Asymmetric Organocatalysis and Photoredox Catalysis for the α-Functionalization of Tetrahydroisoquinolines

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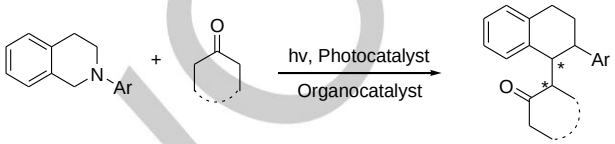
Abstract: The asymmetric α-alkylation of tetrahydroisoquinolines with cyclic ketones has been accomplished in the presence of a combined catalytic system consisting of a visible-light photoredox catalyst and a chiral primary amine organocatalyst. The desired products were obtained in good yields, high enantioselectivity and good to excellent diastereoselectivity.

The harnessing of visible light sensitization as a powerful strategy for initiating organic reactions is attractive and becoming an important tool in synthesis due to its favorable features, including low cost, convenience and environmentally friendliness.[1] Recently, the possibility to combine visible-light photoredox catalysis with Lewis acids, Brønsted acids, transition-metal as well as metal free organocatalysts attracted increasing attention and successful protocols have been described by different groups.[2] In these processes, two distinct catalysts, which can simultaneously activate different reaction partners, giving a significant opportunity to considerably lower the HOMO-LUMO gap for organic transformations, are commonly used.[2,3]

Regarding the dual catalytic approach involving a photoredox and an organocatalyst, various transformation including the α- and β-functionalization of carbonyl derivatives and α-functionalization of tetrahydroisoquinolines (THIQs) have been recently successfully accomplished in an asymmetric manner.[2] The functionalization of THIQs is, in general, an interesting research area owing to the importance of this nitrogen containing motif for both medicinal and organic chemistry.[4] In this context, a highly enantioselective protocol for the α-acylation of THIQs was reported by Rovis using a dual catalytic system consisting of a *N*-heterocyclic carbene and a photoredox catalyst.[5] Furthermore, Jacobsen and Stephenson reported recently an enantioselective synthesis of β-amino esters using silyl enol ethers and THIQs via sequential photoredox and thiourea anion-binding catalysis.[6-9]

Earlier reports on the α-alkylation reaction of THIQ-derived tertiary amines with acyclic ketones applying a combination of organo- and photoredox catalysts resulted in no or low enantioselectivity.[10] Hence, our attention focussed on developing a suitable catalytic system for accomplishing the demanding but challenging asymmetric α-functionalization of THIQs.[11] In particular, cyclic ketones were selected which are more challenging substrates in the enantioselective oxidative coupling reaction with tertiary amines (Scheme 1).[12]



Scheme 1. Enantioselective α-Functionalization of THIQs with Cyclic Ketones via Combined Organo- and Photoredox Catalysis

We began our investigation by using 2-(4-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline (**1a**) as electrophile precursor and cyclohexanone (**2a**) as nucleophile. With 1 mol% of $Ir(ppy)_2(bpy)PF_6$ as photoredox catalyst and under irradiation with an 11 W fluorescent bulb, different solvents, chiral primary amine catalysts and temperatures were initially explored. Firstly, the reaction of **1a** with **2a** was tested in EtOH (1 mL) using $Ir(ppy)_2(bpy)PF_6$ and different L-amino acids (Cat-**1** to Cat-**8**) as co-catalysts (Table 1, entries 1-8). Among them, D-α-phenylglycine Cat-**3** afforded the desired product **3a** with promising results (49% yield, 47% ee, and 4:1 dr, Table 1, entry 3). Hence, Cat-**3** was used as co-catalyst with different solvents such as DCM, DMSO, THF, toluene, MeCN, DMF and EtOAc. To our great delight, when DCM was used, the desired product **3a** could be obtained in good yield (66%) and diastereomeric ratio (5:1), with 57% ee (Table 1, entry 9). Although MeCN gave the best result in terms of enantioselectivity (60% ee), only a moderate yield was observed (Table 1, entry 13). In order to avoid possible side reactions in our system,[13] we decided to attempt the activation of substrates separately. For this purpose, 2-(4-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline (**1a**) and $Ir(ppy)_2(bpy)PF_6$ were dissolved in DCM (1 mL) and stirred for 10-16 hours under an O_2 atmosphere, with the reaction mixture being irradiated by a 11 W fluorescent bulb light. We were pleased to see that the iminium ion intermediate was formed and **1a** was consumed. The DCM was evaporated at 0 °C and a DCM (1 mL) solution of **2a** and Cat-**3** was dropwise injected into the reaction mixture under argon. The resulting reaction mixture was removed from the light source and stirred for 36 hours. The desired product **3a** was isolated and, although the yield was slightly lower compared to the one-pot reaction (60 vs. 66%), a better enantioselectivity and diastereoselectivity were obtained (77% ee, and 9:1 dr, Table 1, entry 15). These results indicated that the iminium ion intermediate was formed and stabilized in the reaction mixture and could further be used as active species without purification.[14]

