Photochemical type II reaction of atropchiral benzoylformamides to point chiral oxazolidin-4-ones. Axial chiral memory leading to enantiomeric resolution of photoproducts†

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Atropisomeric benzoylformamides 1 undergo Type II reaction leading to *cis*-2 and *trans*-2 oxazolidin-4-one photoproducts. The N–C(Aryl) chiral axis is maintained during the course of the phototransformation in spite the reaction proceeding through a near planar intermediate(s). As the rotational barrier of the N–C(Aryl) chiral axis in the *cis*-2 and *trans*-2 photoproducts is lowered when compared with the reactant 1, the isolated optically pure *trans*-2 isomer is converted to the *ent-cis*-2 isomer without affecting the C-5 stereogenic center, resulting in resolution of the *cis*-2 enantiomers.

Asymmetric induction during photochemical transformations in solution has presented formidable challenges to chemists.[1–7] Due to the short lifetime of the excited state(s)/intermediate(s) involved during phototransformations, constraining molecular motions using confined environments have shown promise for achieving high stereoselectivity.[8,9] However, achieving high stereoselectivity in solution leading to enantiomerically enriched photoproducts by a generalized methodology is yet to be established.[6,10] In this regard we have been exploring the use of axially chiral compounds to achieve high stereoselectivity in the photoproducts during light induced transformations in solution.[11,12] In this communication, we report the Type II reaction of axially chiral benzoylformamides **1** leading to point chiral oxazolidin-4-ones **2** in which the N–C(Aryl) chiral axis is maintained during the course of the photochemical transformation. The low rotational barrier of the N–C(Aryl) chiral axis in the photoproducts **2** was utilized to resolve photoproduct enantiomers with high optical purity (>95% ee) and in good yields (80% isolated yield), in spite of the reaction proceeding with very low diastereoselectivity (*cis*/*trans* selectivity).

We recently reported[11,12] that α-oxoamides with *o-tert*-butyl-substituent on the N-phenyl ring are axially chiral due to the restricted N–C(Aryl) bond rotation,[13–16] and successfully employed them for Norrish/Yang cyclization leading to β-lactam as the photoproduct with very high enantiomeric excess in $CHCl_3$.

This provided us with an opportunity to investigate the Type II reaction involving atropisomeric benzoylformamides **1a–d** leading to point chiral oxazolidin-4-one **2a–d**. Previous investigations[17–21] involving achiral benzoylformamides have established the formation of oxazolidin-4-ones as photoproducts *via* a planar zwitterionic intermediate (**Z_2**) or *via* a diradical intermediate (**D**) depending on the substituents on the amide nitrogen and the reaction conditions.[17–21]

We synthesized atropchiral benzoylformamide derivatives **1a–b** with N-(2-propyl), **1c** with N-(cyclopentyl) and **1d** with N-(cyclohexyl) substituents. The individual *P* and *M* isomers were easily isolable on a chiral stationary phase and were characterized by NMR spectroscopy, CD spectroscopy, optical rotation, HRMS and single crystal XRD.‡[22] These axially chiraloptically pure **1a–d** were stable at room temperature and can be stored for months without enantiomerization. Even at 50 °C, the rate of enantiomerization was slow, and hence the $\Delta G^{\ddagger}$ of enantiomerization ($\Delta G^{\ddagger}_{enant}$) of optically pure **1** was performed at 75 °C. For example, in the case of **1b**, $\Delta G^{\ddagger}_{enant}$ was found to be ~30.8 kcal. mol^{-1} (k_{enant}: 3.3 × 10^{-7} s^{-1}; $t_{1/2}$: ~12 days at 75 °C).[22]

Photoirradiation of optically pure atropisomers (*P* or *M* isomers) of **1a–d** (Scheme 1) was performed using a 450 W medium pressure Hg lamp with Pyrex cutoff and a cooling jacket under constant flow of nitrogen at various temperatures (5, 25 and 50 °C). The reaction progress was followed by ^{1}H NMR spectroscopy and was found to be clean and efficient with >90% conversion and an ~80% isolated yield **2a–d**. The photoproduct **2** was purified by chromatography and characterized by NMR spectroscopy, CD spectroscopy, optical rotation and single crystal XRD.[22] The oxazolidin-4-one **2** photoproduct was found to be a mixture of *cis*-**2** and *trans*-**2** isomers based on the orientation of the *o-tert*-butyl group with respect to the phenyl substituent at the C-5 chiral center. ^{1}H NMR spectroscopy analysis of photoproducts showed a *cis*-**2**:*trans*-**2** ratio (diastereomeric ratio, *d.r.*) of ~66 : 34 irrespective of the reaction temperature (Table 1; entries 1–6). HPLC analysis of the individual *cis*-**2** and *trans*-**2** photoproducts gave the ee values (enantiomeric excess) as listed in Table 1. The optical antipode of **1** gave *ent-cis*-**2** and *ent-trans*-**2** photoproduct (enantiomeric photoproducts), indicating that the system was well behaved. The absolute configuration at the C-5 stereogenic center was opposite in *cis*-**2** and *trans*-**2** photoproducts from a given optically pure axially chiral benzoylformamides **1**. The *cis*-**2** and *trans*-**2**

