Enantioselective Intermolecular [2+2] Photocycloadditions of Isoquinolone Mediated by a Chiral Hydrogen-Bonding Template

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Bach, T. et al.
J. Am. Chem. Soc. **2013**, *135*, 14948-14951.

Technische Universität München

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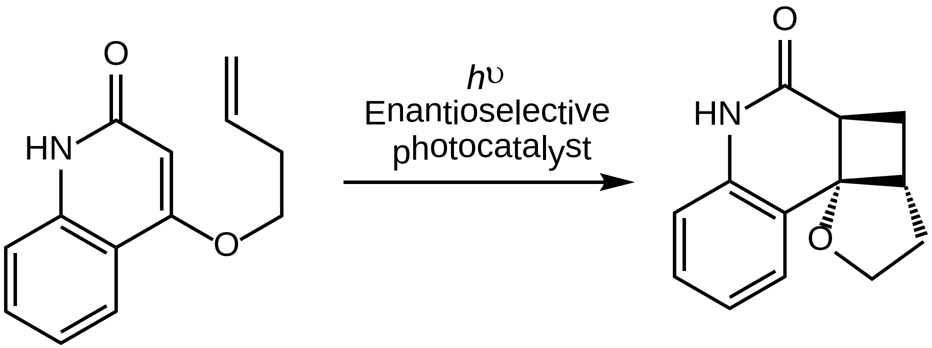
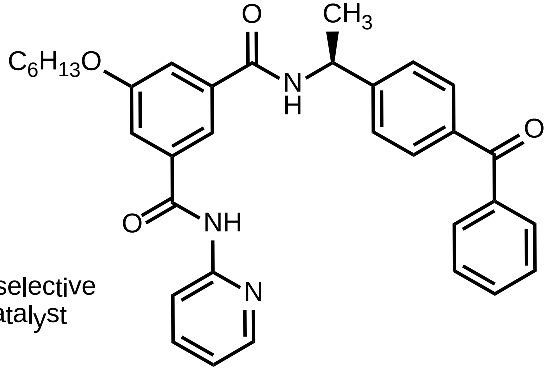
Introduction



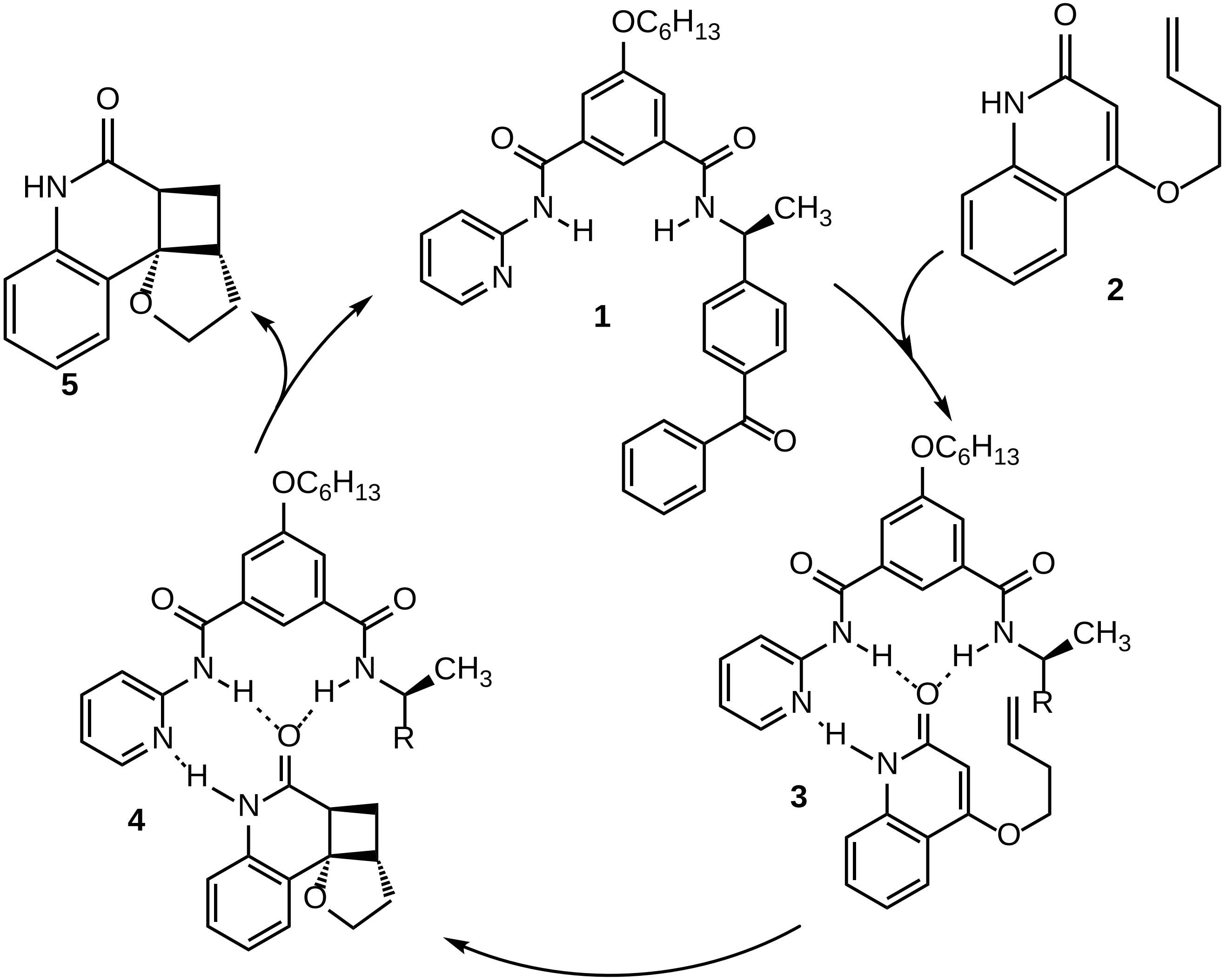
19% ee with
25 mol% of catalyst

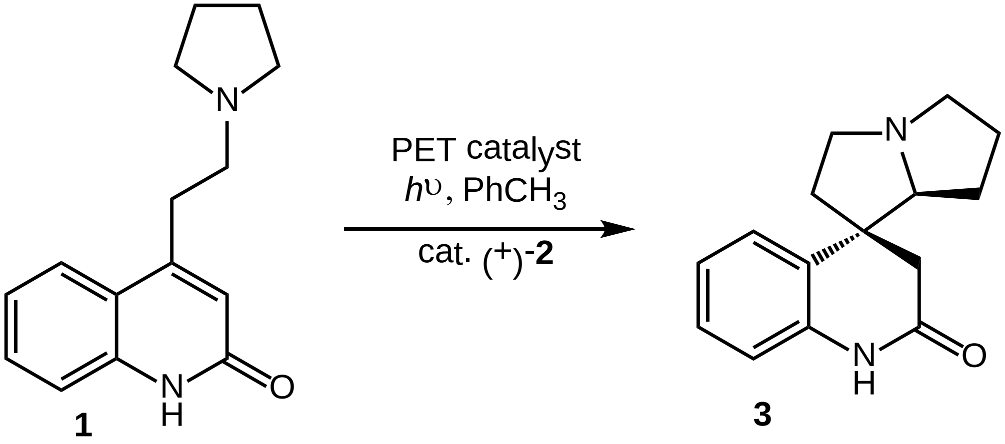


Enantioselective
photocatalyst

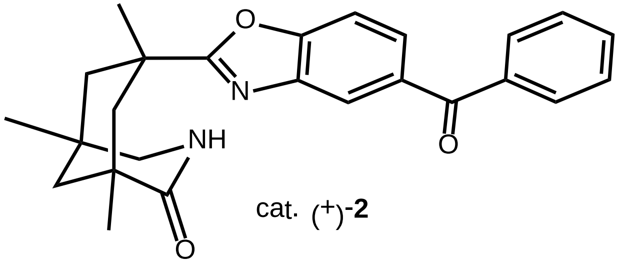
Krische, M. J. et al. *J. Org. Chem*. **2003**, *68*, 15–21.

