me	50	CH_2Cl_2	−75	84	91:9	82
10	**7d**	CF_3	Me	20	CH_2Cl_2	−75	82	77:23	54
11[d]	**7d**	CF_3	Me	20	$ClCH_2CH_2Cl$	−35	87	89:11	78

[a] The reactions were carried out in a de-aerated solvent at the indicated temperature (irradiation in a RPR-100 reactor with Philips black light blue lamps, 8 W for 5 h) and with a substrate concentration of 20 mM (see Supporting Information). [b] Yield of product isolated after column chromatography. [c] The enantiomeric ratio (e.r.) was determined by chiral GC. [d] The reaction was run at a substrate concentration of 50 mM.

The best *ee* (82%) is obtained in entry 9 with 84% yield.

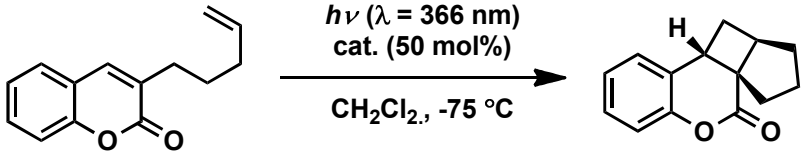
the review of the utility of cationic oxazaborolidines: E. J. Corey *ACIE*, 2009, *48*, 2100.



Two bonds fix the conformation of the coumarin.

♥ Without the H at C3, the *ee* significantly decreases.

T. Bach *Chem. Eur. J.*, 2012, *18*, 7552.



(unable to form the H bond) **21% *ee*** **significantly lower than 82% *ee*!**

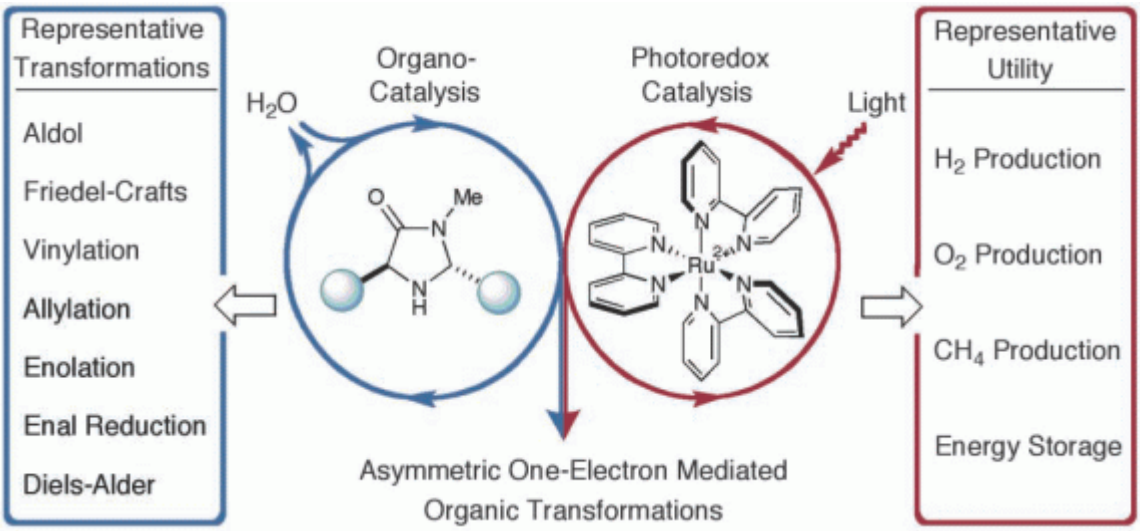
Catalytic reaction has been achieved, but there are yet few substrates the Bach's chemistry is applicable to. It's mainly because
1) the substrate scope is limited to finely-selected lactams and lactones, and
2) the reaction type is almost limited to photocyclizations.

→ More general methods are desired:
1) targeting ubiquitous functional groups
2) aiming intermolecular C-C, C-N, C-O bond formation

2-3. the Combination of Chiral Catalyst with Photosensitizer

- asymmetric reactions assisted by chiral organocatalysts
- photoactivation assisted by photosensitizers

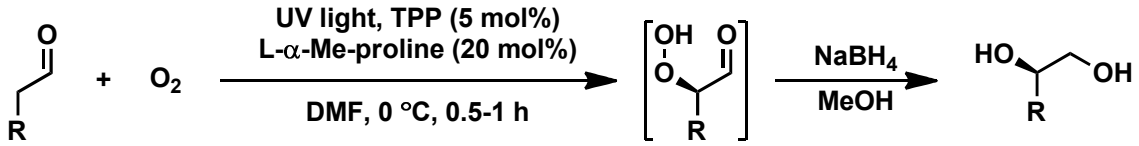
→ The combination of these two enables asymmetric photoreactions.



D. W. C. MacMillan *Science*, 2008, *322*, 77.

- α-oxygenation of aldehydes

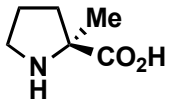
A. Córdova *JACS*, 2004, *126*, 8914.



entry	R	cmpd	yield (%)[b]	ee (%)[c]
1	CH_2Ph	**1**	77	66
2	CH_2Ph[d]	**1**	72[d]	66[d]
3	*i*-Pr	**3**	75	57
4	*n*-Pent	**4**	77	54
5	*n*-Bu	**5**	73	57

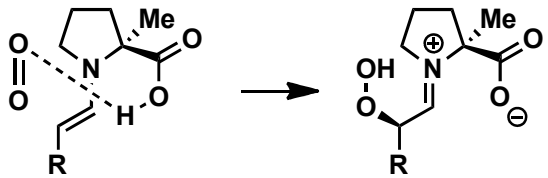
[a] In a typical experiment, the amino acid (20 mol %) was stirred in the DMF (1 mL) for 20 min followed by addition of tetraphenylprophine (TPP) (5 mol %) and the aldehyde (1 mmol). The reaction was initiated and performed by bubbling a continuous flow of molecular oxygen or air for 0.5−3 h in the presence of visible light by a 250-W high-pressure sodium lamp. [b] Isolated yield after silica gel column chromatography. [c] Determined by chiral-phase HPLC or GC. [d] The reaction performed with air as the oxygen provider.

TPP: tetraphenylporphine

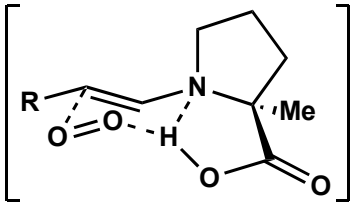
L-α-Me-proline: 

When a normal proline is used, the *ee*s decrease (16 ~ 48% *ee* for the same substrates).

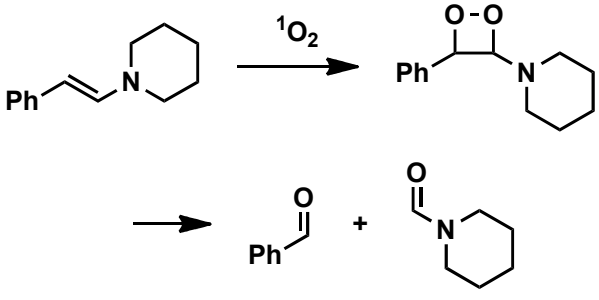
Supposed mechanism



CO_2H is more bulky than Me, but O_2 comes from CO_2H side.
→ CO_2H is likely to be a directing group.

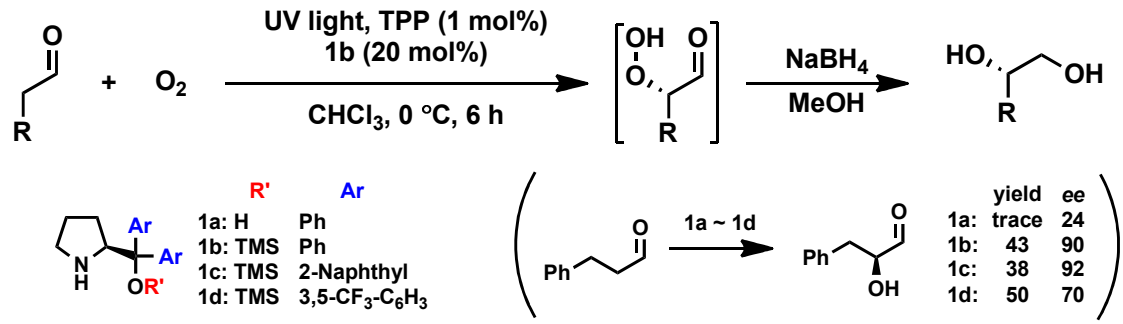


cf.: C. S. Foote *Acc. Chem. Res.*, 1968, *1*, 104.



This report rules out the [2 + 2] cycloaddition of $^1O_2$ and the enamines followed by ring opening.

A. Córdova *TL*, 2006, *47*, 4659.



	R'	Ar
1a:	H	Ph
1b:	TMS	Ph
1c:	TMS	2-Naphthyl
1d:	TMS	3,5-CF_3-C_6H_3

	yield	*ee*
1a:	trace	24
1b:	43	90
1c:	38	92
1d:	50	70

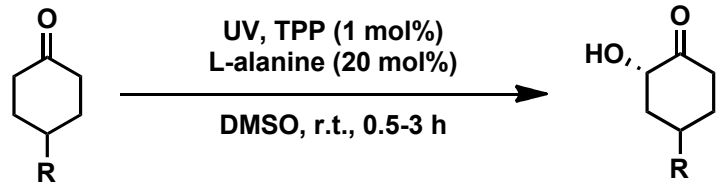
(substrate scope)

Entry	Aldehyde	R	Prod.	Yield[a] (%)	ee[b] (%)
1	**2a**	Bn	**4a**	70	87
2	**2a**	Bn	**4a**	50[c]	90[c]
3	**2b**	*n*-Pent	**4b**	67	75
4	**2c**	4-$NO_2C_6H_4CH_2$	**4c**	64	98
5	**2d**	4-$ClC_6H_4CH_2$	**4d**	71	98
6	**2e**	4-$BrC_6H_4CH_2$	**4e**	68	98
7	**2f**	*n*-Butyl	**4f**	76	74

[a] Isolated yield of pure diacetylated **4a**.
[b] Ee as determined by chiral-phase HPLC or GC analyses.
[c] 10 mol % catalyst.