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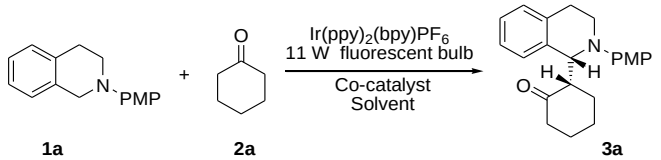
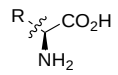
Table 1. Optimization of the reaction conditions.[a]



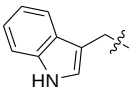
1a **2a** **3a**



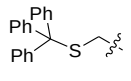
Co-catalyst

Cat-**1**: R = Me
Cat-**2**: R = OH
Cat-**3**: R = Ph
Cat-**4**: R = Bn
Cat-**5**: R = *i*Pr
Cat-**6**: R = *i*Bu

R:



Cat-**7**



Cat-**8**

Entry	Co-cat.	Solvent	Temp. (°C)	Yield (%)[b]	ee (%)[c]	dr[d]
1	Cat-**1**	EtOH	rt	42	25	1:1
2	Cat-**2**	EtOH	rt	39	43	1:1
3	Cat-**3**	EtOH	rt	49	47	4:1
4	Cat-**4**	EtOH	rt	52	33	3:1
5	Cat-**5**	EtOH	rt	45	46	3:1
6	Cat-**6**	EtOH	rt	48	41	3:1
7	Cat-**7**	EtOH	rt	45	25	2.5:1
8	Cat-**8**	EtOH	rt	30	17	1:1
9	Cat-**3**	DCM	rt	66	30	5:1
10	Cat-**3**	DMSO	rt	42	20	2.5:1
11	Cat-**3**	THF	rt	46	28	1.5:1
12	Cat-**3**	Toluene	rt	20	6	3:1
13	Cat-**3**	MeCN	rt	52	60	3:1
14	Cat-**3**	ethyl acetate	rt	45	26	2:1
15[e]	Cat-**3**	DCM/DCM	rt	60	77	9:1
16[e]	Cat-**3**	DCM/toluene	rt	58	82	9:1
17[e,f]	Cat-**3**	DCM/toluene	rt	47	89	11:1
18[e,f]	Cat-**3**	DCM/toluene	0	36	60	6:1
19[e,f]	Cat-**3**	DCM/toluene	15	51	92	11:1
20[e,f]	Cat-**3**	DCM/toluene	35	54	82	8:1

[a] Reaction conditions: **1a** (0.1 mmol), $Ir(ppy)_2(bpy)PF_6$ (1 mol%), cyclohexanone (**2a**, 0.3 mmol), Co-cat. (20 mol%) and DCM (1 mL) were stirred for about 48 h under an air atmosphere and irradiation with an 11 W fluorescent bulb light. [b] Yield after purification by column chromatography. [c] The enantiomeric excess was determined by HPLC on commercial chiral columns. [d] The diastereomeric ratio was determined by ^{1}H-NMR spectroscopy. [e] A stepwise procedure was used in which **1a** and $Ir(ppy)_2(bpy)PF_6$ were dissolved in DCM (1 mL) and stirred under an oxygen atmosphere for 10-16 h under irradiation with visible light; upon consumption of the starting material DCM was evaporated at 0 °C and 1 mL of solvent solution of Cat-**3** and **2a** was injected into the mixture under argon. The resulting reaction mixture was stirred for 24-48 h. [f] 0.05 M concentration: 0.05 mmol scale in 1 mL solvent.