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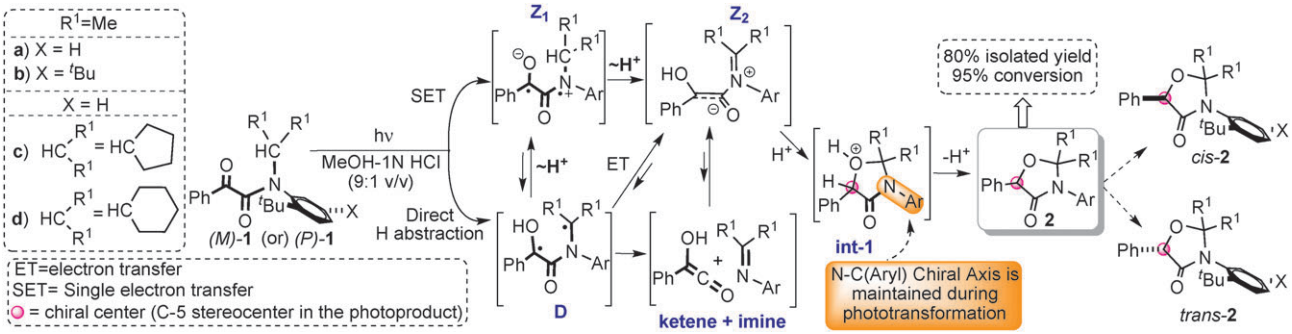

Scheme 1 Photochemical type II reaction axially chiral **1** in which the N–C(Aryl) chiral axis is maintained in the photoproduct **2**.

Table 1 Enantiomeric excess in the oxazolidin-4-one photoproduct **2**[a]

Entry	Compd	Time/h	T °C	% Conv	*cis*-**2**:*trans*-**2** (*d.r.*)	% ee (*trans*-**2**)	% ee (*cis*-**2**)
1	(+)**1a**	18	5	40	69 : 31	99 (B)	99 (A)
2		15	25	95	65 : 35	97 (B)	97 (A)
3		12	50	98	64 : 36	88 (B)	86 (A)
4	(−)**1a**	18	5	40	69 : 31	99 (A)	99 (B)
5		15	25	95	65 : 35	97 (A)	97 (B)
6		12	50	98	63 : 37	89 (A)	87 (B)
7	(+)**1b**	15	25	80	64 : 36	93 (A)	94 (A)
8	(−)**1b**	15	25	82	64 : 36	93 (B)	93 (B)
9	(+)**1c**	15	25	81	65 : 35	98 (B)	97 (A)
10	(−)**1c**	15	25	80	64 : 36	97 (A)	98 (B)
11	(+)**1d**	15	25	83	67 : 33	98 (B)	99 (A)
12	(−)**1d**	15	25	81	66 : 34	98 (A)	98 (B)

[a] Values are an average of 3 runs (±3% error). (+)-**1** and (−)-**1** represents the sign of optical rotation. *cis*-**2**:*trans*-**2** ratio and % conversion based on relative integration by ^{1}H NMR spectroscopy using succinimide as internal standard. Mass balance >95% (isolated yield ~80%). A and B refers to the first and second peak that elutes in the HPLC on a chiral stationary phase for a given pair of enantiomers.