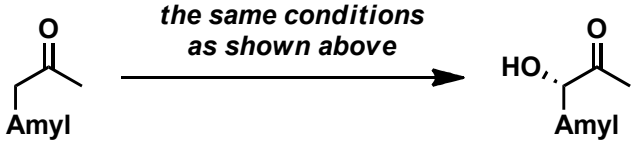
Córdova also achieved to convert cyclic ketones into α-hydroxyketones with moderate *ee*s by using Jørgensen-type catalyst (proline catalysis furnishes 18% ee).

A. Córdova *ACIE*, 2004, *43*, 6532.



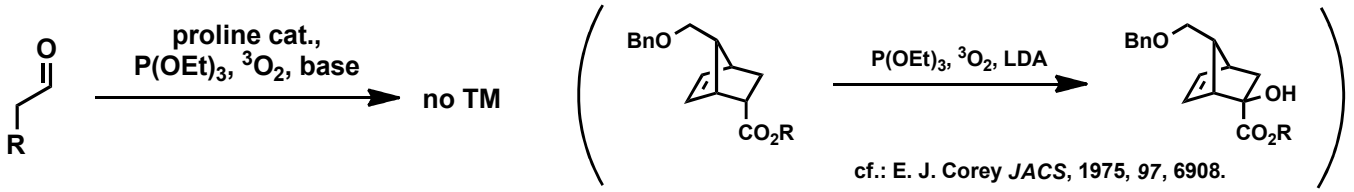
R	yield	*ee*	
H	93	56	
Me	67	72	
Et	61	60	(solv. is NMP)
i-Pr	58	52	(solv. is NMP)

♥ **An acyclic ketone produces poor *ee*.**

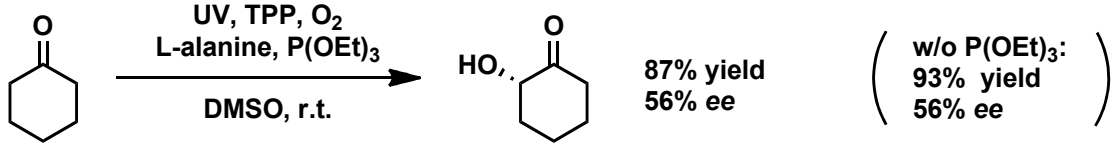


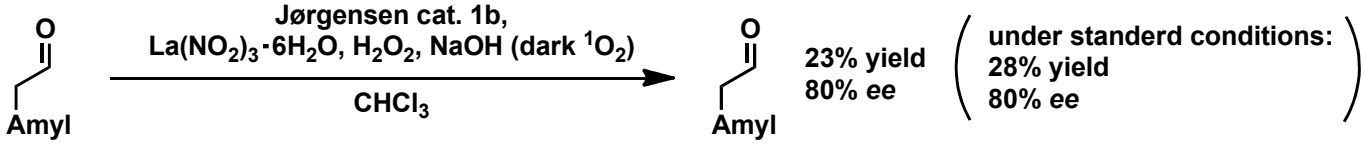
50%, 28% *ee*

The reaction with $^3O_2$ did not provides the desired product.



cf.: E. J. Corey *JACS*, 1975, *97*, 6908.

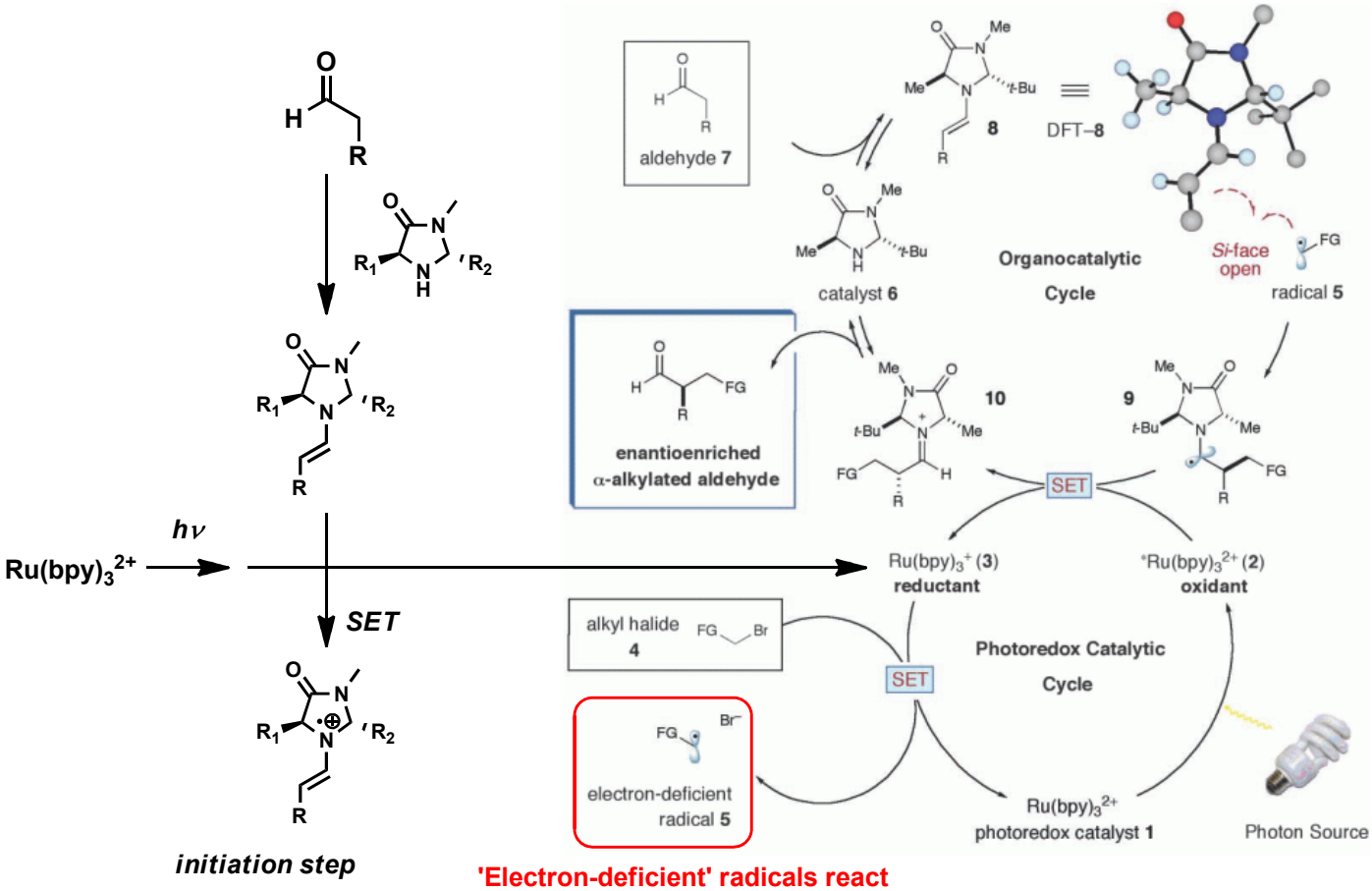




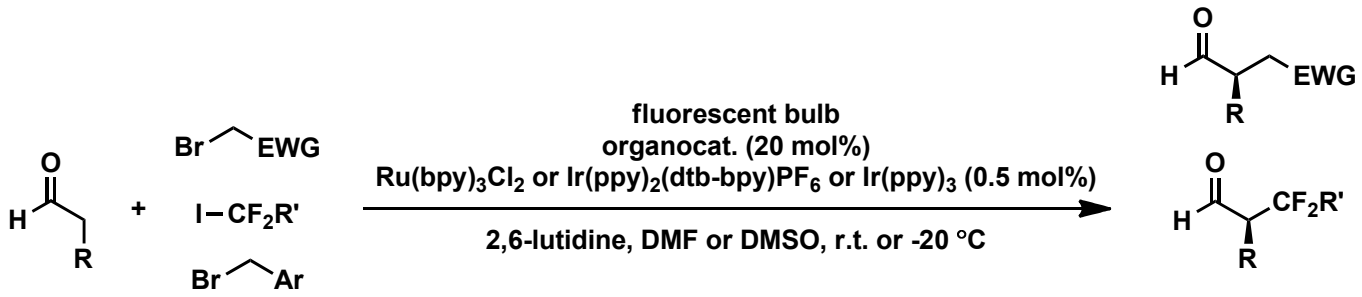
dark $^1O_2$: P. L. Alsters and J.-M. Aubry *Chem. Eur. J.*, 2003, *9*, 435.

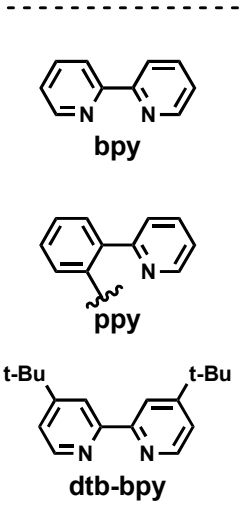
• α-alkylation of aldehydes (and ketones)

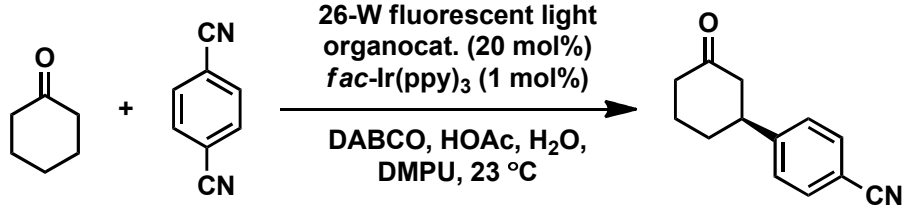
D. W. C. MacMillan *Science*, 2008, *322*, 77. : α-alkylation
D. W. C. MacMillan *JACS*, 2009, *131*, 10875. : α-trifluoromethylation, perfluoroalkylation, ...
D. W. C. MacMillan *JACS*, 2010, *132*, 13600. : α-benzylation
D. W. C. MacMillan *Science*, 2013, *339*, 1593. : β-arylation (only one example for asymmetric reaction)
D. W. C. MacMillan *JACS*, 2013, *135*, 11521. : α-amination

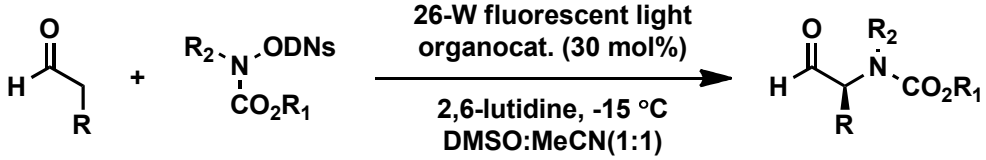


'Electron-deficient' radicals react with 'electrn-rich' enamines.