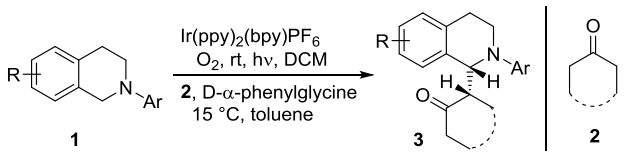
Next, different solvents such as toluene, DMF, THF, EtOH, 1,1,2-trichloroethane, and 1,1,2,2-tetrachloroethane were evaluated for the second step, with toluene providing **3a** in 58% yield, 82% ee and 9:1 dr (Table 1, entry 16). The other mentioned solvents failed to give the desired product **3a** (see Supporting information for details). In view of the amino acid co-catalyst not having a good solubility in toluene, we suspected that a decrease in the concentration may give rise to an improvement in the yield, enantio- and diastereoselectivity. When the reaction scale was reduced from 0.1 to 0.05 mmol in a 0.05 M solution, **3a** was obtained in 47% yield, 89% ee, and 11:1 dr (Table 1, entry 17).

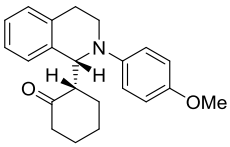
Finally, different temperatures for the second step were tested and the results evidenced that the reaction was quite sensitive to temperature. At -20 °C, the desired product **3a** was obtained in 37% yield and 40% ee, whereas at 0 °C **3a** was isolated in 41% yield and 60% ee. It is likely that the low solubility of D-*α*-phenylglycine Cat-**3** in toluene at low temperatures reduces the catalyst loading in the reaction mixture leading to a lower yield and ee. Increasing the temperature to 35 °C and 60 °C increased the yield to 56% and 59% respectively, but lowered the ee to 82% and 54%. Pleasingly, when the second step of the reaction was performed at 15 °C, the desired product **3a** was obtained in 51% yield with 92% ee and 11:1 dr (Table 1, entries 18-20, see Supporting information for details).

With the optimal conditions identified, the scope of this transformation was next evaluated. First, the versatility of the tetrahydroisoquinoline derived tertiary amines was examined by using a series of tetrahydroisoquinolines bearing different substituents on the *N*-aryl group. Both electron-withdrawing and electron-donating groups in the *para*- position were investigated. All were compatible with the developed procedure giving the corresponding products in good yields and high enantioselectivities. Notably, electron-withdrawing groups gave better enantioselectivities (92%, 94%, 88% ee for fluoro-, chloro-, bromo- respectively) compared to electron-donating groups (84%, 87%, 85% ee for methyl-, methoxyl-, and ethyl- respectively), however electron-donating groups seemed to give a better diastereoselectivity. In addition to testing the electronic properties of the substrates, the effect of the position of the substituent on the *N*-aryl group was also investigated and the results showed that it has a significant influence on the yield and diastereoselectivity of the product. For example, the *meta*-substituted methoxy derivative provided the product **3h** with higher yield (64%) and lower diastereoselectivity (4:1) compared to product **3a** of *p*-methoxy substituted derivative. Moreover, different aromatic groups as protecting group on the substrate were evaluated. 2-(Naphthalen-2-yl)-1,2,3,4-tetrahydroisoquinoline was synthesized and subjected to the reaction conditions and gave the desired product **3i** with good enantioselectivity and excellent diastereoselectivity (83% ee, 9:1 dr). When substituents were placed on the tetrahydroisoquinoline ring, the corresponding product **3j** was obtained in good yield (58%), with high enantio- and diastereoselectivity (89% ee, 7:1 dr).

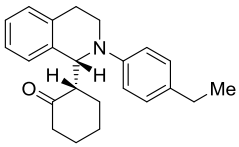
Different cyclic ketones such as cyclopentanone and dihydro-2*H*-pyran-4(3*H*)-one were employed in the reaction and gave the desired products **3k** and **3l** in satisfying yields, with moderate enantioselectivities (60% and 56% ee respectively). Cyclopentanone gave the desired product **3k** as single diastereomer (>20:1 dr) although the enantioselectivity was lower compared to cyclohexanone.

