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Synthesis of Supramolecular Iridium Catalysts and Their Use in Enantioselective Visible-Light-Induced Reactions

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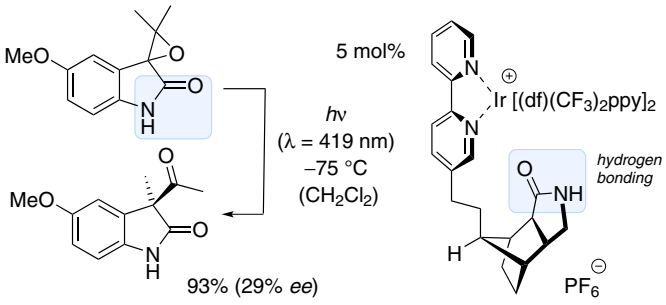

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Abstract Iridium complexes were prepared which are covalently linked via a bipyridine ligand to a chiral octahydro-1*H*-4,7-methanoisoindol-1-one skeleton. The skeleton allows for two-point hydrogen bonding to prochiral lactams, which can be processed in iridium-catalyzed photochemical reactions. Attempts to use the iridium complexes in reactions, which typically involve photoinduced electron transfer, failed to provide the desired enantioselectivity. If employed as triplet sensitizers the complexes showed an improved performance and moderate enantioselectivities (up to 29% ee) were achieved in a photochemical epoxide rearrangement.

Key words catalysis, enantioselectivity, iridium, photochemistry

In recent years, the catalysis of photochemical reactions by ruthenium and iridium complexes has received enormous attention from synthetic organic chemists.[1,2] A major benefit of their use rests on the fact that they allow reactions to be performed with visible light, which had previously required UV irradiation. In addition, the low catalyst loading and the robustness of the catalysts make ruthenium and iridium complexes attractive for large-scale applications. Although photoinduced electron transfer (PET) has so far been the most frequently invoked mode of action for these catalysts (photoredox catalysis), recent work has established that their relatively high triplet energy also allows for catalysis by triplet energy transfer (sensitization).[3]

In many photochemical reactions, stereogenic centers are created. In any instance, in which a prochiral substrate is converted into a chiral product, it is desirable to control the absolute configuration of the product by a chiral catalyst. In the past, a photoredox catalyst had been mostly combined with a second chiral catalyst to achieve enantioselectivity.[4] Recently, Meggers and co-workers showed that an iridium complex with a stereogenic metal center can serve both purposes, that is, it enabled a photoredox process and provided high enantioface differentation.[5,6]

In our group, we have been working on chiral supramolecular catalysts,[7] in which the metal center is spatially separated from a chiral entity which in turns allows for coordination of the substrate by hydrogen bonding (structure **A**, Figure 1).[8] The concept requires a chiral ligand that binds to the metal and simultaneously features a lactam unit to facilitate hydrogen bonding. Alkyne **1a**[9] serves as useful starting material to construct these ligands because the alkyne part can be readily coupled to compounds, which in turn enable metal coordination. Given our interest in the enantioselective catalysis of photochemical reactions,[10] we have recently commenced to prepare supramolecular iridium catalysts from **1a**, which could be potentially used for enantioselective photochemical reactions. Our preliminary results are disclosed in this communication.

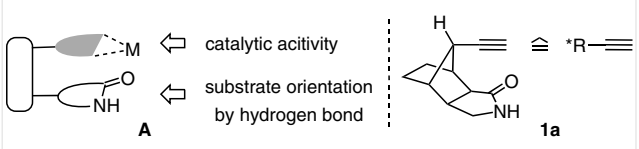
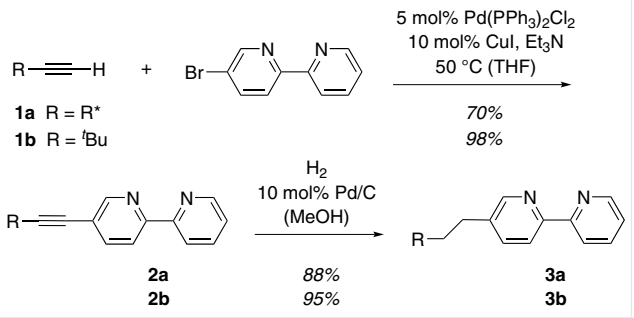