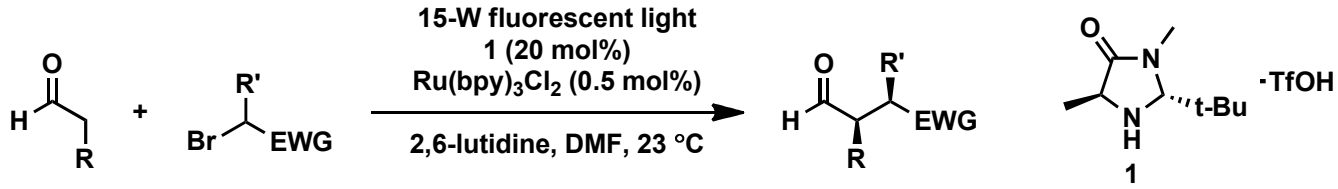


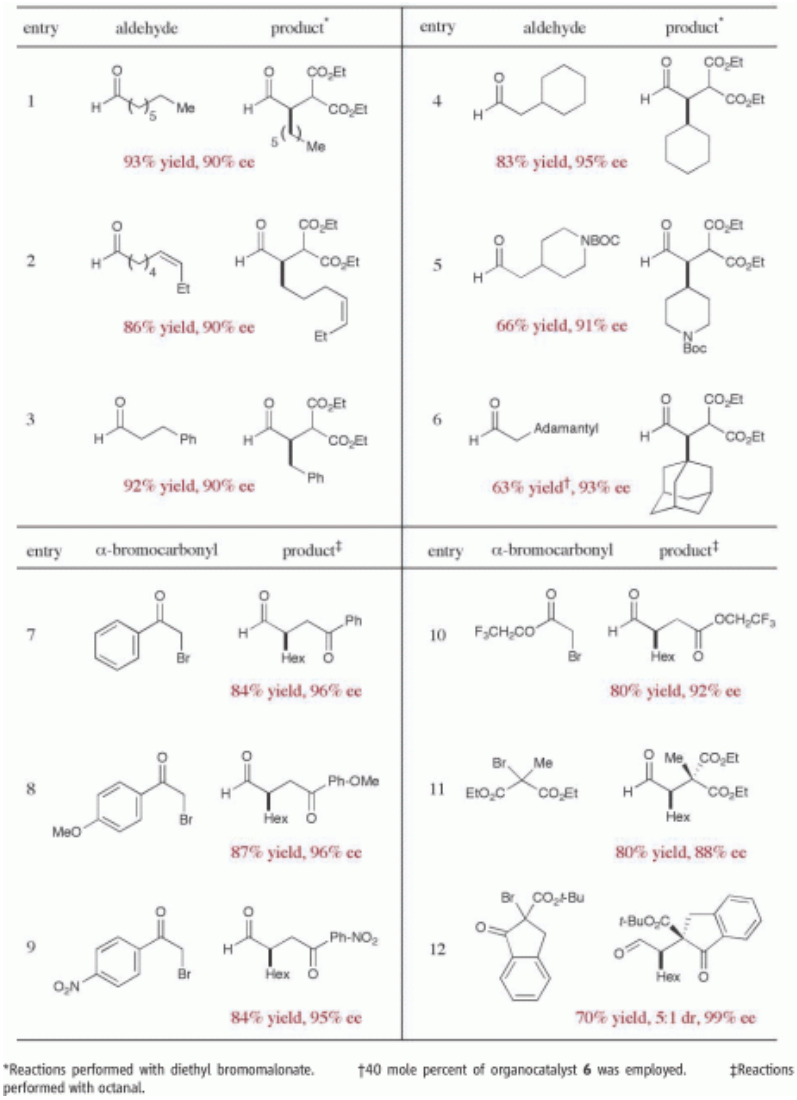






D. W. C. MacMillan *Science*, 2008, *322*, 77.





*Reactions performed with diethyl bromomalonate. †40 mole percent of organocatalyst **6** was employed. ‡Reactions performed with octanal.

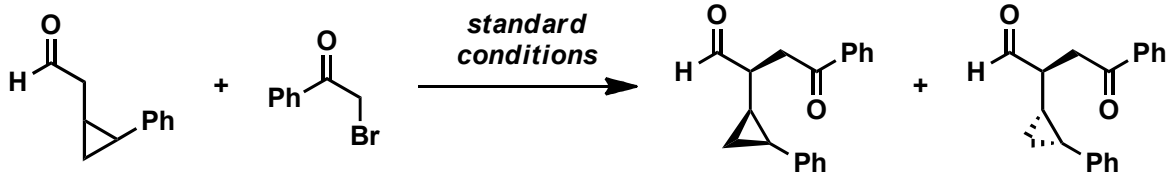
- 1,4-diketones are obtained.
- 2-bromodiethylmalonate (entry 1 to 6) and various α-bromocarbonyls (7 to 12) can effectively serves as alkylating agents.
- An olefin (entry 2), a benzylic C-H (entry 3), a carbamate (entry 5) are all tolerated under the reaction conditions.
- Quaternary carbons can be constructed effectively (entry 11 and 12) in good yields and excellent *ee*s.
- When CF_3 is replaced with CH_3 in entry 10, the yield decreases to 53% with the same *ee* (94% *ee*).

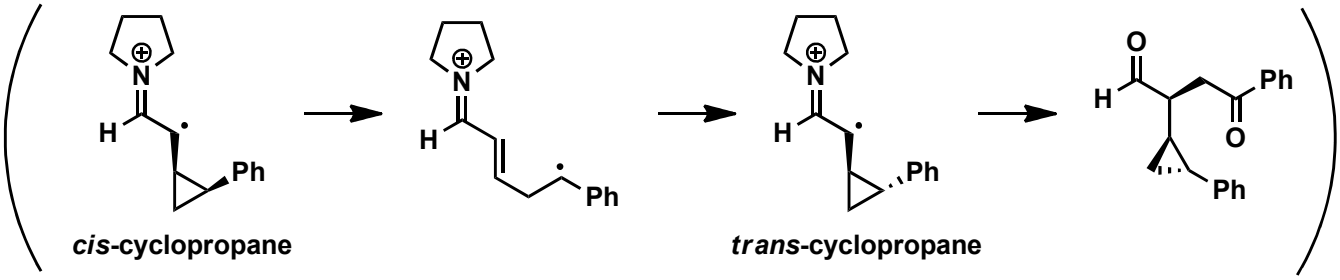
Control Experiments

- no light → N.R.
- no $Ru(bpy)_3^{2+}$ → < 10% yield unless UV (300 to 350 nm) is used
- 465-nm photon source is used instead.* → Overall rate is accelerated as compared with the use of a fluorescent light (6 h → 90 min).

*$Ru(bpy)_3^{2+}$ MLCT absorption band: 465 ± 20 nm
15-W fluorescent bulb: ~ 400 to 700 nm

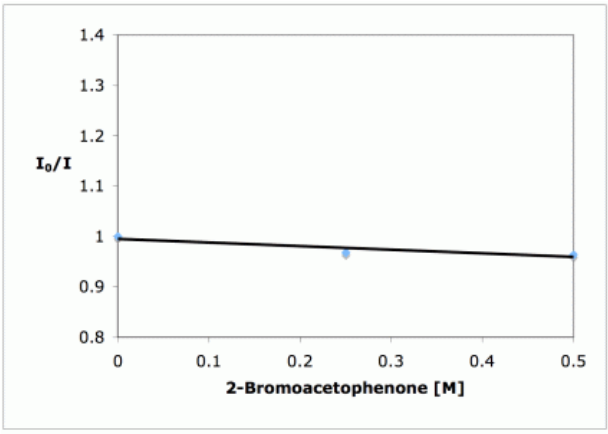
→ Ru is surely involved in the catalytic cycle.



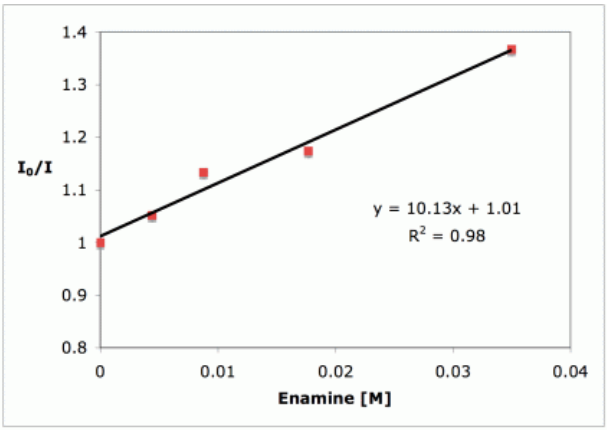


trans-substituted cyclopropanes are not detected.
→ The radical doesn't generate at the α-position of the carbonyl group.