Proposed catalytic cycle





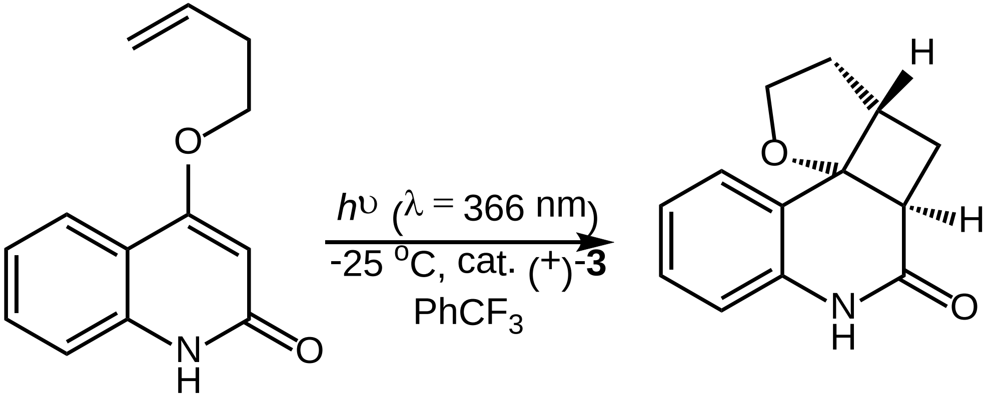
Up to 70% ee with
30 mol% of catalyst



cat. (+)-**2**

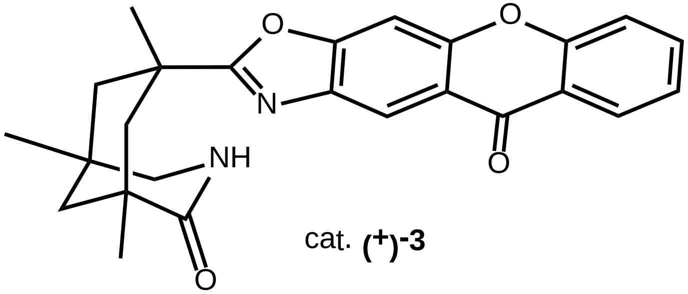
PET= photoinduced electron transfer

Bach, T. et al. *Nature* **2005**, *436*, 1139–1140.



