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Light-induced stereospecific intramolecular [2+2]-cycloaddition of atropisomeric 3,4-dihydro-2-pyridones†‡§

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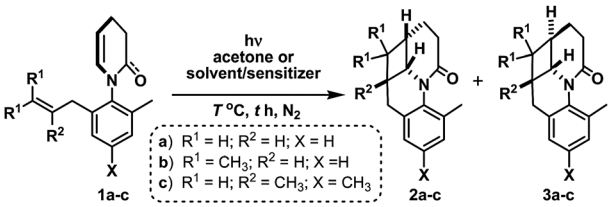
Atropisomeric 3,4-dihydro-2-pyridones undergo stereospecific [2+2]-photocycloaddition in solution with high stereoselectivity (ee > 98% and de > 96%) in the product. The chiral transfer during phototransformation was rationalized based on the stability/reactivity of the biradical.

The field of asymmetric organic photochemistry has been witnessing rapid development in recent years due to the prospect of synthesizing complex structural motifs with control of stereochemistry.[1] This progress is in part due to the understanding of the nature of the excited states and manipulation of their reactivity by channeling the excited state energy through molecular confinement by employing different organized supramolecular assemblies.[2] Organized supramolecular assemblies like crystals,[2c–e] zeolites,[2f] cyclodextrins[2g] and molecular recognition motifs[2h] have been employed with varying degrees of success to achieve high enantioselectivity during photochemical transformations. Developing a general strategy for achieving high stereoselectivity in solution during photoreactions to complement established asymmetric thermal transformations however still remains an elusive task.[1a] To address this problem, we have been working on a general methodology that employs nonbiaryl atropisomeric compounds that undergo stereospecific photoreaction in solution leading to high enantioselectivity in the photoproducts.[3] Using this strategy we have successfully achieved high enantioselectivity in the photoproduct during 6π-photocyclization of acrylanilides,[3a] Norrish–Yang reactions of α-oxoamides[3b,c] and photochemical 4π-ring closure of 2-pyridones.[3d] In our continuing efforts to extend this methodology, we now wish to report a new class of atropisomeric[4] 3,4-dihydro-2-pyridones **1a–c** that undergo efficient intramolecular [2+2]-photocycloaddition[5] under triplet sensitized irradiation conditions to access photoproduct(s) in good yields with excellent stereoretention (diastereomeric ratio > 98 : 2 and enantioselectivity > 98%).



Scheme 1 Intramolecular [2+2]-photocycloaddition of **1a–c**.

The [2+2]-photocycloaddition reactions have remained a valuable tool in organic synthesis to obtain various chiral building blocks,[5] due to the ease of accessing various natural products.[5e] This prompted us to investigate stereospecific intramolecular [2+2]-photocycloaddition of **1a–c** (Scheme 1), which we felt would expand the existing arsenal for organic synthesis to build chiral building blocks with quaternary chiral centers. Axially chiral **1a–c** were synthesized and characterized by NMR spectroscopy and mass spectrometry.[6] The axial chirality arising due to the restricted rotation of N–C (aryl) substituents led to *P* and *M* isomers that were easily separated by HPLC on a chiral stationary phase. The purity of the individual *P* and *M* isomers of **1** was established by optical rotation.[6]

In order to utilize atropisomeric compounds for stereospecific photochemical transformation, it is essential to ascertain the barrier for racemization *i.e.*, N–C (aryl) rotation barrier in **1a–c**.[7] Our kinetic study established that **1a–c** racemize slowly at room temperature indicating a high energy barrier for N–C (aryl) bond rotation. Due to slow racemization of optically pure **1a–c** at room temperature (no racemization observed after 2 months) racemization kinetics were performed at elevated temperatures in various solvents (Table 1). For example, in the case of **1b** at 75 °C, the activation barrier for racemization $\Delta G^{\ddagger}_{rac}$ in 2-propanol was found to be ~30.46 kcal mol^{-1} with a racemization rate constant (k_{rac}) of 5.4 × 10^{-7} s that corresponds to a half-life of racemization ($\tau_{1/2}$) of 15 days (Table 1, entry 4). These results indicate that newly synthesized atropisomeric **1a–c** have fairly high energy for racemization even at 75 °C.[3d]