isomers were separated by column chromatography or by preparative TLC. The presence of *gem*-alkyl substituents at the C-2 position in oxazolidin-4-one **2** hindered the N–C(Aryl) bond rotation at ambient conditions, but at elevated temperatures (75–120 °C depending on the *gem*-alkyl substituent) the N–C(Aryl) bond was found to rotate freely. It has been previously shown that the N–C(Aryl) bond rotates freely due to the reduced C–N–C bond angle in β-lactams.[11,12,23] This provided an opportunity to convert the enantiopure *trans*-**2** isomer to the corresponding *cis*-**2** isomer. For example, photoirradiation of **1d** resulted in an ee value of >97% at 25 °C in both the *cis*-**2d** and *trans*-**2d** diastereomers. The optically pure *cis*-**2d** and *trans*-**2d** photoproducts were isolated by column chromatography or by preparative TLC. The isolated *trans*-**2d** photoproduct was heated in *n*-octane/isopropanol (4 : 1 v/v) that resulted in an equilibrium ratio of 66 : 34 favoring the *ent-cis*-**2d** photoproduct. Thus we were able to resolve the *cis*-enantiomers without affecting the chirality at the C-5 stereogenic center (Fig. 1).

The mechanism[17–21] concerning Type II photoreaction of achiral benzoylformamides as described by Whitten and co-workers[19] occurred *via* a planar zwitterionic intermediate (**Z$_2$**; Ar = Phenyl) and involved a net hydrogen transfer to the photoexcited carbonyl group either by direct hydrogen abstraction or in a sequential two-step process *viz*. single electron transfer (SET) followed by proton transfer (Scheme 1). Benzoylformamides undergo Type II photoreaction even from the unreactive ππ* triplet excited state by the electron transfer pathway,[17–21] which is in contrast to aromatic ketones that undergo hydrogen abstraction efficiently from nπ* triplet state.[18,19,24] As shown in Scheme 1, the resultant intermediate could be a diradical **D** or a zwitterion **Z$_1$** depending on the reaction conditions[19] (substituent on the amide nitrogen, reaction medium *etc*.) that subsequently leads to the planar zwitterionic intermediate **Z$_2$** (*via* ketene-imine geminate pair if **D** is involved), which cyclizes to **2**.[17–21]

In the present case, based on the stereochemistry of *cis*-**2** and *trans*-**2** photoproducts,[22] the configuration of the chiral axis [(N–C(Aryl) bond] remains unchanged during the photoreaction. Photoirradiation of optically pure (*P* or *M* isomers)

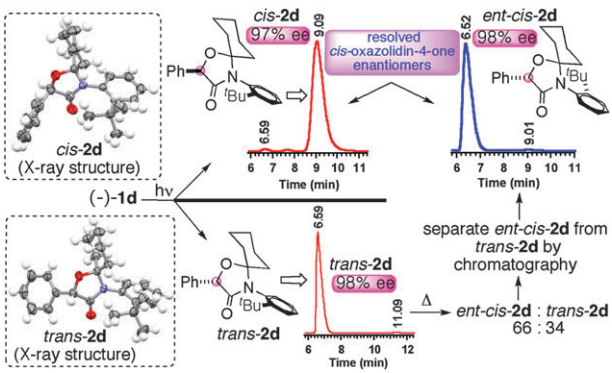

Fig. 1 Resolution of *cis*-**2d** enantiomers. The configuration represented is based on the relative orientation by single crystal XRD.

atropisomers of **1a–d** likely undergoes Type II reaction in a pathway as suggested by Whitten and co-workers[19] for achiral benzoylformamides. The presence of *ortho-tert*-butyl substituent is not expected to affect the type of intermediates proposed by Whitten and co-workers,[19] but is expected to affect the relative population of the reactive intermediates (ketene-imine pair could be converted to the zwitterionic intermediate $\mathbf{Z_2}$ by heterolytic N–C═O bond cleavage). Stereochemical analysis of the photoproducts (Fig. 1) indicates that the configuration of the chiral axis is maintained in the intermediate(s) during the course of the phototransformation. We believe that the relative rate of reaction from the excited-state/intermediates(s) leading to **2** is favored over the N–C(Aryl) bond rotation. Due to the reduced C–N–C bond angle in **2**, the rotational barrier of the N–C(Aryl) chiral axis in the photoproduct **2** is lowered when compared to the reactant **1**. This enables the conversion of the isolated optically pure *trans*-**2** isomer to the *ent-cis*-**2** isomer without affecting the C-5 stereogenic center resulting in enantiomeric resolution of *cis*-**2** oxazolidin-4-one photoproduct with high optical purity (ee values >98%).[22]

Our investigation on employing axially chiral benzoylformamides to chiral oxazolidin-4-one has opened up the opportunity to resolve enantiomers with high optical purity in good yields. The mechanistic analysis indicates that the N–C(Aryl) chiral axis is maintained during the phototransformation in solution. This provides organic chemists with a complementary methodology to resolve enantiomers with high optical purity.[1–4]

Notes and references

‡ X-ray structures of the reactants and the photoproducts are available from Cambridge Crystallographic Data Center. (CCDC deposition #759989 to 759993).