1 **2**

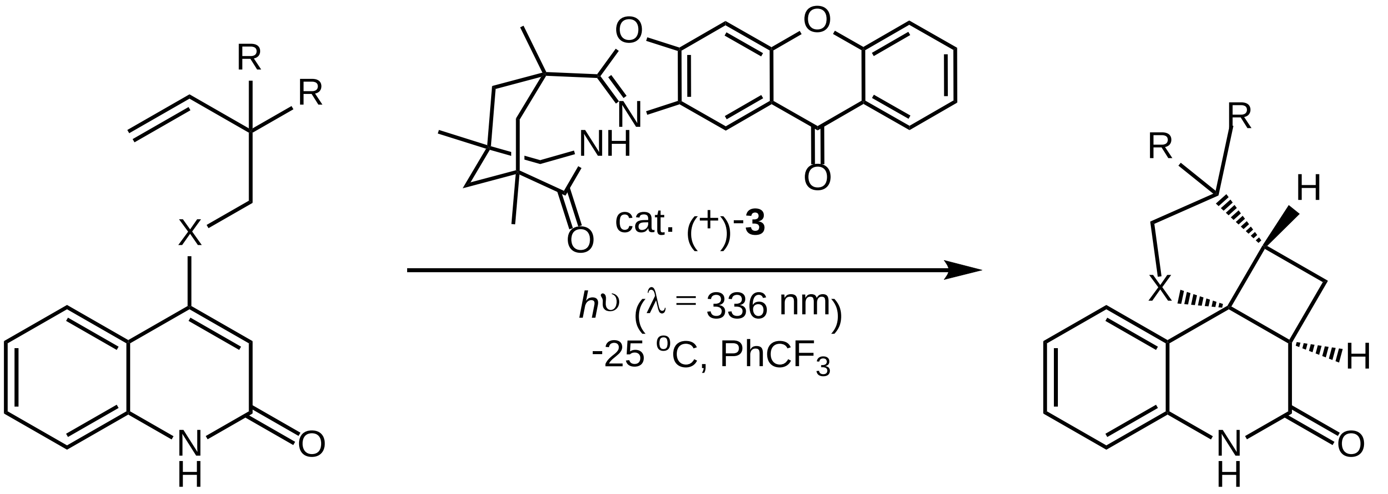
Up to 90% ee with
5 mol% of catalyst



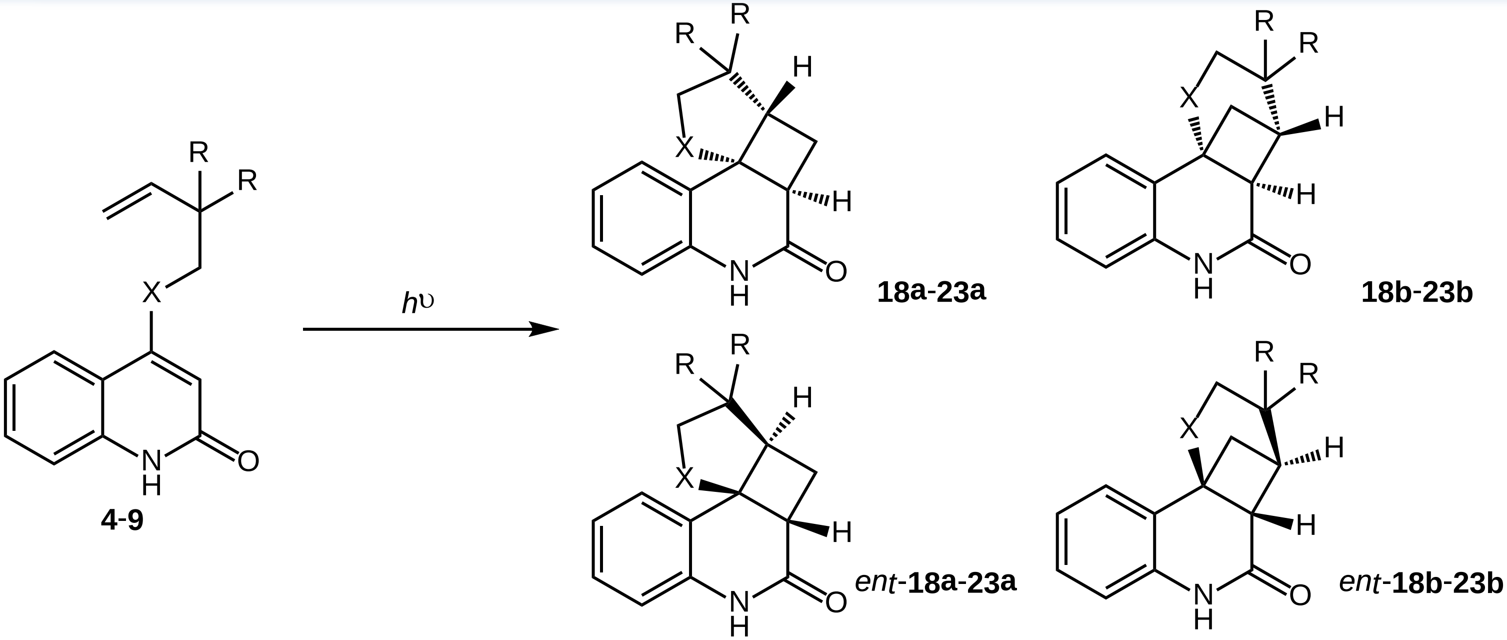
cat. **(+)-3**

Bach, T. et al. *Angew. Chem. Int. Ed*. **2009**, *48*, 6640–6642.

Photocycloaddition Reactions of 4-Substituted Quinolones



Bach, T. et al. *J. Am. Chem. Soc*. **2011**, *133*, 16689–16697.



entry	substrate	X	R	Product	t [h]	r.r.	yield [%]
1	**4**	O	H	*rac*-**18**	9[a]	86/14	78
2	**5**	OCH_2	H	*rac*-**19**	9	90/10	99
3	**6**	O	Me	*rac*-**20**	7	91/9	95
4	**7**	S	H	*rac*-**21**	2	>95/5	99
5	**8**	SO_2	H	*rac*-**22**	2	>95/5	92
6	**9**	CH_2	H	*rac*-**23**	0.5	>95/5	99

[a]:The reaction remained incomplete after 9 h (83% conversion)

4.2 Absorption Spectra of Substrates **4-9**

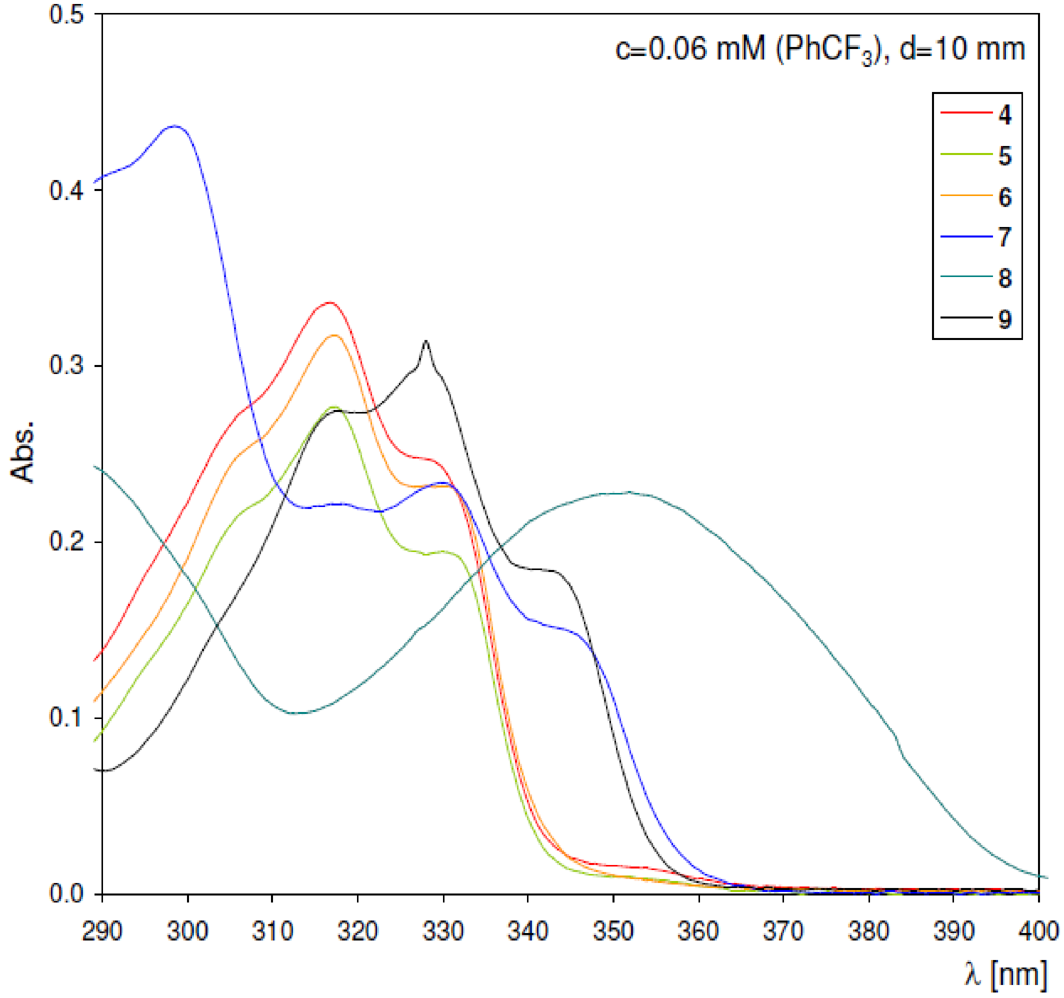
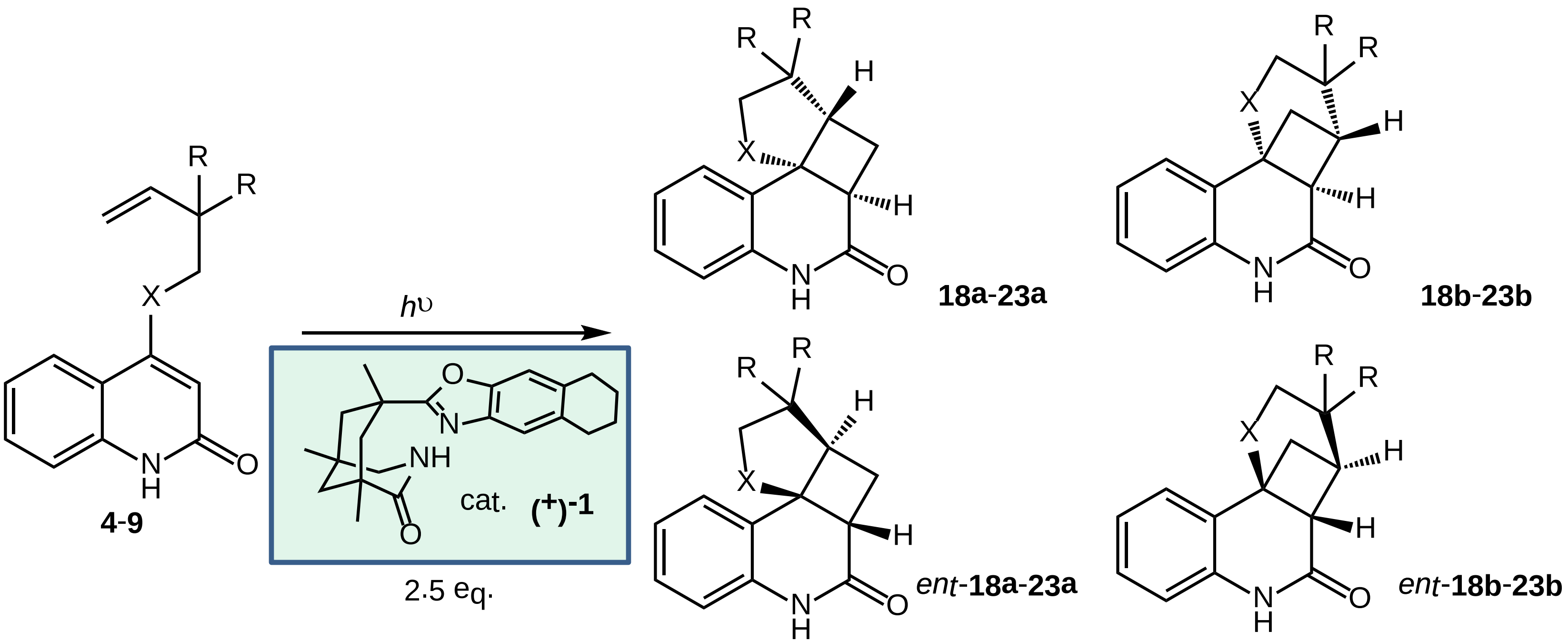