Figure 1 Concept of enantioselective supramolecular catalysts of type **A** (M = metal) and structure of chiral ligand precursor **1a** with an octahydro-1*H*-4,7-methanoisoindol-1-one skeleton (R*)

Since many photoactive iridium complexes exhibit at least one 2,2′-bipyridine ligand, it was attempted to link alkyne **1a** to 5-bromo-2,2′-bipyridine (Br-bpy)[11] by Sonogashira cross-coupling.[12–14] The reactions were performed in parallel with *tert*-butylacetylene (**1b**), the products of which were meant to mimic the scalar properties of the chiral ligands (Scheme 1). Cross-coupling reactions proceeded smoothly and delivered the desired alkynylated bi-

pyridines **2** in high yields. The triple bond could be readily reduced to the respective single bond by hydrogenation delivering bipyridines **3**. In product **3a**, the bipyridine is linked to the octahydro-1*H*-4,7-methanoisoindol-1-one fragment via an ethano bridge.



Scheme 1 Synthesis of bipyridine ligands **2** and **3** from alkynes **1** and 5-bromo-2,2′-bipyridine (Br-bpy)

Regarding the nature of the iridium catalyst, it seemed best to prepare a catalyst, which could be simultaneously used for photoredox reactions and for sensitized transformations. In order to mimic the common catalyst [4,4′-bis(*tert*-butyl)-2,2′-bipyridine]bis{3,5-difluoro-2-[5-(trifluoromethyl)-2-pyridinyl]phenyl} iridium(III) hexafluorophosphate[15] it was attempted to prepare related catalysts, in which the 4,4′-bis(*tert*-butyl)-2,2′-bipyridine unit was replaced by bipyridines **2** or **3**. Introduction of an iridium metal with two 3,5-difluoro-2-[5-(trifluoromethyl)-2-pyridinyl]phenyl [(df)(CF_3)$_2$ppy] ligands was accomplished by heating bipyridines **2** or **3** with complex {Ir[(df)(CF_3)$_2$ppy]$_2$Cl}$_2$[15] in ethylene glycol at 150 °C.[16] Anion exchange was subsequently performed with an aqueous NH_4PF_6 solution and delivered the metal complexes **4** and **5** in the yields given in Figure 2. Since the iridium atom in the complexes is stereogenic, compounds **4a** and **5a** were obtained as mixtures of inseparable diastereoisomers (diastereomeric ratio dr = 50:50). The chirality of the iridium center should not influence the hydrogen bonding event at the chiral lactam entity which is decisive for the enantioface differentiation. It was therefore not attempted to separate the diastereoisomers nor to resolve the antipodes of racemic complexes **4b** and **5b**.

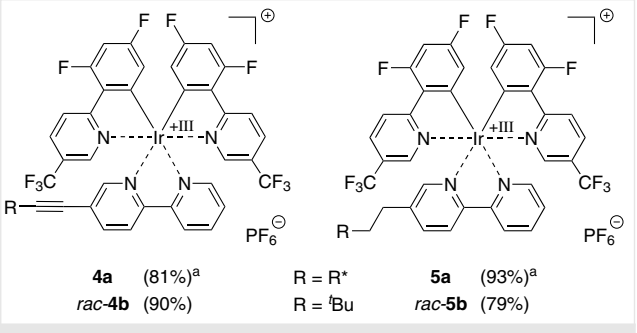
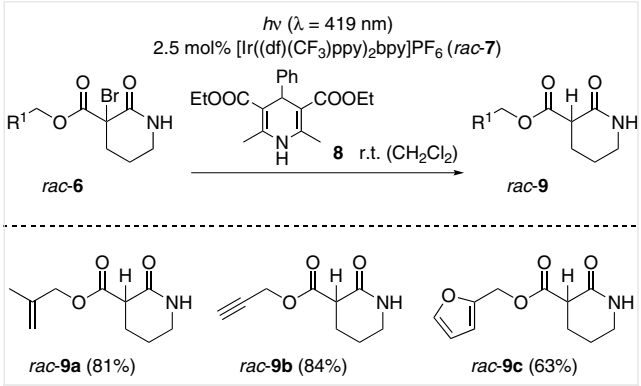