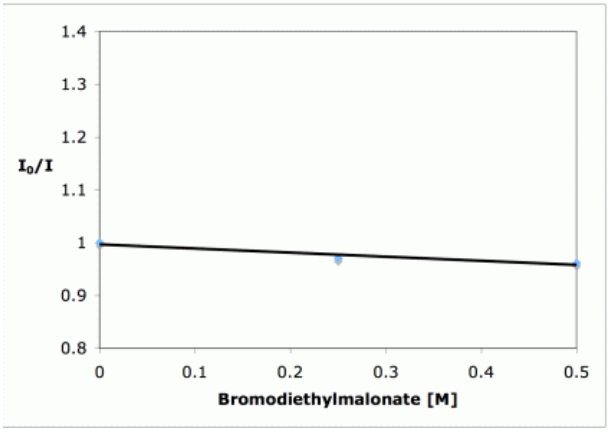
• luminescent quenching study of $Ru(bpy)_3Cl_2$



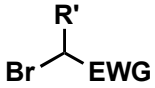
$Ru(bpy)_3Cl_2$ Emission Quenching by 2-Bromoacetophenone



$Ru(bpy)_3Cl_2$ Emission Quenching by Enamine



$Ru(bpy)_3Cl_2$ Emission Quenching by Bromodiethylmalonate

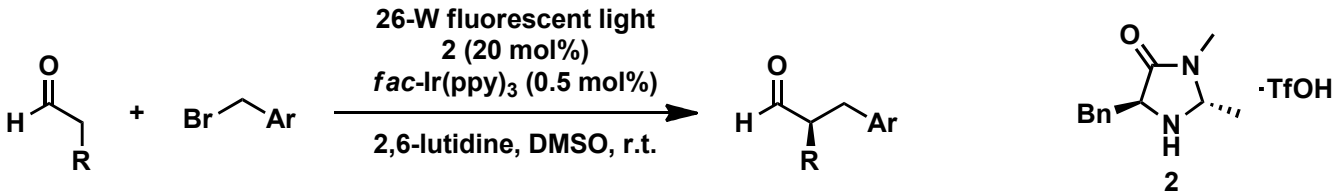
$Ru(bpy)_3Cl_2$ doesn't oxidize 

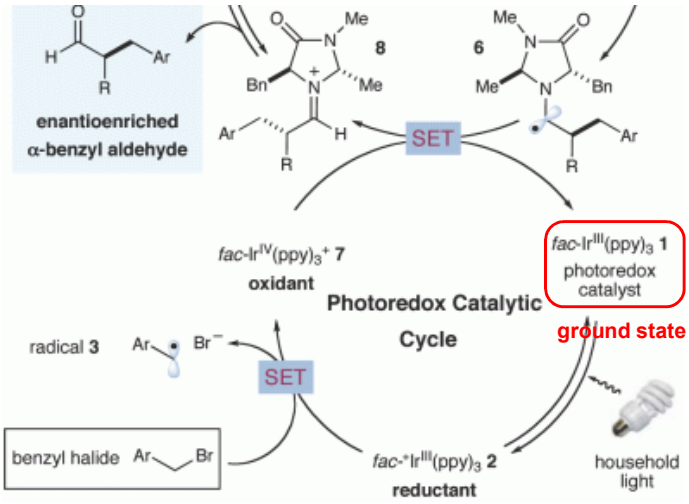
but does enamine.

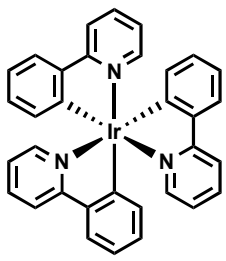
→ The reactions start with the oxidation of enamines by the photoactivated $Ru(bpy)_3Cl_2$ as shown in the previous page.

I_0 = Emission intensity of $Ru(bpy)_3^{2+}$ in the absence of quencher.
I = Emission intensity of $Ru(bpy)_3^{2+}$ in the presence of quencher.

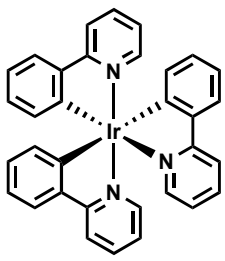
D. W. C. MacMillan JACS, 2010, 132, 13600.





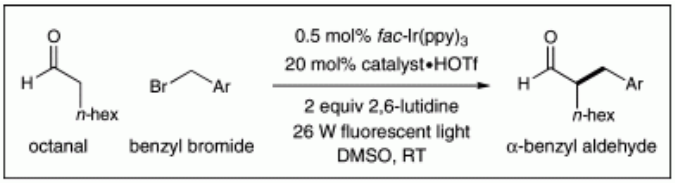


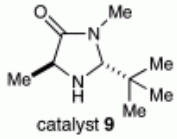
fac-Ir(ppy)$_3$

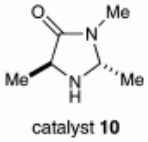


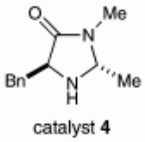
mer-Ir(ppy)$_3$

(initial trial)




catalyst **9**


catalyst **10**


catalyst **4**

entry	Ar	catalyst	% yield[a]	% ee[b]
1	Phenyl	9	0	ND
2	2,4-$(NO_2)_2C_6H_3$	9	74	97
3	2,4-$(NO_2)_2C_6H_3$	10	93	82
4	2,4-$(NO_2)_2C_6H_3$	4	94	92
5[c]	4-Pyridinyl	9	0	ND
6[c]	4-Pyridinyl	10	81	78
7[c]	4-Pyridinyl	4	86	90

[a] Isolated yields. [b] Enantiomeric excess determined by chiral HPLC. [c] 4-(Bromomethyl)pyridine added as the hydrobromic acid salt with an additional equivalent of 2,6-lutidine.

'Ar' must be electrondeficient.

$Ru(bpy)_3^+$ MLCT: -1.33 V vs SCE in MeCN
***fac*-*Ir(ppy)$_3$: -1.73 V vs SCE in MeCN**
BnBr: -1.85 V vs SCE in MeCN
(SCE: saturated calomel electrode)

← **BnBr completely recovered.**

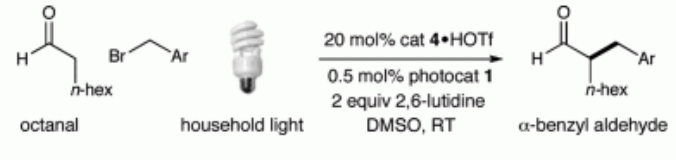
← **$ArCH_2Br$ rapidly decomposed.**

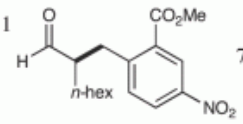
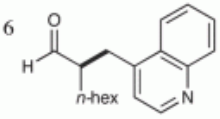
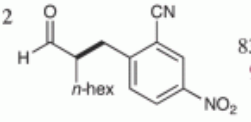
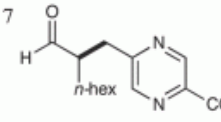
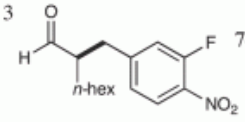
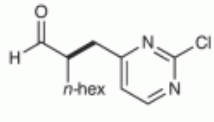
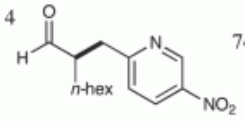
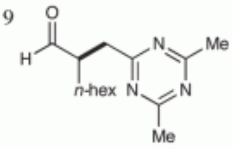
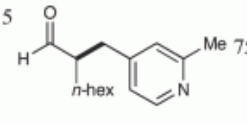
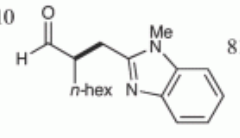
↓

A higher concentration and increased spatial exposure of the enamine should increase the rate of the radical-olefin addition step.

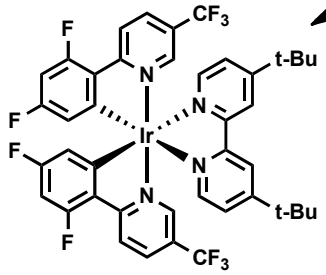
↓

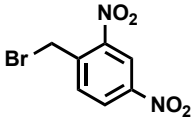
Catalyst 10 and 4 are better than catalyst 9 as expected (entry 6 and 7).

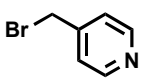


entry	product[a]	yield, ee[b]	entry	product[a]	yield, ee[b]
1		76% yield 93% ee	6		90% yield[e] 82% ee
2		83% yield 90% ee	7		73% yield[f] 90% ee
3		74% yield[c] 90% ee	8		78% yield 87% ee
4		74% yield[d] 90% ee	9		68% yield[g] 91% ee
5		75% yield[e] 91% ee	10		81% yield[e,h] 88% ee

[a] Stereochemistry assigned by chemical correlation or by analogy. [b] Enantiomeric excess determined by chiral SFC or HPLC. [c] 30 mol% organocatalyst used. [d] Performed at 15 °C using $Ru(bpy)_3Cl_2$ as the photoredox catalyst; ref 14. [e] Substrate added as the hydrobromic acid salt with an additional equivalent of 2,6-lutidine. The free base organocatalyst was used. [f] Yield determined by ^1H NMR. [g] Ir(dF(CF$_3$)ppy)$_2$(dtbbpy)PF_6 was employed as the photoredox catalyst; ref 15. [h] Isolated yield of the corresponding alcohol.