Figure SI-2: Absorption spectra of substrates **4** - **9**.

4	(c = 0.06 mM, d = 1.0 cm)	
λ_{max}	317 nm	$\varepsilon = 5600$
5	(c = 0.06 mM, d = 1.0 cm)	
λ_{max}	317 nm	$\varepsilon = 4613$
6	(c = 0.06 mM, d = 1.0 cm)	
λ_{max}	317 nm	$\varepsilon = 5288$
7	(c = 0.06 mM, d = 1.0 cm)	
λ_{max-1}	298 nm	$\varepsilon = 7265$
λ_{max-2}	330 nm	$\varepsilon = 3899$
8	(c = 0.06 mM, d = 1.0 cm)	
λ_{max}	352 nm	$\varepsilon = 3802$
9	(c = 0.06 mM, d = 1.0 cm)	
λ_{max}	327 nm	$\varepsilon = 4998$



4-9

18a-23a

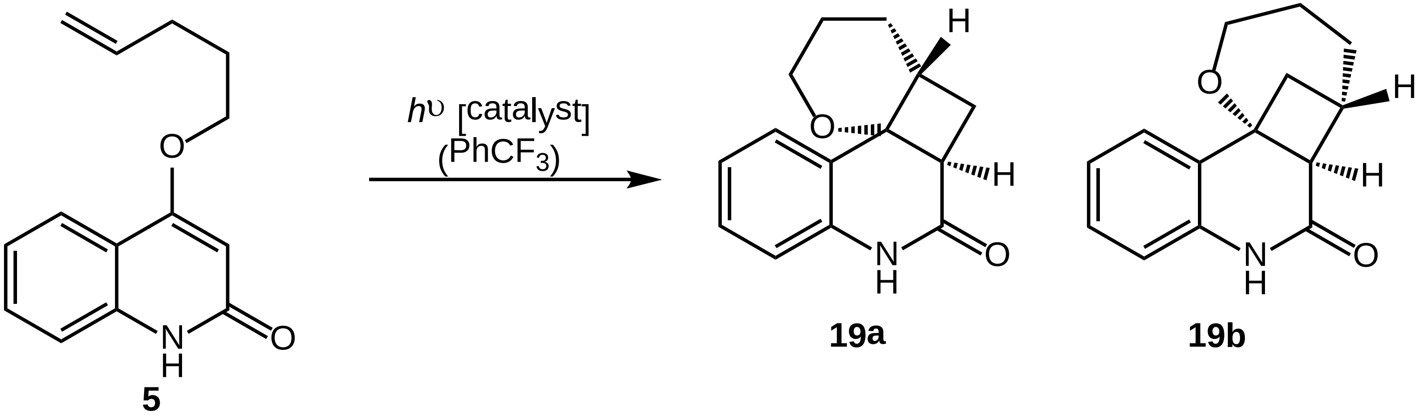
18b-23b

ent-**18a-23a**

ent-**18b-23b**

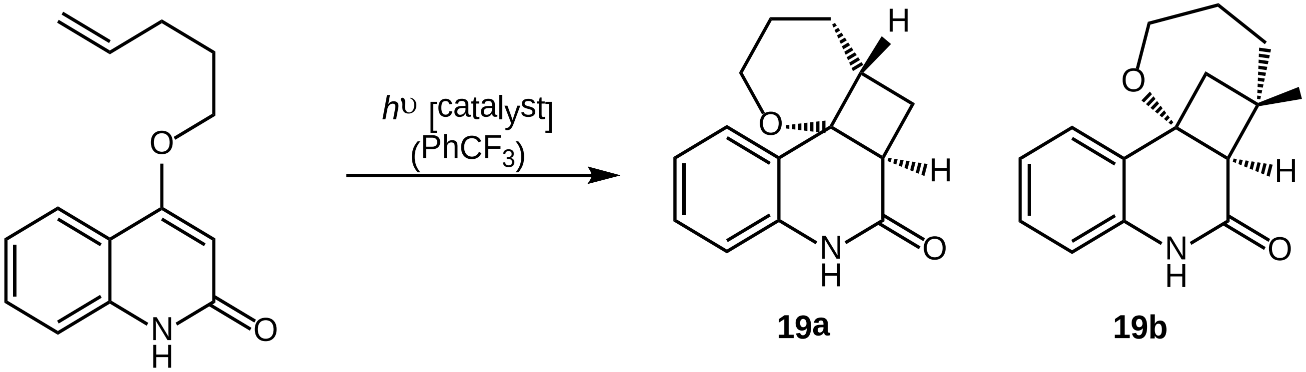
entry	substrate	X	R	product	λ [nm]	t [h]	ee [%]	yield [%]
1	**4**	O	H	**18a**	300	3	89	43
2	**5**	OCH_2	H	**19a**	300	1	>90	87
3	**6**	O	Me	**20a**	300	6	83	66
4	**7**	S	H	**21a**	366	1	89	89
5	**8**	SO_2	H	**22a**	366	1	90	99
6	**9**	CH_2	H	**23a**	366	2	94	99

