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

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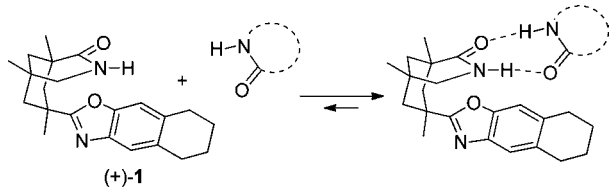
Supporting Information

ABSTRACT: The first examples of enantioselective intermolecular [2+2] photocycloadditions of isoquinolone with alkenes are reported. Photoreactions were carried out at low temperature in the presence of a chiral hydrogen-bonding template, which effectively shields one face of the substrate through formation of a hydrogen-bonded supramolecular complex. Functionalized cyclobutane products were obtained in excellent yields (86−98%) and with outstanding regio-, diastereo-, and enantioselectivity (88−99% ee).

The [2+2] photocycloaddition[1,2] 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,[3] 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.[4] However, although the [2+2] photocycloadditions of isoquinolones have been studied in the racemic series,[5,6] 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.

Enantioselective photochemical reactions in solution remain a challenge,[7] with few effective methods developed that do not rely on chiral auxiliary-based approaches. The ability to carry out enantioselective photochemical reactions solely by means of non-covalent interactions has great potential to streamline photochemical synthetic routes, since the introduction and removal of chiral auxiliaries would no longer be necessary. To this end, chiral template **1**[8,9] was developed by our group to mediate enantioselective photoreactions of prochiral lactam-containing substrates. Template **1** is able to form two hydrogen bonds to such substrates, generating a supramolecular complex in which the tetrahydronaphtho[2,3-*d*]oxazole unit (the "steric shield") effectively shields one face of the substrate, thus allowing reaction only on the exposed face (Scheme 1).

Scheme 1. Chiral Template (+)-1 Forms a Supramolecular Complex with Prochiral Amide- and Lactam-Containing Substrates



Thus far, the use of chiral template **1** has been largely focused on intramolecular reactions, allowing intramolecular photoreactions of quinolones, isoquinolones, and pyridones to occur with excellent enantioselectivity. Conversely, the corresponding intermolecular photoreactions have received relatively little attention. Such intermolecular reactions are inherently more challenging than intramolecular reactions, since these reactions do not benefit from the favorable entropy effects and preorganization that enable the exquisite selectivity often associated with intramolecular photoreactions. Herein, we describe in preliminary form the successful extension of our recently reported intramolecular isoquinolone work,[6d] delivering the first examples of the enantioselective intermolecular [2+2] photocycloadditions of isoquinolone with a variety of alkenes, mediated by chiral template **1**.

Intermolecular [2+2] photocycloadditions of isoquinolones are known to take place readily with electron-deficient alkenes, and are thought to proceed through a triplet excited state.[5] Of particular note, Kaneko et al. published an in-depth report of the [2+2] photocycloadditions of isoquinolone with a variety of chlorinated alkenes,[5e] while Gilbert et al. reported the corresponding reactions employing a range of acrylonitriles and acrylates.[5j] In both cases, the reactions were carried out in polar solvents (acetonitrile or methanol), irradiating with a 350 nm light source. Initially, we explored the scope of the [2+2] photocycloadditions of isoquinolone in nonpolar solvents, since nonpolar solvents are required in order to achieve high enantioselectivity using chiral template **1**. Reactions were carried out in toluene (10 mM) at room temperature using ten equivalents of alkene, irradiating at 300, 350, or 366 nm. Photocycloadditions proceeded well using electron-deficient alkenes, generating the corresponding functionalized cyclobutane products in 1−2 h (irradiation with 300 nm light) or 8−