- **Various aldehydes react with**  **and**

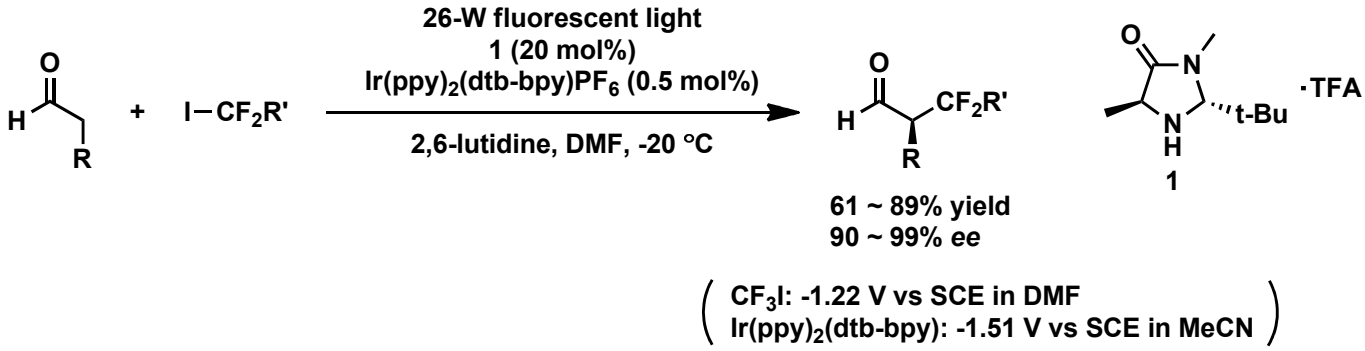
 **in high yield (72 ~ 91%) and *ee* (87 ~ 90%).**

(the table not shown here)

- **Various electrondeficient aryl and heteroaryl methylene bromides can participate in this enantioselective benzylation reaction.**

→ Applicable to medicinal chemistry.

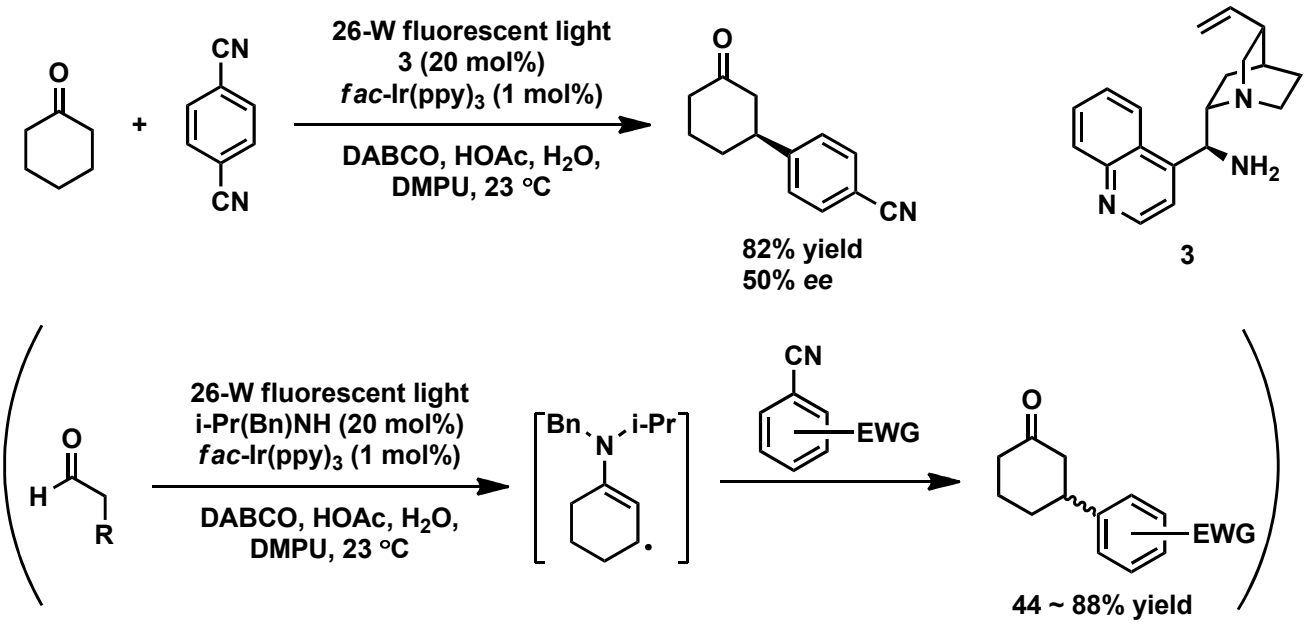
D. W. C. MacMillan *JACS*, 2009, *131*, 10875.



61 ~ 89% yield
90 ~ 99% *ee*

(CF_3I: -1.22 V vs SCE in DMF
$Ir(ppy)_2(dtb\text{-}bpy)$: -1.51 V vs SCE in MeCN)

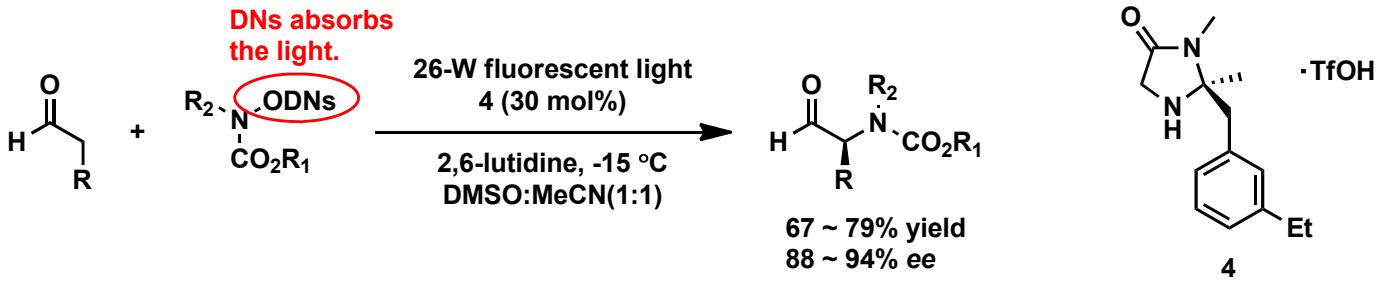
D. W. C. MacMillan *Science*, 2013, *339*, 1593.



82% yield
50% *ee*

44 ~ 88% yield

D. W. C. MacMillan *JACS*, 2013, *135*, 11521.

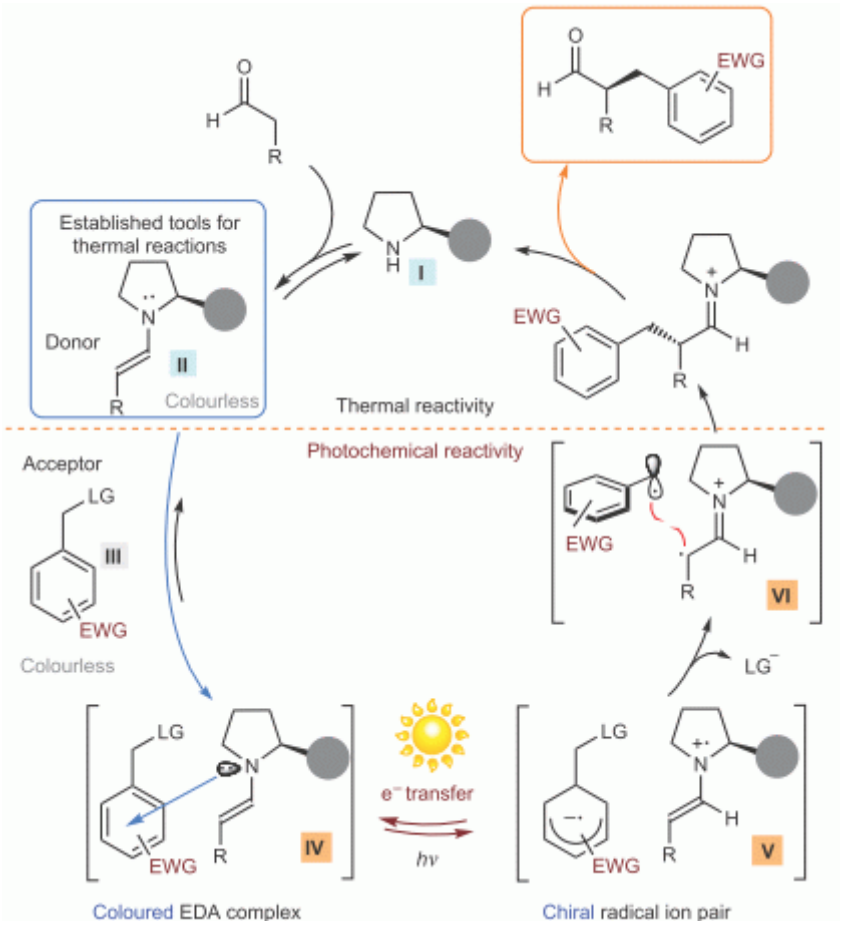


67 ~ 79% yield
88 ~ 94% *ee*

2-4. the Reaction via EDA Pathway

In contrast to Córdova and MacMillan's case, Melchiorre succeeded in asymmetric photoreaction WITHOUT photoredox catalysts by employing the chemistry of EDA complex (electron donor-acceptor complex, also called as charge transfer (CT) complex).