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Table 1 Racemization[a] rate constant (k_{rac}), half-life ($\tau_{1/2}$) and activation free energy ($\Delta G^{\ddagger}_{rac}$) for optically pure **1a–c**

Entry	Compound	Solvent	T (°C)	k_{rac} (s^{-1})	$\tau_{1/2}$ (days)	$\Delta G^{\ddagger}_{rac}$ (kcal mol^{-1})
1	**1a**	Acetone	50	9.3×10^{-8}	86.6	29.35
2		IPA	75	8.2×10^{-7}	9.82	30.17
3	**1b**	Acetone	50	4.5×10^{-8}	177	29.81
4		IPA	75	5.4×10^{-7}	15	30.46
5	**1c**	Acetone	50	4.6×10^{-8}	176	29.81
6		IPA	75	7.8×10^{-7}	10.2	30.20

[a] Racemization values carry an error of ±5%. In MeOH at 50 °C, $\tau_{1/2}$ = 355 days for **1a** and no racemization was observed even after 60 days for **1b** and **1c**. Refer to ESI for experimental details.

Photoirradiation[6] of optically pure atropisomers (*P* and *M* isomers with ee values above 98%) was carried out at a given temperature (−30 °C for **1a–b** and 25 °C for **1c**) in dry acetone (acetone serving as both the solvent and a triplet sensitizer) and in methanol (with acetophenone or xanthone as a triplet sensitizer) using a 450 W medium pressure Hg lamp placed inside a water-cooled jacket with a Pyrex cutoff filter under constant flow of nitrogen.[6] The reaction progress was monitored by thin layer chromatography. After the consumption of reactant **1**, the solvent was evaporated and the residue was purified by chromatography to get pure photoproducts. The photoproducts were analyzed by NMR spectroscopy, HRMS, CD spectroscopy, optical rotation and single crystal XRD.[6,8] The relative orientation of the hydrogen atoms in the cyclobutane fused to the lactam ring was *cis* in photoproduct **2**, while it was *trans* in the case of photoproduct **3**. The diastereomeric ratio (dr) between photoproducts **2** and **3** was ascertained by ^{1}H-NMR spectroscopy of the crude photoreaction mixture. The enantiomeric relation in the photoproduct was established by CD spectroscopy and by its optical rotation values. Variable temperature ^{1}H-NMR studies on optically pure **2a** did not show any diastereomeric protons upon varying the temperature (−50 to 50 °C) indicating the lack of diastereomers in the photoproduct.[6] HPLC analyses after irradiation of **1** on a chiral stationary phase gave the ee values for the photoproduct (Table 2).

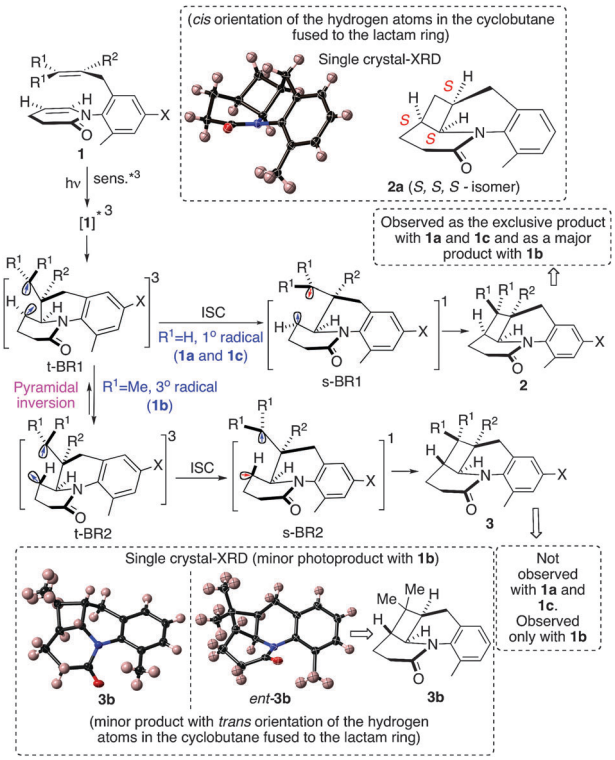
Inspection of Table 2 reveals a very high enantiomeric excess in the photoproduct (ee values of 98% or higher). In the case of **1a** and **1c**, photoproduct **2** was observed exclusively (dr > 98 : 2; Table 2, entries 1–6 and 13–18). On the other hand, in the case of **1b** both photoproducts **2** and **3** were observed with a dr of 2.8 : 1 for acetone sensitization (Table 2, entries 7 and 8) and a dr of 4.3 : 1 for acetophenone and xanthone sensitization (Table 2, entries 9–12). For example, triplet sensitized irradiation of (−)-**1a** gave (+)-(*S*,*S*,*S*)-**2a** as the photoproduct. Similarly, triplet sensitized irradiation of (+)-**1a** gave the optical antipode of the photoproduct (−)-(*R*,*R*,*R*)-**2a** suggesting that the system was well behaved.[6] To ascertain the reaction pathway and to gain insight into the reaction multiplicity, we performed steady state emission and lifetime measurements[6] for compounds **1a–c** in both polar (ethanol) and non-polar (methylcyclohexane) solvents. All the three compounds showed similar emission and lifetime profiles. For example, in ethanol at room temperature, a structureless fluorescence emission with a λ_{max} centered around 383 nm was observed. Phosphorescence emission in ethanol glass at 77 K for **1** revealed a slightly structured emission with a lifetime of ∼0.49 s. The triplet energy (E_T) of **1a–c** was established to be around ∼73 kcal mol^{-1} above the ground state. The E_T of **1** provided insight into the photochemical reactivity where the conversion to the photoproduct for a given irradiation time was dependent on the type of sensitizer that was employed (Table 2). For example, in the case of **1a** for 3 h irradiation, the conversion with acetone and xanthone as triplet sensitizers was 70% and 76%, respectively. On the other hand, the conversion with acetophenone as a triplet sensitizer was 29%.