Figure 2 Structure of iridium catalysts **4a**, *rac*-**4b**, **5a**, and *rac*-**5b**.
[a] Due to the stereogenic iridium atom, complexes **4a** and **5a** were obtained as a 50:50 mixture of diastereoisomers

Conceptually, it was envisaged that the iridium catalyst would, upon excitation and oxidative quenching, generate an iridium(II) species which would act as a reductant. Prochiral halides seemed therefore suited as test substrates, which would generate a radical upon reduction and carbon–halogen bond cleavage.[17] Since we expected an intermolecular reduction of the prochiral radical center to occur slowly, we searched for substrates which would rather undergo a fast intramolecular C–C bond formation. Indeed, previous work had revealed that two-point hydrogen bonding generates kinetically labile complexes with other lactams the lifetime of which is in the range of 10–100 ns. Bromides *rac*-**6** were readily accessible from *N*-*tert*-butoxycarbonyl(Boc)-protected piperidinone[18] by a sequence of acylation,[19] deprotection, and α-bromination (see Supporting Information).[20] In the presence of iridium complex *rac*-**7** and Hantzsch ester **8**, photochemical reactions revealed, however, that neither one of the substrates underwent cyclization. Hydrodebromination was instead observed, and products **9** were isolated in high yields. Experiments with chiral iridium complexes confirmed our suspicion that the hydrodebromination reaction was not enantioselective, and products related to *rac*-**9** were all found to be racemic (Scheme 2).

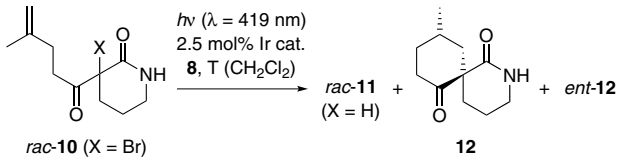


Scheme 2 Attempted iridium-catalyzed cyclization reactions of substrates *rac*-**6** led exclusively to debrominated products *rac*-**9**

Contrary to substrates **6**, the alkenoyl-substituted 3-bromopiperidone *rac*-**10** was found to be susceptible to a cyclization reaction. The reaction delivered product **12** and its enantiomer *ent*-**12** as single diastereoisomers and it was studied whether the cyclization could be rendered enantioselective upon catalysis by complexes **4a** and **5a** (Table 1). Iridium catalyst **4a** showed essentially no enantioselectivity at ambient temperature (Table 1, entry 1). The reaction temperature was lowered to favor hydrogen bonding (Table 1, entries 2, 3). Disappointingly, cyclization became disfavored and the debrominated product *rac*-**11** was the only

isolable material. It was tested, whether the iridium catalysis was required, which proved to be the case (Table 1, entry 4).

Table 1 Light-Induced Debromination and Cyclization of Alkenoyl-Substituted 3-Bromopiperidone *rac*-**10** Catalyzed by Chiral Iridium Complexes **4a** and **5a**



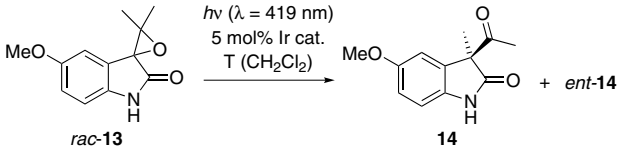
Entry	Ir cat.	Temp (°C)	*rac*-**11** (%)[a]	**12**/*ent*-**12** (%)[a]	ee (%)[b]
1	**4a**	30	–[c]	26	2
2	**4a**	0	31	–[c]	–
3	**4a**	–75	41	–[c]	–
4	–	30	–[c]	–[c]	–
5	**5a**	30	–[c]	42	<2
6	**5a**	0	24	7	9
7	**5a**	–25	48	–[c]	–
8	**5a**	–75	51	–[c]	–

[a] Yield of isolated products after chromatographic purification.
[b] The enantiomeric excess was calculated from the ratio of enantiomers (**12**/*ent*-**12**) as determined by chiral HPLC analysis.
[c] No significant amounts of the respective products were isolated.