XRD Structure determination: Single crystal X-ray diffraction data sets were collected on a SIEMENS diffractometer with a 1 K CCD area detector (graphite-monochromated Mo-Kα radiation, crystals protected with Parathone-N oil). All structures, except *cis*-**2a**, were solved by direct methods and refined on F^2 using the SHELXL, after integration and absorption corrections with SAINT 6.45 A. Compound *cis*-**2a** was solved by direct method, but the integrations and absorption corrections were performed with SAINT 7.34 A and SADABS version 2007/4.

Crystal data for **1a** (colorless plate): $C_{21}H_{25}NO_2$, M = 323.42, Monoclinic, space group $P2_1/n$, a = 8.698(4) Å, b = 16.685(8) Å, c = 13.029(6) Å, β = 99.478 (9)°, V = 1864.9(15) Å^3, z = 4273 K, crystal size 0.78 × 0.72 × 0.10 mm, μ(Mo-Kα) = 0.073 mm^{-1}, 13 357 reflections measured, 3261 independent reflections (R_{int} = 0.0349). The final $R(I > 2\sigma(I))/R$(all data) were: R_1 [%] = 4.51/7.48 and wR_2 [%] = 13.77/15.68. The goodness of fit on F^2 was 1.030.

Crystal data for **1d** (colorless prism): $C_{24}H_{29}NO_2$, M = 363.48, Monoclinic, space group $P2_1/c$, a = 12.312(3) Å, b = 8.543(2) Å, c = 19.637(5) Å, β = 94.405 (4)°, V = 2059.4(8) Å^3, z = 4293 K, crystal size 0.66 × 0.40 × 0.20 mm, μ(Mo-Kα) = 0.074 mm^{-1}, 16 527 reflections measured, 4062 independent reflections (R_{int} = 0.0610). The final $R(I > 2\sigma(I))/R$(all data) were: R_1 [%] = 4.69/6.93 and wR_2 [%] = 12.51/14.29. The goodness of fit on F^2 was 1.034.

Crystal data for *cis*-**2a** (colorless chunk): $C_{21}H_{25}NO_2$, M = 323.42, Triclinic, space group $P\bar{1}$, a = 9.354(4) Å, b = 9.792(5) Å, c = 10.162(5) Å, α = 79.581 (9)°, β = 85.526 (10)° γ = 87.199 (10), V = 912.1(8) Å^3, z = 2, 273 K, crystal size 0.66 × 0.22 × 0.14 mm, μ(Mo-Kα) = 0.075 mm^{-1}, 7296 reflections measured, 3296 independent reflections (R_{int} = 0.0597). The final $R(I > 2\sigma(I))/R$(all data) were: R_1 [%] = 5.58/12.01 and wR_2 [%] = 14.01/17.63. The goodness of fit on F^2 was 0.938. Crystal data for *trans*-**2d** (colorless chunk): $C_{24}H_{29}NO_2$, M = 363.48, Monoclinic, space group $P2_1/n$, a = 12.223(8) Å, b = 10.426(6) Å, c = 16.072(10) Å, β = 93.259 (9)°, V = 2045(2) Å^3, z = 4293 K, crystal size 0.4 × 0.4 × 0.36 mm, μ(Mo-Kα) = 0.074 mm^{-1}, 13 837 reflections measured, 3657 independent reflections (R_{int} = 0.0555). The final $R(I > 2\sigma(I))/R$(all data) were: R_1 [%] = 4.64/6.22 and wR_2 [%] = 12.63/13.94. The goodness of fit on F^2 was 1.059.

Crystal data for *cis*-**2d** (colorless plate): $C_{24}H_{29}NO_2$, M = 363.48, Monoclinic, space group $P2_1/n$, a = 8.784(2) Å, b = 10.399(2) Å, c = 22.804(5) Å, β = 99.457 (3)°, V = 2054.6(7) Å^3, z = 4293 K, crystal size 0.56 × 0.50 × 0.15 mm, μ(Mo-Kα) = 0.074 mm^{-1}, 18 137 reflections measured, 4488 independent reflections (R_{int} = 0.0489). The final $R(I > 2\sigma(I))/R$(all data) were: R_1 [%] = 5.05/7.84 and wR_2 [%] = 13.86/16.20. The goodness of fit on F^2 was 1.069.

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