P. Melchiorre *Nat. Chem.*, 2013, *5*, 750.



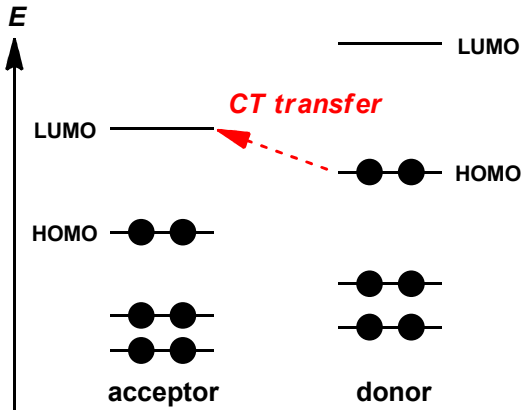
D: donor (electron-donating)
A: acceptor (electron-accepting)

$$D + A \rightleftharpoons [D^{\delta+} \cdots A^{\delta-}]$$

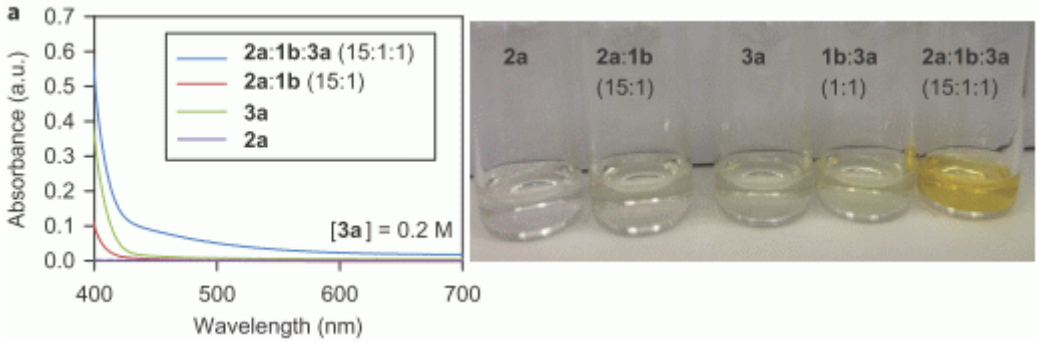
EDA Complex

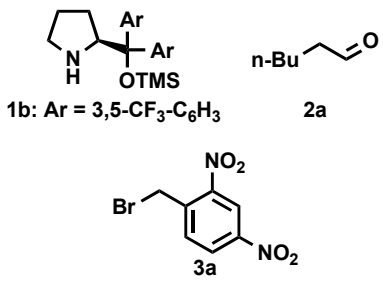
$$\left([D^{\delta+} \cdots A^{\delta-}] \xrightarrow[ET]{h\nu} [D^{+\bullet} \cdots A^{-\bullet}] \right)$$

EDA complexes absorb light (UV ~ visible) by charge transfer electron transition.



One of the most characteristic properties of EDA complex is its color charge-transfer bands (CT bands): a well-known example is the complex formed by iodine when combined with starch, which exhibits an intense blue color.

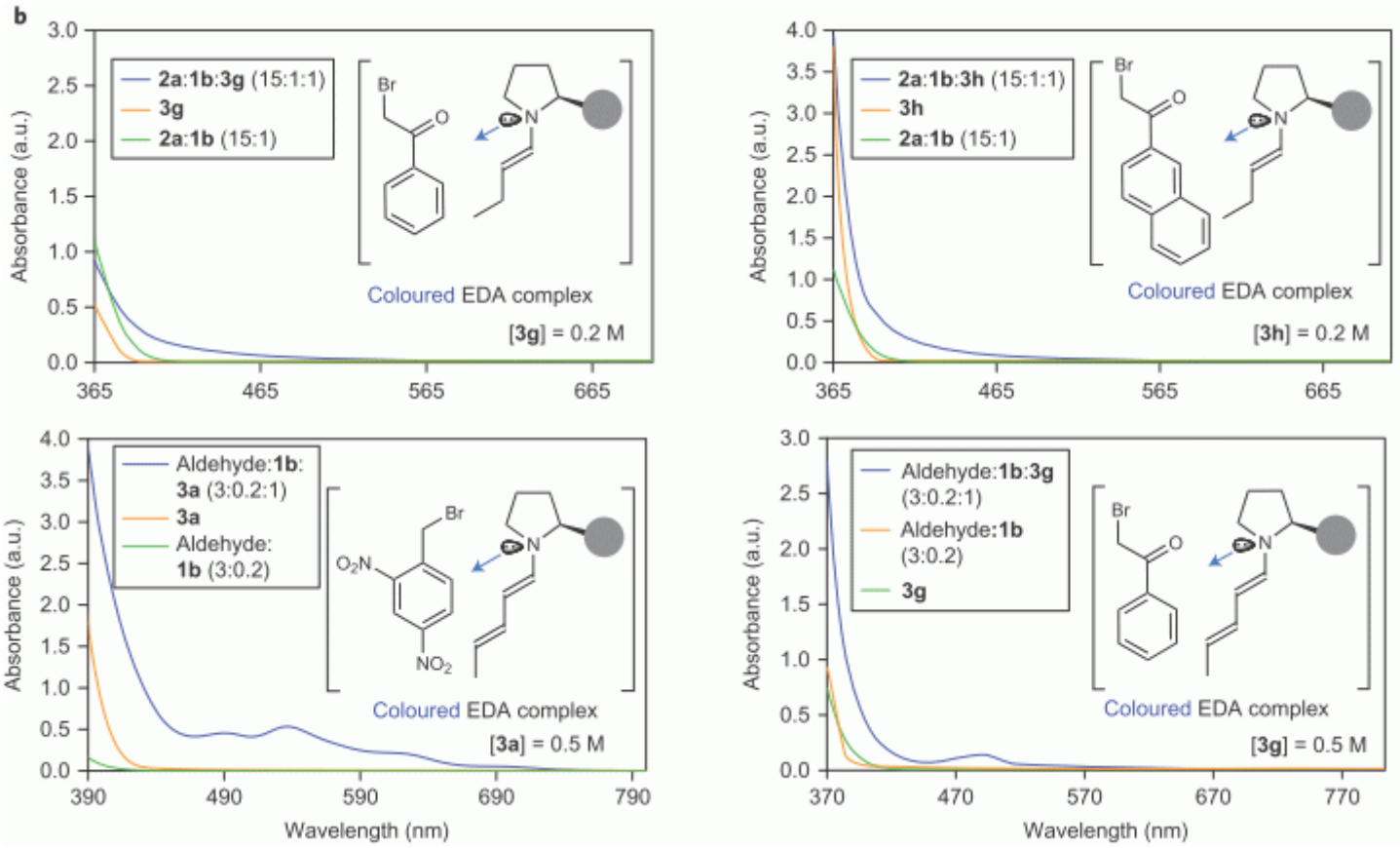




Some EDA complexes absorb visible light as shown above.

→ **It is probably possible that visible light activates substrates that don't normally absorb visible light without external photosensitizers.**

- **EDA complexes of *tert*-amines with electrondeficient arenes**

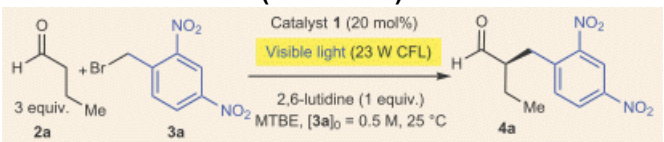


Representative optical absorption spectra of EDA complexes with enamines and extended enamines formed in situ (recorded in MTBE in 1 mm path quartz cuvettes using a Shimadzu 2401PC UV-visible spectrophotometer)

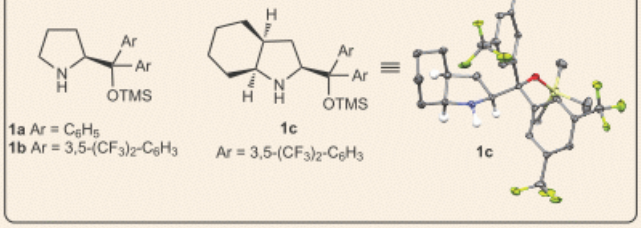
Main difficulty:
an unproductive, fast reverse ET, which restores the ground-state EDA complex and thus renders any further reactivity improbable.

→ **Suitable leaving group within the radical anion partner may trigger a fragmentation rapid enough to compete with the reverse ET.**

(initial trial)



Catalysts used in this study

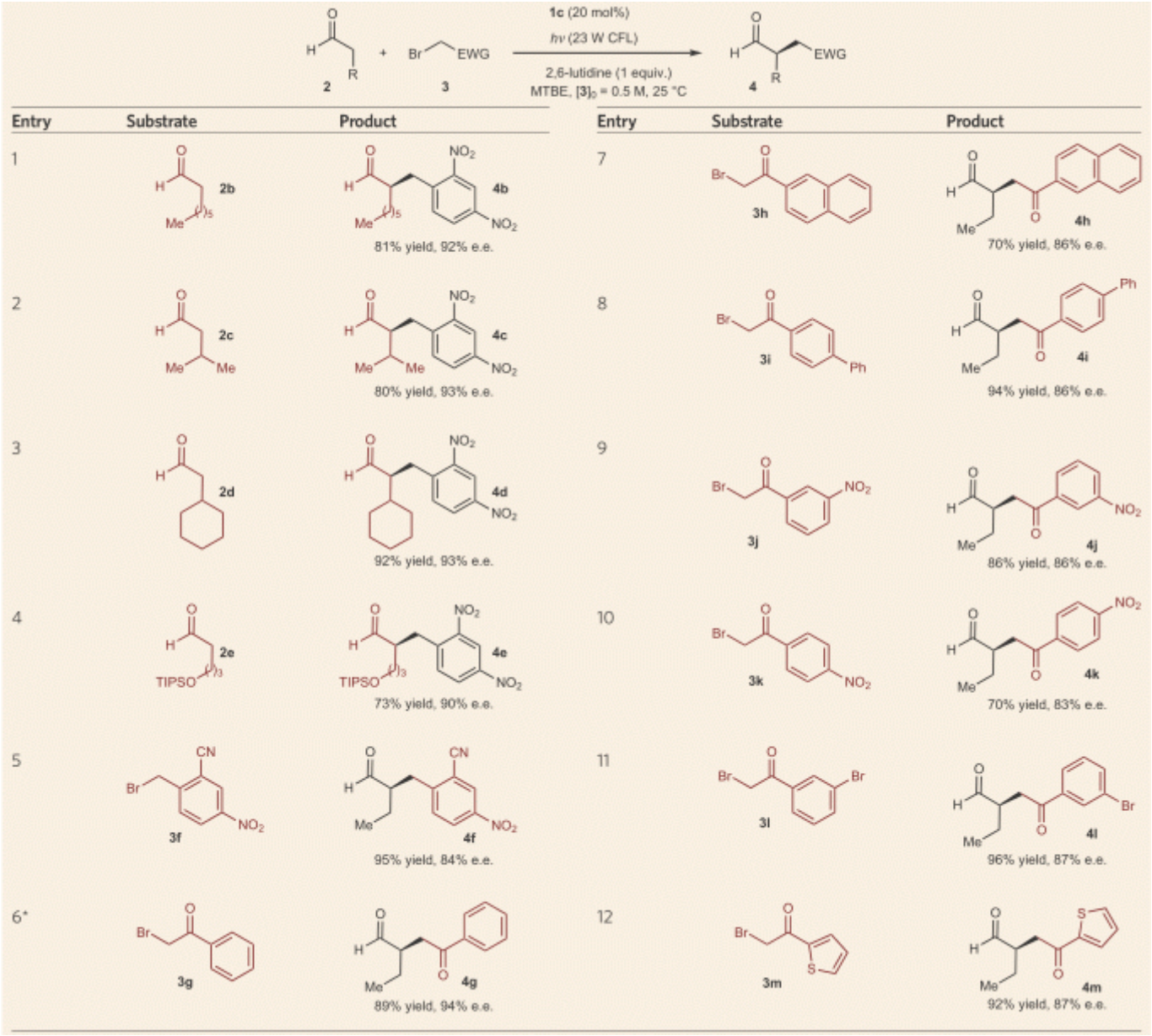


Entry	Catalyst	Light	Time	Yield (%)	e.e. (%) 4a
1	1a	ON	6 h	98	75
2	1b	ON	6 h	98	83
3*	1b	ON	6 h	94	82
4	1b	OFF	48 h	0	-
5	1b	OFF, 50 °C	48 h	0	-
6	-	ON	48 h	0	-
7	1b	ON, LED†	16 h	89	82
8	1b	ON, in air	40 h	78	84
9	1c	ON	48 h	87	92