The effect of achiral catalyst

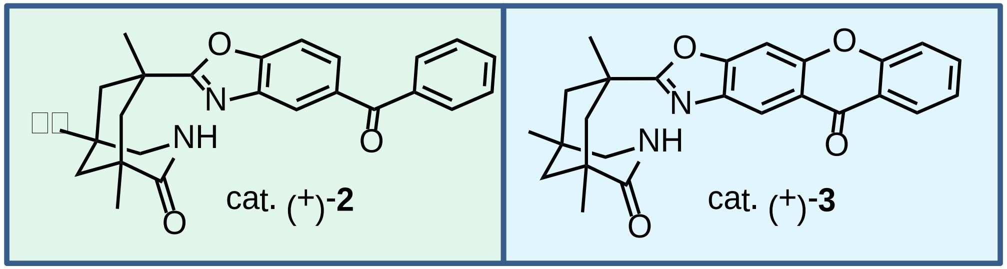


entry	catalyst	product	t [h]	**19a/19b**	conv. [%]	yield [%]
1	--	*rac*-**19**	4	91/9	46	22
2	benzophenone	*rac*-**19**	4	91/9	96	89
3	xanthone	*rac*-**19**	4	91/9	94	93

The effect of chiral catalyst (+)-2 and (+)-3



5 **19a** **19b**

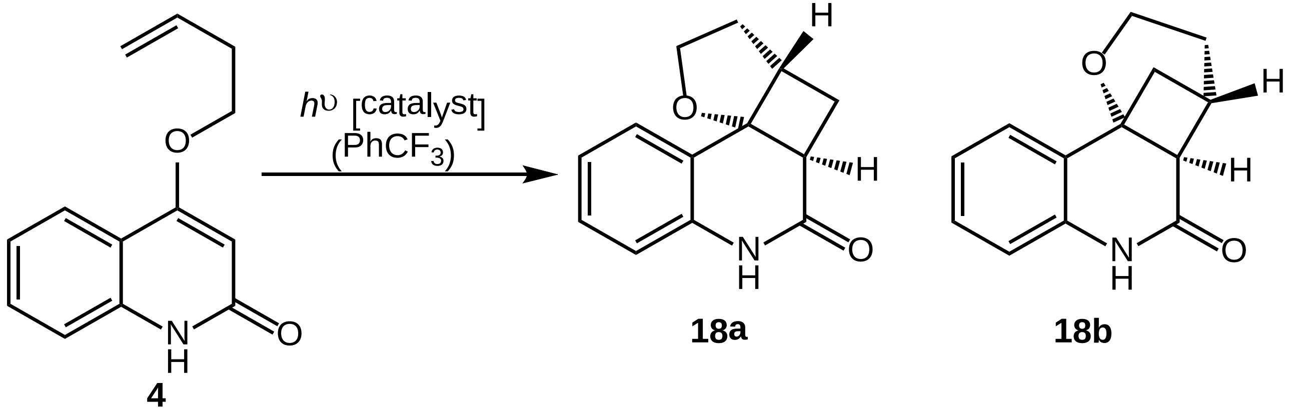


cat. (+)-**2** cat. (+)-**3**

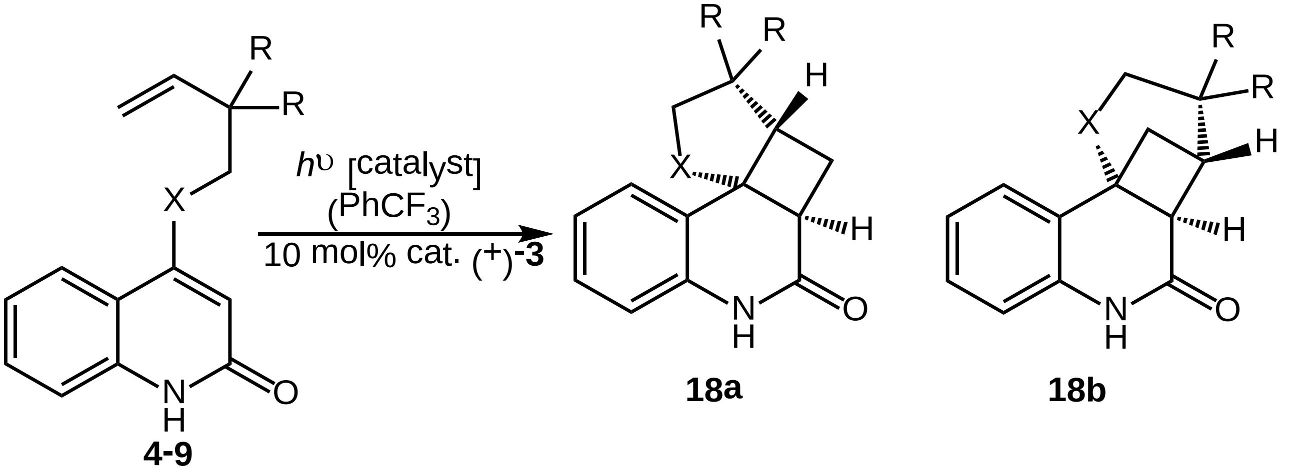
entry	catalyst	mol %	**19a/19b**	conv. [%]	ee [%]	yield [%]
1	(+)-**2**	10	82/18	60	12	45
2	(+)-**3**	5	80/20	55	21	39
3[a]	(+)-**3**	10	76/24	58	27	42
4	(+)-**3**	20	80/20	65	35	48
5	(+)-**3**	30	70/30	69	41	62

366 nm for 4 h at -25 °C. [a]: after 1 h , 40% conversion, 37% ee.

The effect of chiral catalyst (+)-2 and (+)-3



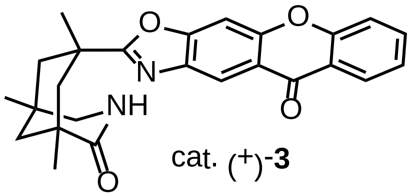
entry	catalyst	mol%	t [h]	r.r.	conv. [%]	ee [%]	yield [%]
1	--	--	1	n.d	19	--	5
2	(+)-**2**	10	1	84/16	57	39	51
3	(+)-**3**	10	1	78/22	64	92	58
4	(+)-**3**	10	2	77/23	81	90	75
5	(+)-**3**	10	4	>99/1	90	91	50
6	(+)-**3**	10	10	>99/1	100	89	46
7	(+)-**3**	5	1	78/22	50	90	48
8	(+)-**3**	20	1	79/21	73	94	53