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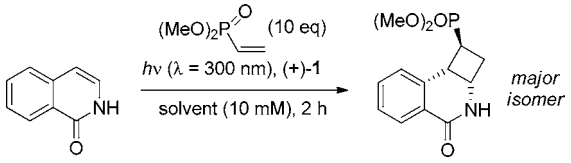
16 h (irradiation with 350 or 366 nm light). The range of alkenes employed in these reactions has been rather limited thus far (to acrylates, acrylonitriles, vinyl ketones, and chlorinated alkenes) and we were particularly interested in widening the scope of these reactions in order to increase the synthetic potential of the resulting photoadducts. Pleasingly, we found that a range of other, more synthetically versatile alkenes also undergo efficient photocycloaddition with isoquinolone, including a vinyl phosphonate, a vinyl sulfone, a vinyl sulfoxide, a vinyl boronate ester, and an alkene bearing a perfluoroalkyl chain. Notably, these reactions are the first examples (on any enone substrate) of [2+2] photocycloadditions involving alkenyl sulfoxides and alkenyl phosphonates as reaction partners. Likewise, despite the great synthetic potential of boronate ester-containing intermediates, only a single example of [2+2] photocycloaddition with an alkenyl boronate derivative has been previously reported.[10,11] In line with previous literature reports, mixtures of regio- and diastereoisomers were formed upon reaction at ambient temperature, the major isomer in each case being the "*exo*-head-to-tail" product (for further details, see the Supporting Information).

Having explored the parameters of the racemic reaction, we next turned our attention to the enantioselective version, employing chiral template (+)-**1**. Using the [2+2] photocycloaddition of isoquinolone **2** with dimethylvinylphosphonate as a model reaction, the effects of the solvent, reaction temperature, and template loading were examined (Table 1). The best results were obtained at lower temperatures, presumably due to increased association of the isoquinolone and the chiral template.[12] Thus, at room temperature (Table 1, entry 2), cyclobutyl phosphonate **3a** was obtained with moderate diastereo- and regioselectivity (all four possible isomers were formed; see the Supporting Information for details) and poor enantioselectivity. On the contrary, when the reaction was performed at −75 °C (Table 1, entry 10) the desired product **3a** was obtained with excellent enantioselectivity, accompanied by only traces of a second isomer. In terms of the choice of solvent, toluene was found to be superior to trifluorotoluene, displaying a marked improvement in diastereoselectivity at −40 °C (Table 1, compare entry 6 with entry 7). Interestingly, reducing the loading of chiral template (+)-**1** to 1.5 equivalents (from 2.5 equiv) led to only a slight decrease in enantioselectivity (Table 1, compare entry 8 to entry 9, and entry 10 to entry 11). In all cases, the chiral template was easily recovered after flash chromatography (usually ≥95% recovery).

Table 1. Optimization Studies for the [2+2] Photocycloaddition of Isoquinolone with Dimethylvinylphosphonate



2 **3a**

entry	*T* (°C)	solvent	(+)-**1** (equiv)	yield (%)[a]	isomer ratio[b]	ee (%)[c]
1	rt	PhMe	–	75	3:1[d]	–
2	rt	PhMe	2.5	78	5:1[d]	26
3	rt	$PhCF_3$	2.5	74	5:1[d]	36
4	0	$PhCF_3$	2.5	83	4:1[d]	62
5	−20	$PhCF_3$	2.5	86	5:1[d]	70
6	−40	$PhCF_3$	2.5	95	5:1[d]	80
7	−40	PhMe	2.5	95	12:1[d]	72
8	−60	PhMe	2.5	97	12:1	90
9	−60	PhMe	1.5	99	12:1	84
10	−75	PhMe	2.5	93	16:1	93
11	−75	PhMe	1.5	95	16:1	86

[a]Yield of **3a** and its isomer **3a′** after column chromatography (see Supporting Information for full details). [b]Ratio determined (by ^{1}H NMR spectroscopy) for the major isomer **3a** and its isomer **3a′** after column chromatography. [c]Enantiomeric excess of the major isomer **3a** (by chiral HPLC). [d]Small amounts of a further two isomers were formed but were not collected after column chromatography.