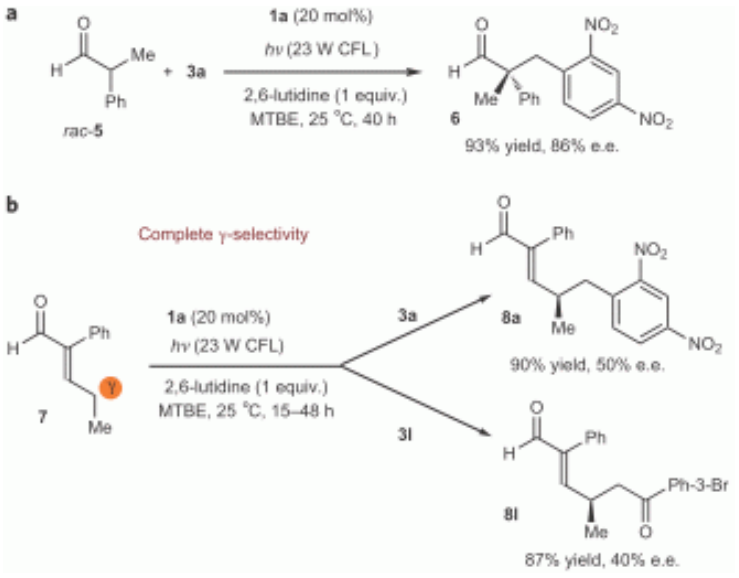
*Reaction performed using 1 equiv. NaOAc instead of 2,6-lutidine. †460 nm LED, irradiance 13.8 W m^{-2}. TMS, trimethylsilyl.

- **The alkylation reactions indeed proceed without any photoredox catalysts in excellent yield and *ee*.**
- **The reaction doesn't proceed in the absence of aminocatalyst or light.**

MTBE: methyl *tert*-butyl ether



***Reaction performed under natural sunlight irradiation on the roof-top of the Institute of Chemical Research of Catalonia, Tarragona (Spain), on a partially cloudy day (27 Feb 2013, from 13:00 until 18:00).**



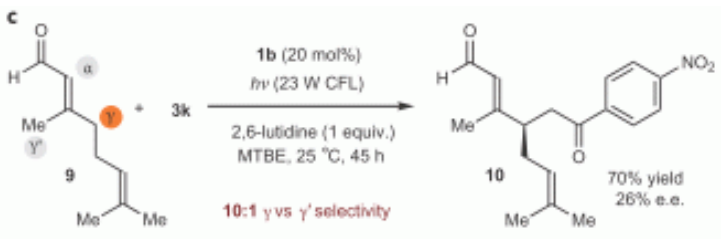


Figure 3 | Evaluating the scope and the strategy's potential to address synthetically relevant problems. a, Forging an all-carbon quaternary stereogenic centre. **b**, Remote stereocontrol and complete γ-site selectivity. **c**, Capacity to differentiate between three potential reactive centres.

- **The substrate scope overlaps with that of MacMillan's alkylation.**
- **This method is also applicable to 1) quaternary carbon construction, and 2) γ-alkylation.**

♥ Mechanistic Consideration

another plausible mechanism

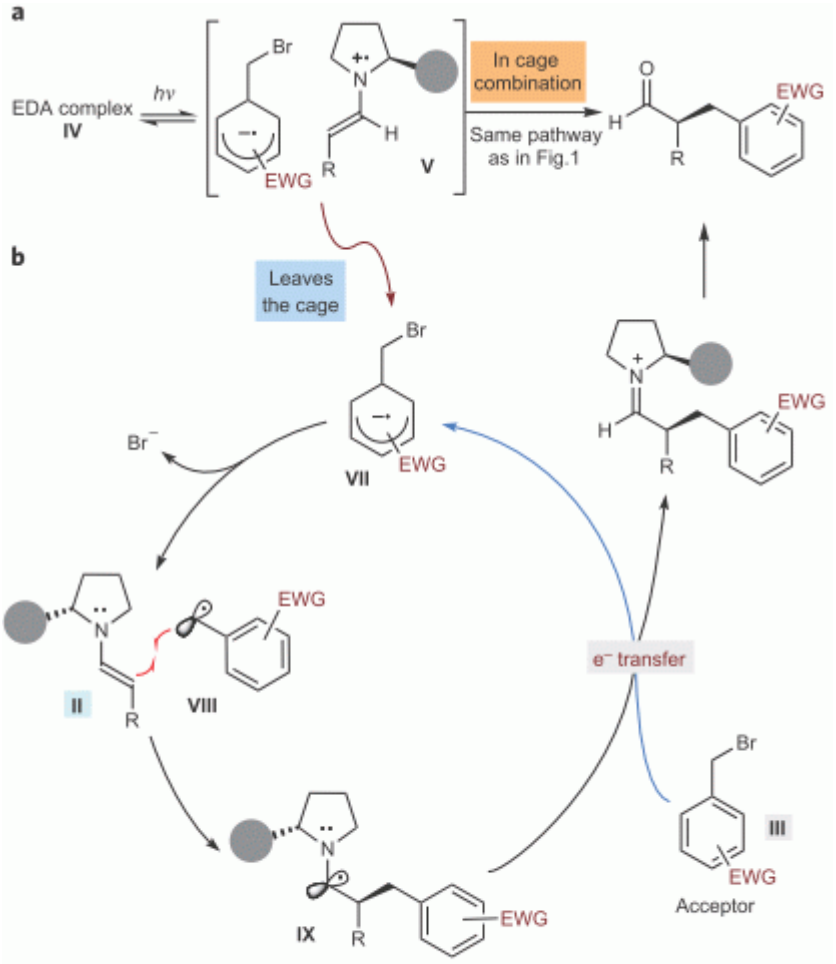
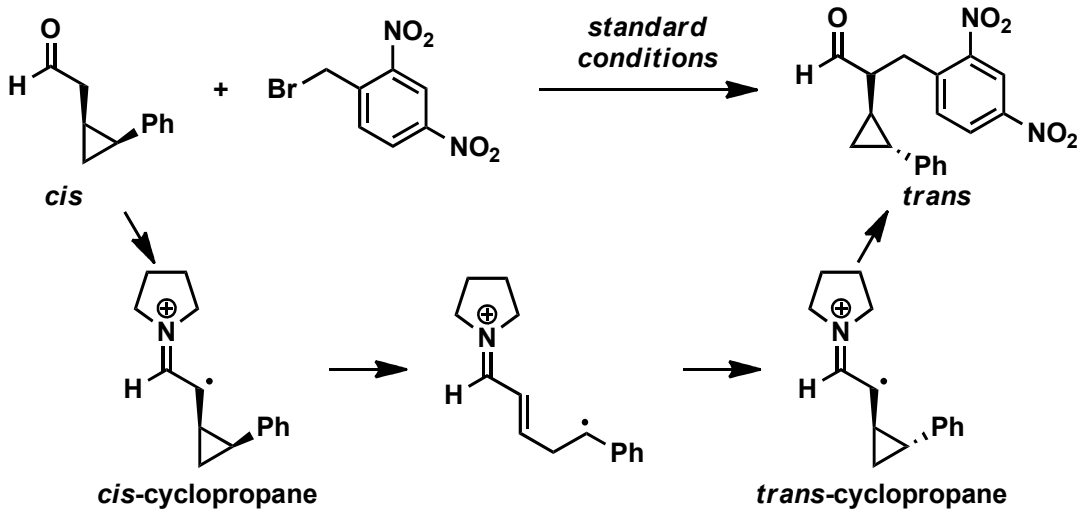


Figure 4 | Two possible reaction mechanisms. a, Our proposed mechanism based on the in-cage radical combination driven by EDA formation (see also Fig. 1). **b**, A plausible Kornblum–Russell alkylation pathway[31,32] via a radical-chain $S_{RN}1$ mechanism.