Catalyst **5a** showed an improved performance compared to **4a** and its use resulted in a moderate yield of products **12**/*ent*-**12** at ambient temperature (Table 1, entry 5). A temperature decrease, however, led again to a preferred hydrodebromination reaction (Table 1, entries 6–8). Minor amounts of cyclization product could be isolated if the reaction was run at 0 °C (Table 1, entry 5) and a minimal enantiomeric excess was detectable. Given the fact that supramolecular catalysts with an octahydro-1*H*-4,7-methanoisoindol-1-one binding site had previously shown high enantioselectivity in dichloromethane,[8,9] we wondered whether there might be intrinsically an issue with applying the concept of Figure 1 to photoredox catalysis. Indeed, it has been shown that several of these reactions do not proceed via closed catalytic cycles but rather as radical chain reactions.[21] In such a scenario, chiral catalysts such as **4a** and **5a** cannot exert any enantioface differentiation because the substrate does not have to be in proximity to the iridium center for electron transfer.

As mentioned in the introduction, iridium catalysts can also be employed for triplet-sensitized photochemical reactions. Based on observations by Zhang and co-workers,[22] we recently studied the reaction of spirooxindole epoxides such as *rac*-**13** (Table 2) in the presence of chiral triplet sensitizers.[23] The same substrate seemed also suitable for triplet sensitization by iridium catalysts. Indeed, catalyst *rac*-**7** was found to promote the desired rearrangement reaction upon irradiation at λ = 419 nm (Table 2, entry 1). Catalysts **4a** and *rac*-**4b** showed an inferior catalytic activity and the conversion remained low even after a reaction time of 21 hours at –75 °C (Table 2, entries 2, 3).

Table 2 Photochemical Rearrangement of Epoxide *rac*-**13** to 3-Acetylindolin-2-ones **14** and *ent*-**14** Catalyzed by Various Iridium Catalysts



Entry	Ir cat.	Temp (°C)	Time (h)[a]	**14**/*ent*-**14** (%)[b]	ee (%)[c]
1	*rac*-**7**	30	2	89	–
2	*rac*-**4b**	–75	21	21	–
3	**4a**	–75	21	21	19
4	*rac*-**5b**	–75	2.5	94	–
5	**5a**	–75	2.5	93	29
6	**5a**	30	2.5	88	23

[a] Reaction time at the indicated temperature.
[b] Yield of isolated products after chromatographic purification.
[c] The enantiomeric excess was calculated from the ratio of enantiomers (**14**/*ent*-**14**) as determined by chiral GLC analysis.

The lack of activity observed for catalysts **4** is likely associated with their lower triplet energy compared to *rac*-**7**, which in turn could be due to the alkynyl substituent at the bipyridine ligand. The respective catalysts **5** with an ethano group bridging the ligand to the hydrogen-bonding device turned out to be more efficient catalysts (Table 2, entries 4–6). Conversion was complete after 150 minutes and yields were high. With catalyst **5a**, the enantiomeric excess in favor of product **14** was determined as 29% ee at –75 °C and as 23% ee at 30 °C.[24]

The absolute configuration of the enantiomers **14** and *ent*-**14** was known from our previous work, which was performed with chiral xanthone catalyst **15** (Figure 3). With this catalyst, product *ent*-**14** was obtained in 88% yield and with 20% ee if the reaction was performed at λ = 366 nm and at –65 °C in a mixture of trifluorotoluene ($PhCF_3$) and *meta*-hexafluoroxylene.[23] The absolute configuration was in line with a presumed association of the oxindole at the lactam binding site of the catalyst and an intramolecular methyl attack from the *Re* face at the prostereogenic center at carbon atom C3 of biradical intermediate **16**. In analogy, the outcome of the reaction *rac*-**13** → **14** can be explained by intermediate complex **5a**·**16** in which the methyl group migrates from the more accessible *Si* face to the prostereogenic carbon atom C3.