Based on the photophysical data and photochemical reaction we believe that the [2+2]-photocycloaddition of **1** proceeds through the excited triplet state of **1** ($[\mathbf{1}]^{*3}$) upon sensitization.

Table 2 Stereospecific [2+2]-photocycloaddition of 3,4-dihydro-2-pyridones **1a–c**[a]

Entry	Solvent	t (h)	Triplet sensitizer	Substrates	T^b (°C)	% ee[c] (**2**)	dr[d] (**2 : 3**)	% Convn[e]	% MB[e]
1	Acetone	3	Acetone	(−)-**1a**	−30	>98% (*S*,*S*,*S*)	>98 : 2	70	96
2				(+)-**1a**	−30	>98% (*R*,*R*,*R*)	>98 : 2		
3	MeOH	3	Xanthone[f]	(−)-**1a**	−30	>98% (*S*,*S*,*S*)	>98 : 2	76	89
4				(+)-**1a**	−30	>98% (*R*,*R*,*R*)	>98 : 2		
5	MeOH	3	Acetophenone[f]	(−)-**1a**	−30	>98% (*S*,*S*,*S*)	>98 : 2	29	92
6				(+)-**1a**	−30	>98% (*R*,*R*,*R*)	>98 : 2		
7	Acetone	24	Acetone	(−)-**1b**	−30	>98% (A)[g]	2.8 : 1	39	79
8				(+)-**1b**	−30	>98% (B)[g]	2.8 : 1		
9	MeOH	3	Xanthone[f]	(−)-**1b**	−30	>98% (A)[g]	4.3 : 1	21	82
10				(+)-**1b**	−30	>98% (B)[g]	4.3 : 1		
11	MeOH	12	Acetophenone[f]	(−)-**1b**	−30	>98% (A)[g]	4.3 : 1	20	87
12				(+)-**1b**	−30	>98% (B)[g]	4.3 : 1		
13	Acetone	2.5	Acetone	(−)-**1c**	25	>98% (*S*,*S*,*S*)	>98 : 2	90	77
14				(+)-**1c**	25	>98% (*R*,*R*,*R*)	>98 : 2		
15	MeOH	2.5	Xanthone[f]	(−)-**1c**	25	>98% (*S*,*S*,*S*)	>98 : 2	92	84
16				(+)-**1c**	25	>98% (*R*,*R*,*R*)	>98 : 2		
17	MeOH	12	Acetophenone[f]	(−)-**1c**	25	>98% (*S*,*S*,*S*)	>98 : 2	33	86
18				(+)-**1c**	25	>98% (*R*,*R*,*R*)	>98 : 2		