4-9

18a

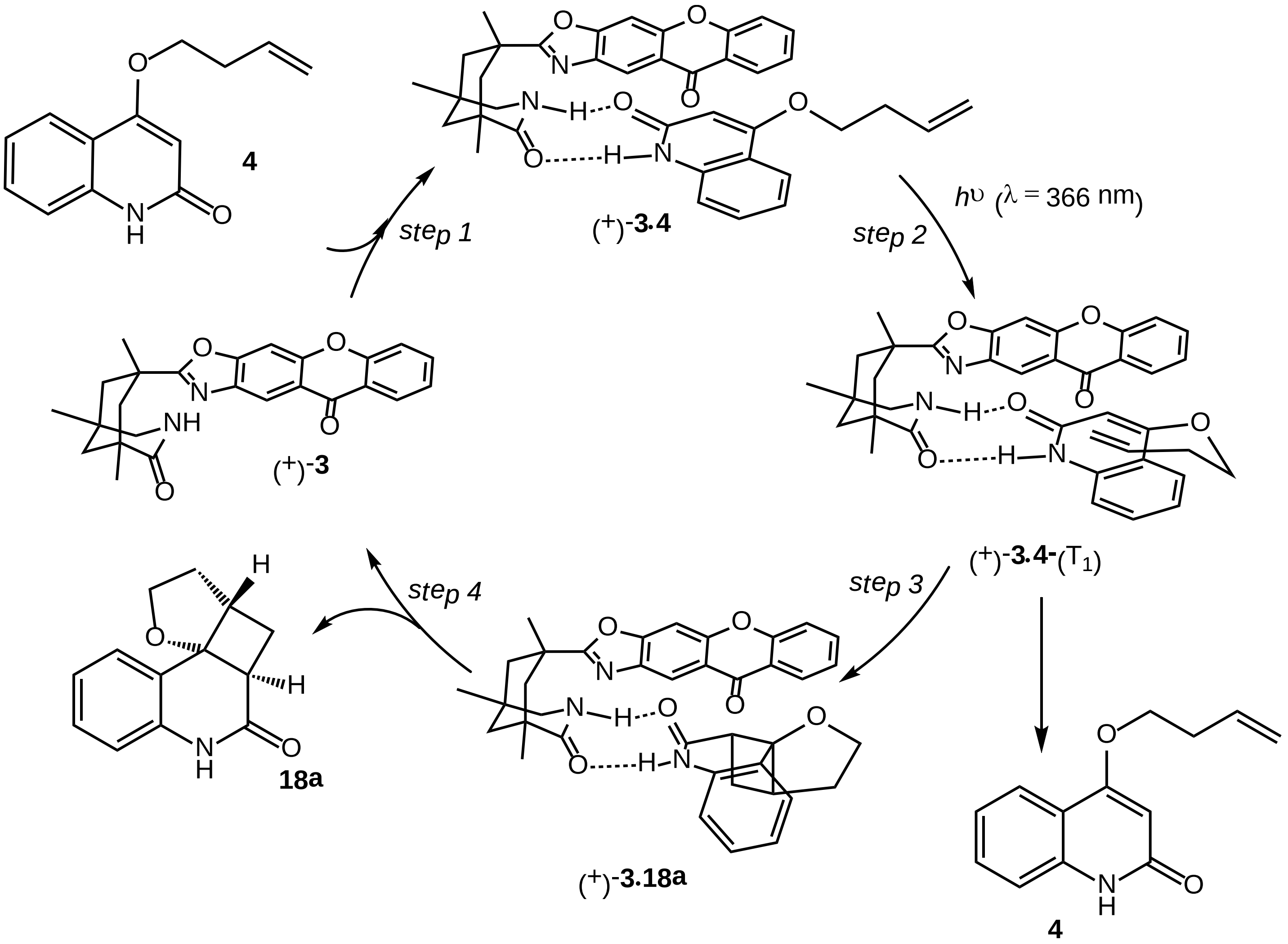
18b



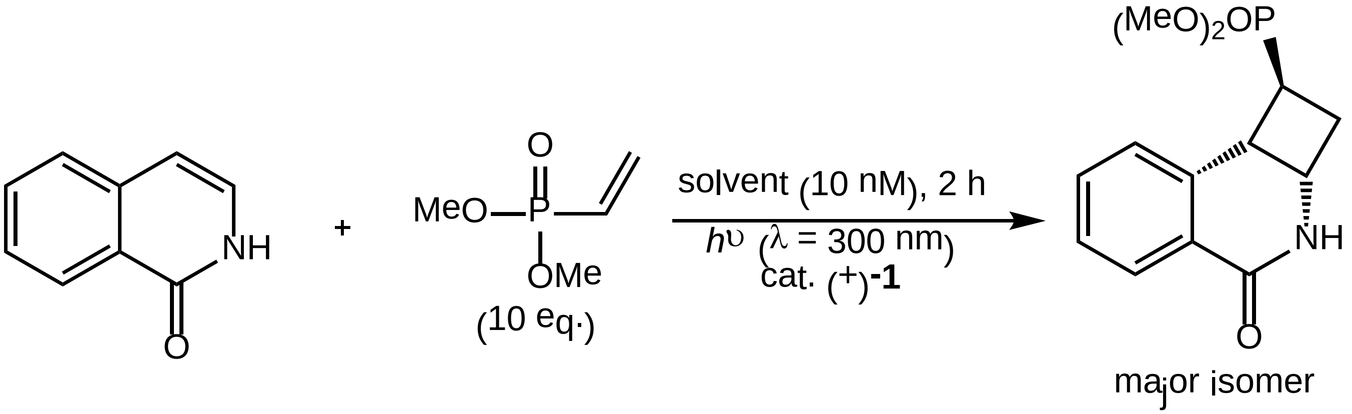
cat. ($^+$)-**3**

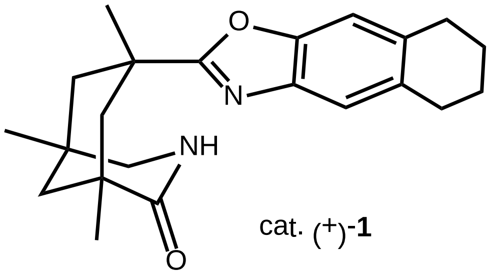
entry	substrate	X	t [h]	**r.r.**	conv. [%]	ee [%]	yield [%]
1	**4**	O	2	77/23	81	90	75
2	**5**	OCH_2	1	78/22	41	38	34
3	**6**	O	1	82/18	79	85	73
4	**7**	S	0.5	>95/5	53	72	21
5	**8**	SO_2	0.5	>95/5	31	6	28
6	**9**	CH_2	0.5	>95/5	84	87	70