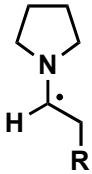
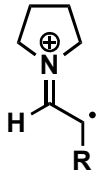
1) **EDA complex (IV) is photoactivated to produce radical ion pair (V).**
2) **(V) diffuses and the radical anion (VII) participates in the further step (the radical cation species is unproductive anymore).**
3) **(VII) reacts with enamine (II) to produce (IX).**
4) **(IX) gives the electron to alkyl bromide (III) to generate the radical anion (VII) and thus close the propagation cycle.**

similar to MacMillan's benzylation

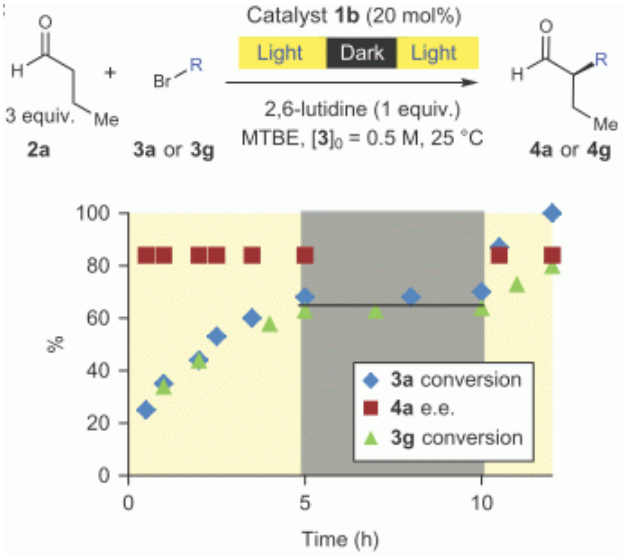
♣ a radical clock experiment

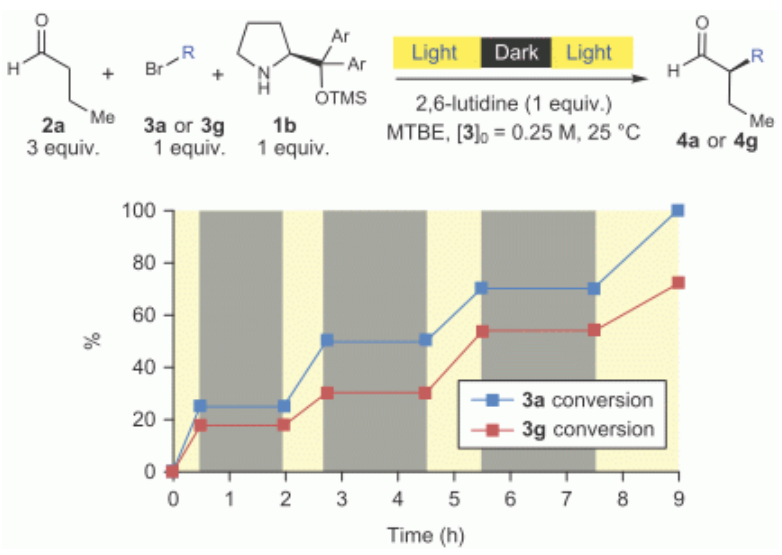


The cyclopropane ring opened during the reaction.

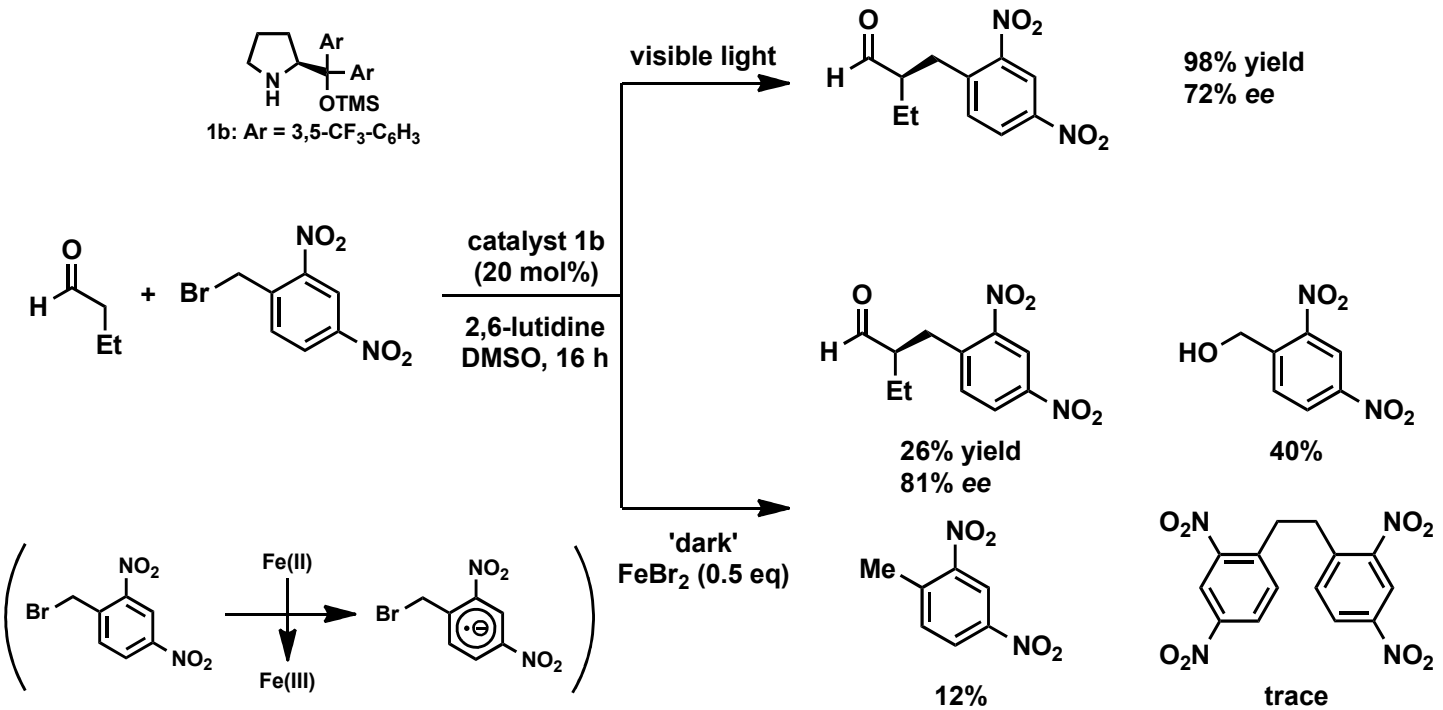
→ The radical species that generates during the reaction is not  **but** 

♣ **experiments with successive intervals of irradiation and dark periods: does the radical chain propagation really occur?**





No reaction proceeds during the dark periods.
→ **There is no radical propagation, or the propagation is very short-lived without the light.**



Under the 'dark' conditions, the ET from $FeBr_2$ to alkyl bromide is the only source of free radical that would be trapped by the enamine.
→ **If the 'another plausible mechanism' really works well, the same results should be obtained under the both conditions shown above, but the outcome differed.**
→ **The radical propagation mechanism should be ruled out.**

3. Summary

Some kinds of asymmetric photoreactions have been achieved:

a) intra- and intermolecular photocycloaddition by chiral photosensitizers or chiral Lewis acids,
b) α-functionalization (C-O, C-N, and C-C formation) of aldehydes, ketones and amines by the combinational use of chiral catalysts and photoredox catalysts.

The latter strategy, decoupling photochemistry from the enantiodifferentiation step, could be more suitable approach to utilizing photochemistry because the well-established ground-state asymmetric catalysis can be applied directly to the asymmetric photoreactions.

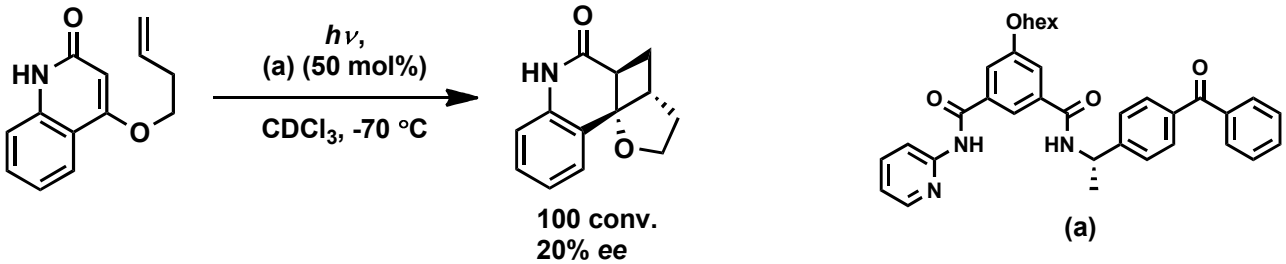
[the directions for designing efficient catalysts]

No reaction occurs in the absence of the catalyst, and the desired reaction proceeds in the presence of the catalyst.

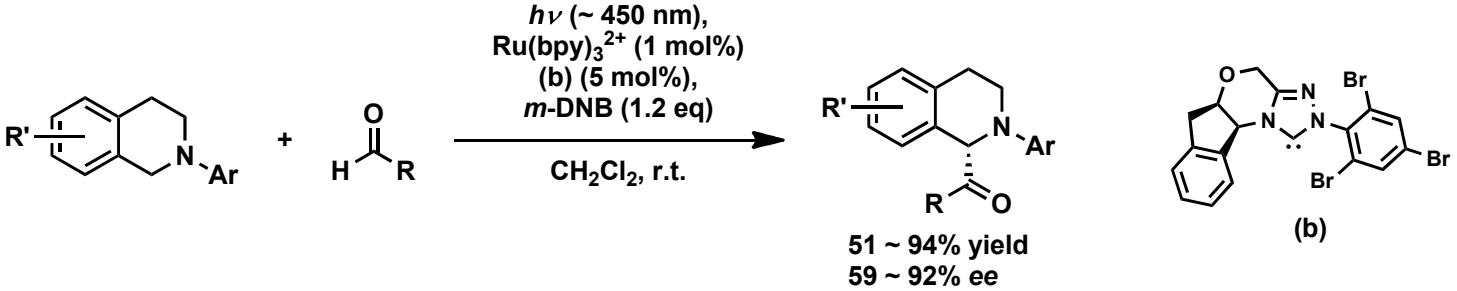
The catalyst should change the electronic properties (e.g. electron-donating catalysts accelerate the oxidation of the substrate by photoredox catalysts), cause the bathochromic shift, and so on.

♣ catalysts unlisted in this seminar

M. J. Krische *JOC*, 2003, *68*, 15.



T. Rovis *JACS*, 2012, *134*, 8094.



Q.-W. Meng *Chem.-Asian J.* 2012, *7*, 2019.