Table 2. Scope of the Enantioselective *α*-Functionalization of THIQs with Cyclic Ketones.[a]

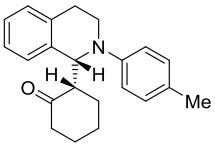




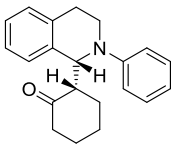
3a, 50% yield,[b] 92% ee, 11:1 dr [c]



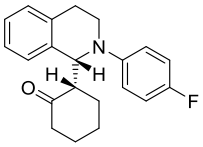
3b, 44% yield, 84% ee, 7:1 dr



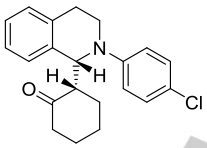
3c, 51% yield, 84% ee, 6:1 dr



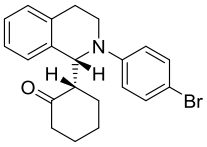
3d, 40% yield, 92% ee, 4:1 dr



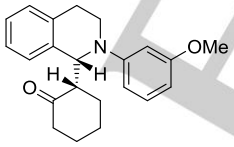
3e, 67% yield, 92% ee, 4:1 dr



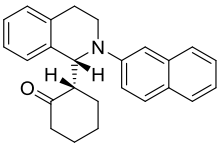
3f, 51% yield, 94% ee, 3:1 dr



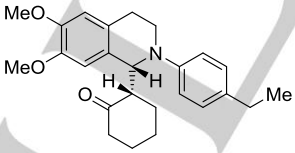
3g, 47% yield, 88% ee, 3:1 dr



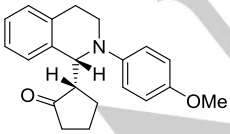
3h, 64% yield, 92% ee, 4:1 dr



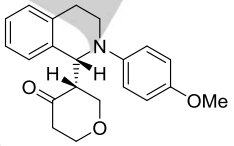
3i, 46% yield, 83% ee, 9:1 dr



3j, 58% yield, 88% ee, 7:1 dr



3k, 67% yield, 60% ee, >20:1 dr



3l, 37% yield, 56% ee, 5:1 dr

[a] Reaction conditions: **1** (0.05 mmol), $Ir(ppy)_2(bpy)PF_6$ (1 mol%) and DCM (1 mL) were stirred under oxygen; cyclic ketone **2** (0.15 mmol) and Cat. **3** (0.01 mmol) in toluene were added. [b] Yield after purification by column chromatography. [c] The enantiomeric excess was determined by HPLC on commercial chiral columns. The diastereomeric ratio was determined by ^{1}H-NMR spectroscopy when the minor diastereomer was observed in the ^{1}H-NMR spectrum; otherwise it is reported as >20:1.

The absolute configuration of product **3g** was assigned as *(R,S)* based on X-ray single-crystal structure analysis and the absolute configuration of the other products obtained in the reaction was assigned as *(R,S)* by correlation with **3g** (Figure 1).

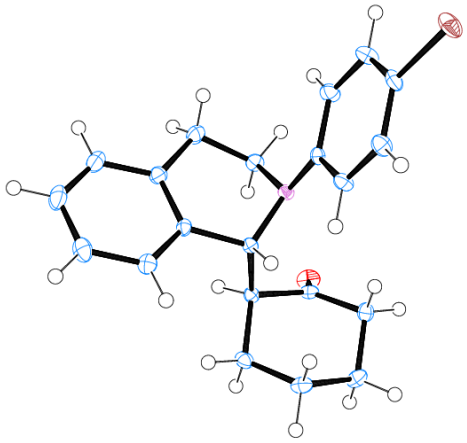


Figure 1. X-ray crystal structure analysis of **3g**.

In summary, we have developed a combined catalytic system for the highly enantio- and diastereoselective *α*-alkylation of tetrahydroisoquinolines. In the present dual catalysis protocol ketones are activated by a chiral primary amine catalyst and tetrahydroisoquinolines are activated by a visible-light photoredox catalyst. The desired *α*-alkylation products were obtained in good yields, with high enantio- and diastereoselectivity. Studies on further challenging asymmetric reactions combining organo- and photoredox catalysis are currently underway in our laboratories.

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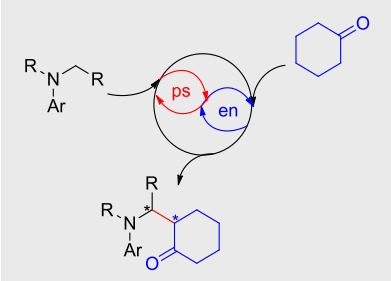
A combined photoredox/ organocatalytic system for the asymmetric *α*-alkylation of THIQs has been developed. A chiral organocatalyst enables a high level of enantio- and diastereocontrol for the oxidative coupling reaction of THIQs with simple cyclic ketones.



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Page No. – Page No.
Asymmetric Organocatalysis and Photoredox Catalysis for the α-Functionalization of Tetrahydroisoquinolines

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