Possible mechanism



Photocycloadditions of Isoquinolone

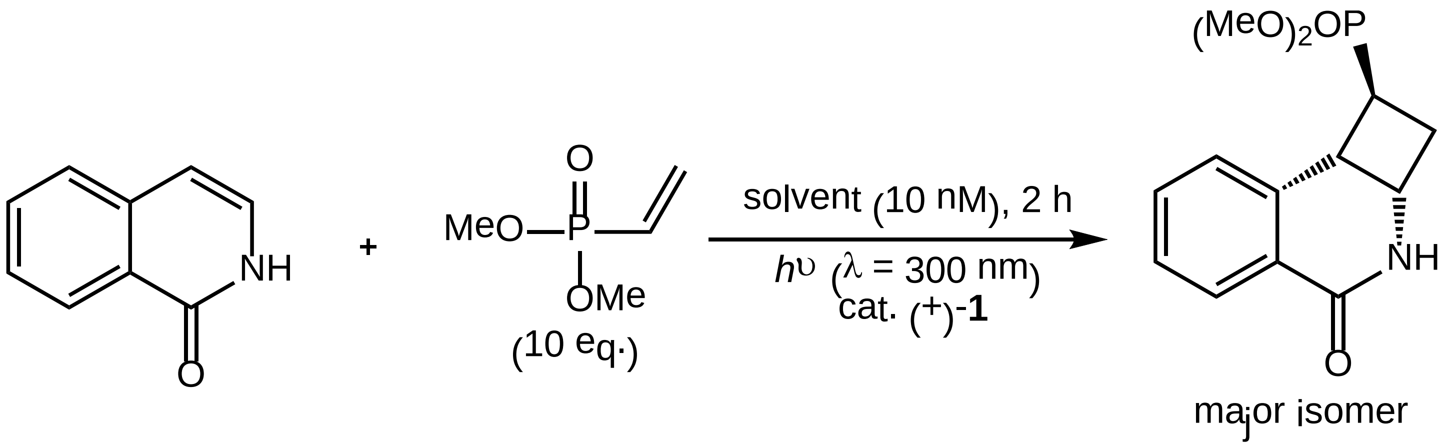




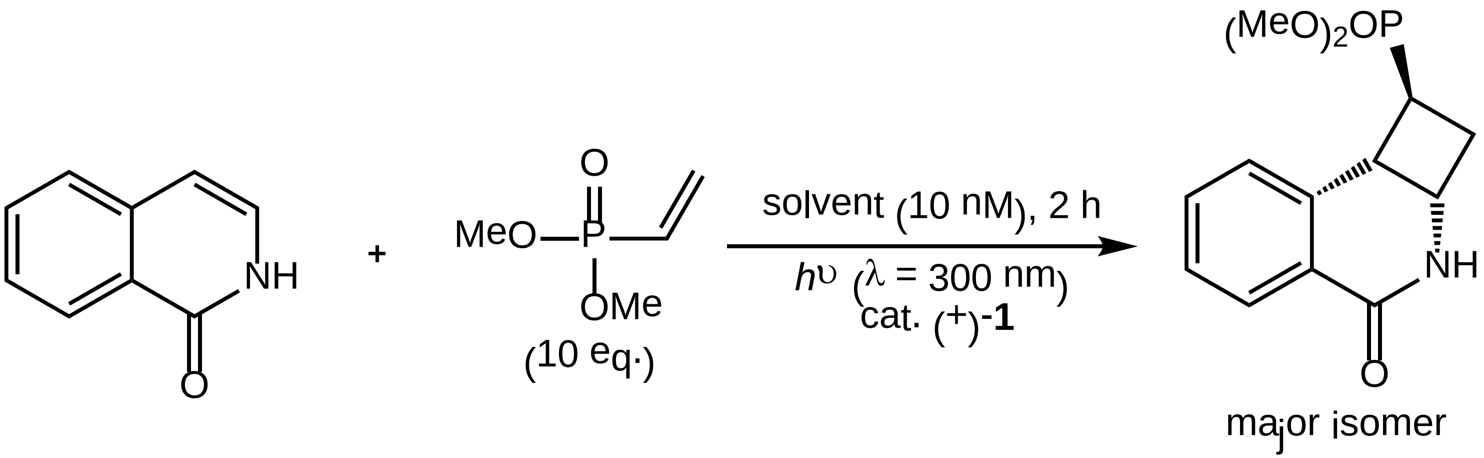
cat. (+)-**1**

Bach, T. et al. *J. Am. Chem. Soc*. **2013**, *135*, 14948–14951.

Optimization reaction conditions

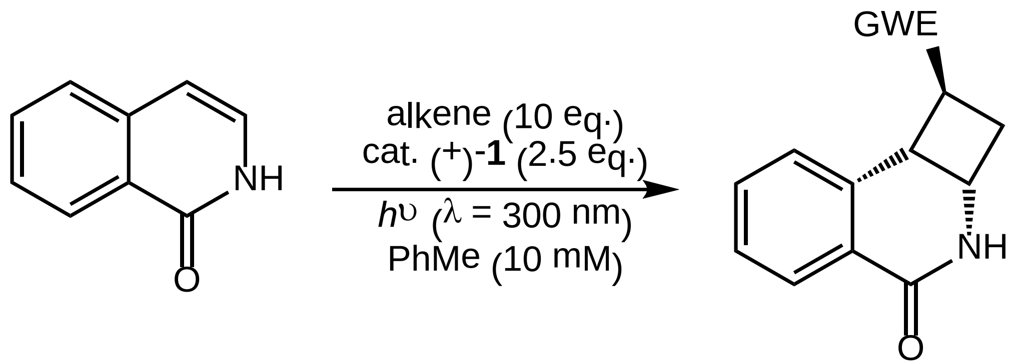


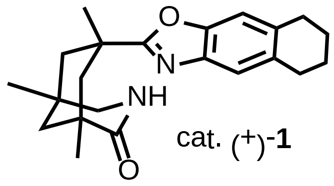
entry	T (^{o}C)	solvent	(+)-**1** (eq.)	ee [%]	yield [%]	Isomer Ratio
1	rt	PhMe	-	-	75	3:1
2	rt	PhMe	2.5	26	78	5:1
3	rt	PhCF$_3$	2.5	36	74	5:1
4	0	PhCF$_3$	2.5	62	83	4:1
5	-20	PhCF$_3$	2.5	70	86	5:1
6	-40	PhCF$_3$	2.5	80	95	5:1



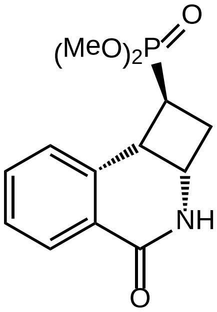
entry	T (ºC)	solvent	(+)-**1** (eq.)	ee [%]	yield [%]	Isomer Ratio
7	-40	PhMe	2.5	72	95	12:1
8	-60	PhMe	2.5	90	97	12:1
9	-60	PhMe	1.5	84	99	12:1
10	-75	PhMe	2.5	93	93	16:1
11	-75	PhMe	1.5	86	95	16:1