[a] (+) and (−) represent the sign of optical rotation (MeOH at 25 °C). Reported values are an average of 3 runs with ±3% error. [b] Reaction temperature was chosen to prevent unwanted side products. For **1a** and **1c** an uncharacterized product was observed with 8–10% yield. No side products were observed with **1b**. [c] A and B refer to the elution order for a given pair of enantiomers in the HPLC. The ee values were determined by HPLC on a chiral stationary phase. Absolute configuration was determined by single crystal XRD using Flack parameters. [d] The diastereomeric ratio (dr) was determined by ^{1}H-NMR spectroscopy. [e] Conversion (% Convn) and mass balance (% MB) were calculated by ^{1}H-NMR spectroscopy with Ph_3CH as an internal standard. [f] 30 mol% of the sensitizer was used. [g] Identical ee values were observed for both photoproducts **2b** and **3b**.



Scheme 2 Mechanistic rationale for stereospecific [2+2]-photocycloaddition of **1a–c**.

This conjecture is quite reasonable as the triplet energy transfer to **1** from acetone ($E_T \sim 79$ kcal mol^{-1}; serving as both a solvent and a sensitizer), xanthone ($E_T \sim 74$ kcal mol^{-1}) and acetophenone ($E_T \sim 73$ kcal mol^{-1}) is energetically feasible. We also ruled out the reaction proceeding *via* the singlet manifold as direct irradiation (in the absence of the sensitizer) in methanol, acetonitrile, chloroform or toluene did not produce the photoproduct **2** or **3** with complete recovery of **1**. Based on the ee values observed for the photoproduct, there is complete transfer of axial chirality from the reactant to point chirality in the photoproduct. A tentative mechanism for transfer of chirality from **1** to the photoproducts is given in Scheme 2. We believe that upon energy transfer from the triplet sensitizer to the substrate **1**, triplet excited **1** ([**1**]*^{3}) is produced which cyclizes to form the triplet 1,4-biradical t-BR1. This triplet 1,4-biradical t-BR1 can be a primary radical at the carbon bearing the R^1 substituent as in the case of **1a** and **1c** or a tertiary radical as in the case of **1b**. Based on the observed selectivity in which there is complete diastereo- and enantio-control, we believe that t-BR1 produced in the case of **1a** and **1c** with a primary radical center at the carbon bearing the R^1 substituent rapidly intersystem crosses to the corresponding singlet 1,4-biradical s-BR1 that subsequently cyclizes to the photoproduct **2**. On the other hand, in the case of **1b** there is leakage in diastereocontrol with high enantioselectivity in the photoproduct (**2b** and **3b**; Table 2, entries 7–12). We believe that t-BR1 produced in the case of **1b** lives much longer (due to a tertiary radical center at the carbon bearing the R^1 substituent), which allows for pyramidal inversion at the β-carbon of the lactam ring leading to t-BR2. The two biradicals, *viz.*, t-BR1 and t-BR2, intersystem cross to the corresponding singlet biradicals s-BR1 and s-BR2 that subsequently cyclize to form diastereomeric photoproducts **2** and **3** respectively. The relative stability of the triplet and singlet biradicals and the ease of intersystem crossing will dictate the diastereomeric ratio for the photoproduct. As we observed high enantioselectivity for the photoproduct, the axial chiral transfer likely occurred in the cyclization step that produced the triplet diradical (*e.g.* t-BR1 for **1a**) with defined stereochemistry at the α-carbon (to the amide nitrogen) and the carbon that bears the R^2 substituent. This also provided us an opportunity to build quaternary chiral centers (*e.g.* substrate **1c** with R^2 alkyl substituent) with high optical purity.

Thus our study has uncovered axial to point chirality transfer in [2+2]-photocycloaddition involving atropisomeric 3,4-dihydro-2-pyridones. The individual atropisomers are highly stable at room temperature with no noticeable racemization even after 2 months. The photoreaction occurs likely *via* triplet sensitization with excellent ee values in the photoproducts. The diastereocontrol in the reaction is dictated by the allyl substituent(s) on the phenyl ring due to the stability of the type of biradical produced in the reaction pathway. The highly stereospecific chiral transfer opens up avenues to synthesize complex structural motifs with quaternary chiral centers with excellent stereocontrol.

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