Building on our encouraging preliminary results, we next explored the scope of the [2+2] photocycloaddition. To our delight, the reaction of isoquinolone[12] with a range of different electron-deficient alkenes under the optimized conditions furnished the corresponding functionalized cyclobutanes **3a**–**3h** in excellent yields and with outstanding regio-, diastereo-, and enantioselectivity (Scheme 2). In most cases, only a single isomer could be detected (by ^{1}H NMR spectroscopy), with enantiomeric excesses of up to 99%, thus representing the best results ever achieved using chiral template **1**. Since cyclobutyl boronate **3e** was not stable toward purification by flash chromatography, it was first oxidized to the corresponding cyclobutanol[13] and then protected as the benzoate ester (vide infra) before analysis by chiral HPLC. Similarly, cyclobutyl sulfoxide **3d** was obtained as a 1.3:1 mixture of diastereoisomers as a consequence of the extra stereogenic center at sulfur; to simplify the product analysis, purified **3d** was oxidized[14] to the corresponding cyclobutyl sulfone **3c** before analysis by chiral HPLC (see the Supporting Information for full details). It is also possible to carry out these reactions using longer wavelengths of light, although reaction times are significantly longer. For example, the photocycloaddition of isoquinolone **2** with *tert*-butyl acrylate, irradiating at 366 nm for 12 h, gave the corresponding cyclobutyl ester product **3h** in 98% yield, with an enantiomeric excess of 99%. This result is very similar to that obtained when irradiating at 300 nm (93% yield and 98% enantiomeric excess; Scheme 2). These reactions represent the first examples of enantioselective intermolecular [2+2] photocycloadditions of isoquinolones, and significantly increase the scope of the alkene that can be employed.

The absolute configuration of the cyclobutane products was assigned in analogy with the known enantioface differentiation of (+)-**1** in related reactions.[9] Thus, the supramolecular complex formed from isoquinolone and chiral template (+)-**1** (Scheme 1) results in selective shielding of the *si* face of the isoquinolone, allowing photocycloaddition to occur selectively on the *re* face. As already noted for phosphonate **3a** (Table 1), the reaction conditions for the templated reaction also significiantly improve the regio- and diastereoselectivity of the addition. The head-to-tail regioselectivity can be explained by a preferential formation of the best stabilized 1,4-diradical,[1,15] which is presumably formed as an intermediate by addition of the olefin to the excited triplet state of isoquinolone.

The relative configuration of products **3** can be rationalized by a preferential *trans* orientation of the two bulkiest substituents at the cyclobutane core. The substituent EWG resides *exo* relative to the dihydroisoquinolone ring system.

The functionalized cyclobutanes obtained represent very interesting motifs in their own right, but also present tremendous opportunities for further functionalization. Indeed,

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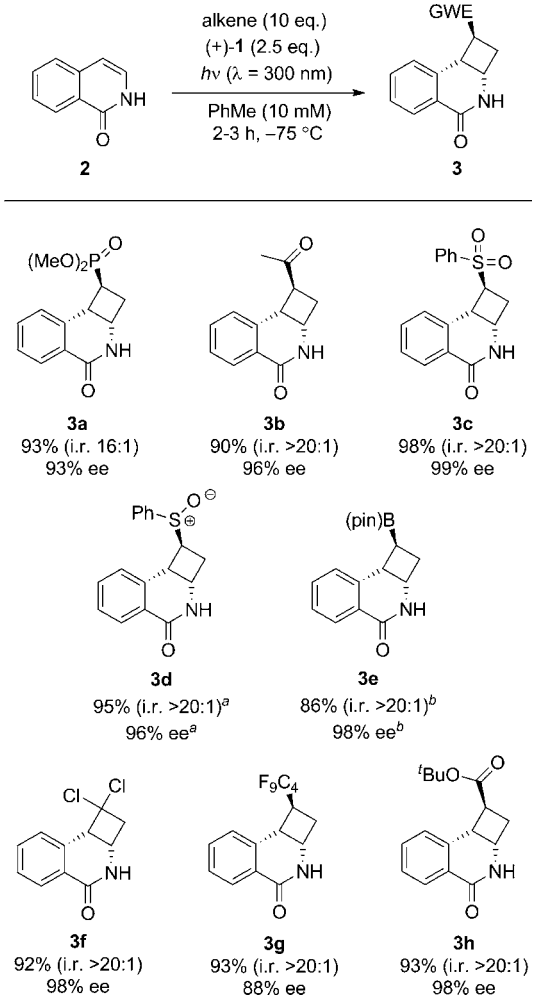
Scheme 2. Enantioselective [2+2] Photocycloadditions of Isoquinolone with Electron-Deficient Alkenes