Substrate scope

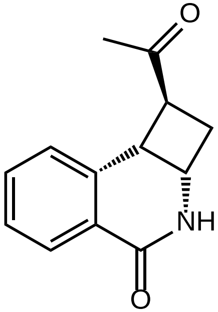




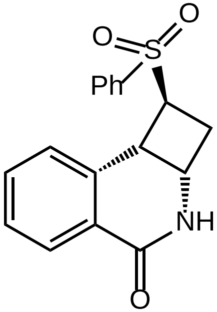
cat. (+)-**1**



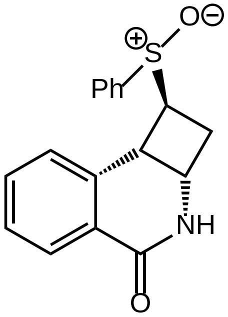
93% (i.r. 16:1)
93% ee



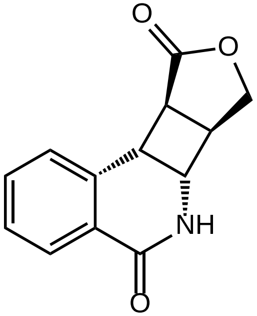
93% (i.r. >20:1)
96% ee



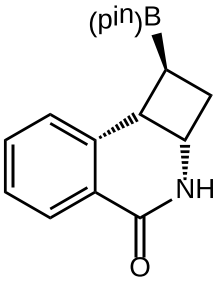
98% (i.r. >20:1)
99% ee



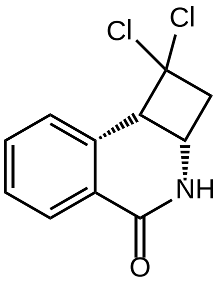
95% (i.r. >20:1)
96% ee



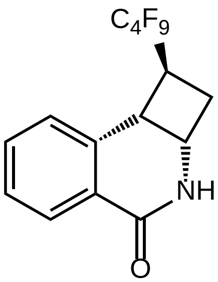
95% (i.r. >20:1)
98% ee



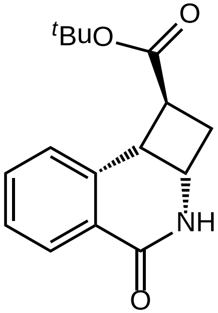
86% (i.r. >20:1)
98% ee



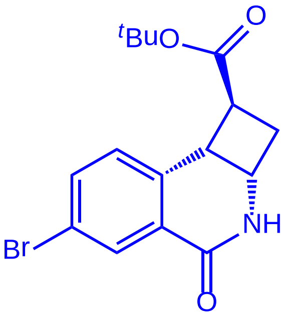
92% (i.r. >20:1)
98% ee



93% (i.r. >20:1)
88% ee

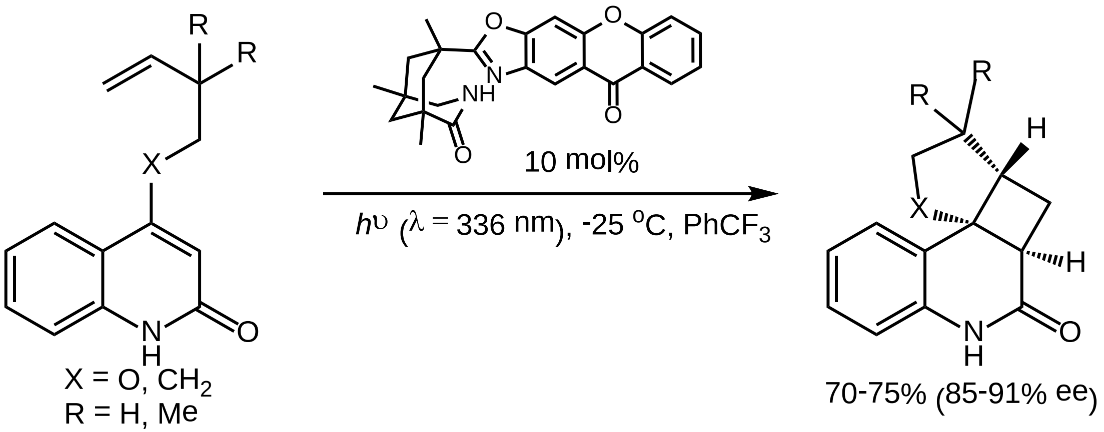


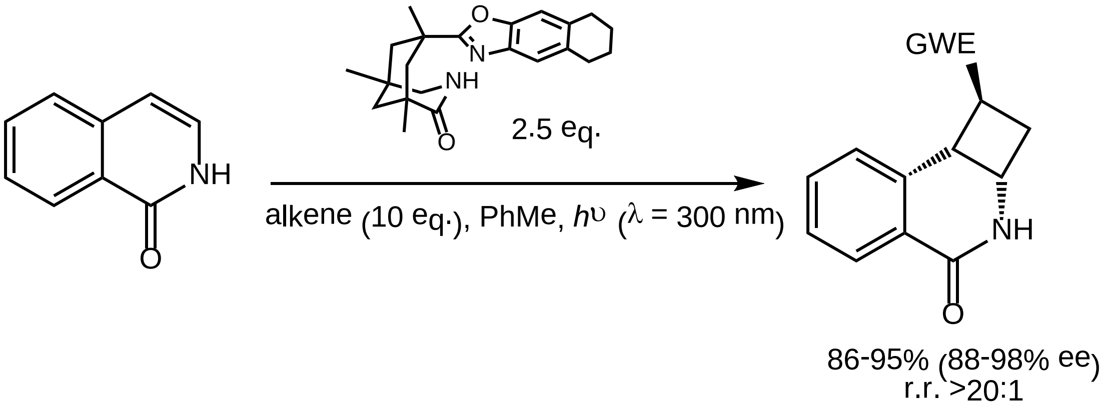
93% (i.r. >20:1)
98% ee



91% (i.r. >20:1)
97% ee

Summary


10 mol%
hυ (λ = 336 nm), -25 °C, PhCF3
X = O, CH2
R = H, Me
70-75% (85-91% ee)


2.5 eq.
alkene (10 eq.), PhMe, hυ (λ = 300 nm)
GWE
86-95% (88-98% ee)
r.r. >20:1

The [2+2] photocycloaddition of isoquinolone substrates represents a particularly attractive entry into the synthesis of isoquinoline-derived target molecules. Given the plethora of isoquinoline-containing products isolated from various natural sources, such reactions, if performed enantioselectively, would represent a powerful tool for the rapid and efficient synthesis of a large range of natural products and pharmaceuticals, as well as other synthetic targets. However, although the [2+2] photocycloadditions of isoquinolones have been studied in the racemic series, no examples of the enantioselective intermolecular [2+2] photocycloadditions of isoquinolones have yet been reported, thus limiting the applicability of such an approach. Furthermore, even in the racemic series, the range of alkenes employed in intermolecular [2+2] photocycloadditions is limited, further restricting the synthetic potential of the photoadducts formed. We set out to address both of these issues, aiming to develop an enantioselective method for the intermolecular [2+2] photocycloaddition of isoquinolones that allows broad alkene scope.

In summary, we have developed the first examples of the enantioselective intermolecular [2+2] photocycloaddition of isoquinolone with a wide range of electron-deficient alkenes, employing (+)-**1** as a chiral template. Our method delivers functionalized cyclobutanes in excellent yields and with outstanding regio-, diastereo-, and enantioselectivity. Furthermore, the photoproducts retain useful synthetic handles that can be exploited for further manipulation. To this end, the derivatization of cyclobutyl boronate **3e** through oxidation has been demonstrated. Finally, preliminary results demonstrating the successful use of a substituted isoquinolone substrate as well as a 1,2-disubstituted alkene partner are reported. Our new methodology holds great promise for use in the asymmetric synthesis of isoquinoline-derived target molecules and natural products; further studies toward this goal will be reported in due course.