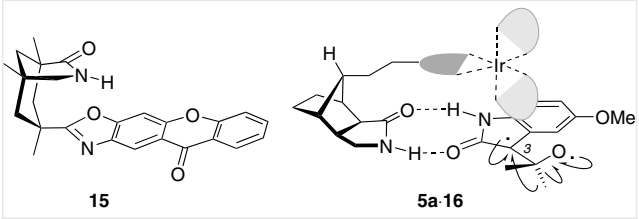


Figure 3 Structure of chiral xanthone catalyst **15** and proposed structure of the complex between catalyst **5a** and intermediate **16**

It is remarkable that the enantioselectivity induced by catalyst **5a** was higher than for **15**. In this regard it should be noted that the enantioselectivity does not only depend on the steric bias of the respective catalytic unit (xanthone, iridium complex) but is also influenced by the rate of dissociation of the intermediate from the complex.[10c,25] If complex dissociation is more rapid than the selectivity-determining step of the reaction, the enantiomeric excess will remain low. Indeed, it had been previously observed that catalyst **15** can exhibit a high degree of enantioface differentiation (>90% ee) if employed in appropriate reactions.[10b,,25,26] Its failure to deliver similar results in the epoxide rearrangement had been hypothesized to be due to the low reaction rate of the rearrangement. The same argument could hold for catalyst **5a** and it could well be possible that the catalyst shows an improved performance in other reactions. Work in this direction is ongoing.

In summary, chiral iridium complexes **4a** and **5a** were readily available by Sonogashira cross-coupling from known 8-ethynyl-octahydro-1*H*-4,7-methanoisoindol-1-one (**1a**). Reduction of the ethynyl bridge in **4a** delivered the ethano-bridged complex **5a**. Both complexes showed catalytic activity in several photoredox reactions performed with visible light (λ = 419 nm) but failed to induce a significant enantioselectivity. Complex **5a** was found to be an excellent catalyst to initiate the rearrangement of spirooxindole epoxide *rac*-**13** upon irradiation at λ = 419 nm. Although the induced enantioselectivity was moderate (up to 29% ee), the catalyst holds promise for further use in triplet-sensitized reactions.

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1561378.

Primary Data

for this article are available online at http://www.thieme-connect.com/products/ejournals/journal/10.1055/s-00000083 and can be cited using the following DOI: 10.4125/pd0075th.

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(24) **Experimental Procedure for the Enantioselective Rearrangement of *rac*-13**

To a solution of 10.0 mg (46.0 µmol, 1.0 equiv) 5-methoxy-3′,3′-dimethylspiro[indoline-3,2′-oxiran]-2-one (*rac*-**13**)[23] in 4.6 mL degassed CH_2Cl_2, 2.72 mg (2.3 µmmol, 0.05 equiv), Ir cat. **5a** was added, and the reaction mixture was irradiated for 2.5 h at –75 °C. After evaporation of the solvent, the crude product was purified by column chromatography (SiO_2, 2.5 × 4 cm, pentane–EtOAc = 2:1 → 1:1) to obtain 9.3 mg (93%, 29% ee) (*S*)-3-acetyl-5-methoxy-3-methylindolin-2-one (**14**)[23] as a colorless solid. ^{1}H NMR (360 MHz, $CDCl_3$, 300 K): δ = 7.79 (br s, 1 H, NH), 6.87 (d, ^3J = 8.4 Hz, 1 H, C7H), 6.82 (dd, ^3J = 8.4 Hz, ^4J = 2.5 Hz, 1 H, C6H), 6.73 (d, ^4J = 2.5 Hz, 1 H, C4H), 3.77 (s, 3 H, OCH_3), 2.05 (s, 3 H, $COCH_3$), 1.59 (s, 3 H, CH_3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 300 K): δ = 200.9 (s, $COCH_3$), 177.6 (s, C2), 156.4 (s, C5), 134.0 (s, C7a), 131.4 (s, C3a), 114.2 (d, C6), 110.7 (d, C7), 110.6 (d, C4), 62.9 (s, C3), 55.9 (q, OCH_3), 26.2 (q, $COCH_3$), 19.1 (q, CH_3) ppm.

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