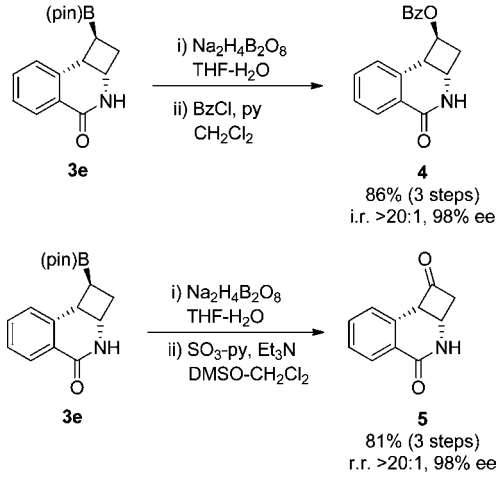


[a]Sulfoxide **3d** was obtained as a 1.3:1 mixture of diastereoisomers; isomer ratio (i.r.) and enantioselectivity were calculated after oxidation to the corresponding sulfone. [b]Yield, isomer ratio, and enantioselectivity were calculated after conversion to the corresponding benzoate ester. EWG = electron-withdrawing group, (pin) = pinacolato.

preliminary experiments yielded encouraging results: Boronated **3e** underwent efficient sodium perborate-mediated oxidation[13] to the corresponding cyclobutanol, which was formed with retention of configuration as expected. The alcohol could be further derivatized to the corresponding benzoate ester **4** or cyclobutanone **5** products respectively (Scheme 3). A number of other useful transformations of several of the other functionalized cyclobutanes can easily be envisaged, and are the subject of further investigations in our laboratory.

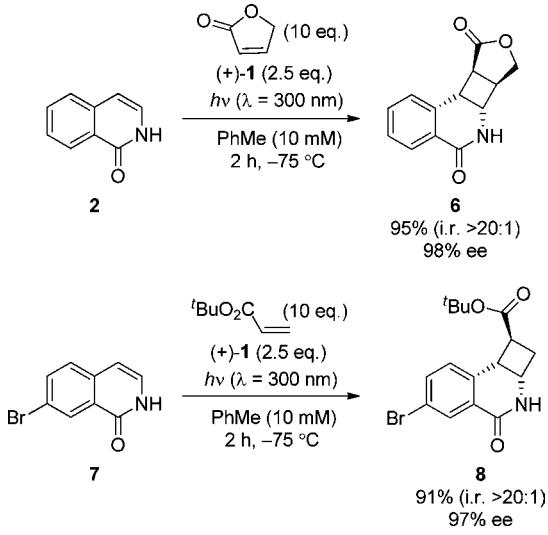
Finally, we wished to investigate further the scope of our methodology. All of the examples reported in Scheme 3 involve terminal alkenes as reaction partners, and we wanted to determine whether more substituted alkenes are also viable reaction partners. Pleasingly, it could be shown that isoquinolone **2** also undergoes [2+2] photocycloaddition with a 1,2-disubstituted alkene, 2-(5*H*)furanone, generating the desired cyclobutane product **6** as a single isomer in 95% yield and with excellent enantioselectivity (98% ee; Scheme 4).

Scheme 3. Derivatization of Cyclobutyl Boronate 3e[a]



[a]Bz = benzoyl, py = pyridine, (pin) = pinacolato, i.r. = isomer ratio, r.r. = regioisomer ratio.

Scheme 4. Scope of the [2+2] Photocycloadditions



In a preliminary experiment we also wanted to determine whether other, substituted isoquinolones can be used as substrates in these reactions. We chose 7-bromoisoquinolone (**7**), since we considered that it would generate a versatile product enabling further reactions at the aryl–bromine bond. Gratifyingly, its [2+2] photocycloaddition with *tert*-butylacrylate furnished the expected cycloadduct **8** as a single isomer in 91% yield, again with very high enantioselectivity (97% ee; Scheme 4).

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

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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.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, analytical data for all new compounds, and NMR spectra of the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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