J|A|C|S COMMUNICATIONS

Published on Web 07/24/2009

Enantiospecific Photochemical Norrish/Yang Type II Reaction of Nonbiaryl Atropchiral α-Oxoamides in Solution—Axial to Point Chirality Transfer

Anoklase Jean-Luc Ayitou, Josepha L. Jesuraj, Nilotpal Barooah, Angel Ugrinov, and J. Sivaguru*

Department of Chemistry and Molecular Biology, North Dakota State University, Fargo, North Dakota 58105

Received June 19, 2009; E-mail: sivaguru.jayaraman@ndsu.edu

Axial chirality has attracted great interest among synthetic chemists in recent years, due to its increasingly significant role in catalytic enantioselective thermal reactions.[1] On the other hand, the use of axial chirality to induce enantioselectivity in photochemical transformations has not been explored in detail. Achieving high enanitoselectivity in photoreactions in solution[2] by utilizing conventional chiral perturbers employed in thermal/catalytic reactions has inherent limitations as it alters the diastereomeric activation energies of the prochiral substrates in the ground state.[2] To achieve high enantioselectivity in photochemical reactions in solution,[2] chiral discrimination between the prochiral faces has to occur within the short lifetime of the excited molecules, intermediates, and/or transition states. Over the decades, elegant methodologies involving supramolecular assemblies[3] have provided opportunities to carry out stereoselective phototransformations with varying degrees of success. Yet, highly enantioselective photoreactions in solution[2] have not met the same level of success as conventional thermal/catalytic reactions. Our approach was to employ molecularly chiral chromophores to achieve high stereoselection during phototransformations in solution.[4] Recently we reported[4] that molecularly chiral acrylanilides could be effectively employed in asymmetric phototransformations leading to >90% enantiomeric excess in solution. Here we report a highly enantiospecific photochemical Norrish/Yang type II reaction (γ-hydrogen abstraction) of axially chiral α-oxoamides **1** [axial chirality arising from restricted N−C(Aryl) bond rotation].[5]

It is well established in literature that *N*-methyl substituted acrylanilide[6] and *N*,*N*′-disubstituted benzamides[7] with bulky *ortho* substituents (*o*-^{t}Bu) in the phenyl ring are axially chiral due to the hindered N−C(Aryl) bond rotation. Based on the above literature precedence, we synthesized α-oxoamides **1** with the *o*-*tert*-butyl substituent on the N-phenyl ring and tested if they would be axially chiral. α-Oxoamides **1** with *o*-*tert*-butyl substitution on the N-phenyl ring were found to be axially chiral (*P* and *M* isomers). The individual *P* and *M* isomers were easily isolable on a chiral stationary phase and were characterized by NMR and CD spectroscopy, optical rotation, HRMS, and single crystal XRD.[8] These axially chiral optically pure α-oxoamides **1a**−**b** were stable at room temperature and could be stored at 0 °C for months without enantiomerization.[8] Due to the slow enantiomerization rate of optically pure **1** at room temperature, the kinetics of enantiomerization was performed at +50 °C, revealing $\Delta G^{\ddagger}$ of enantiomerization to be ∼27 kcal/mol.[8] The optically pure axially chiral **1** were investigated for axial to point chirality transfer during γ-hydrogen abstraction[5] leading to photoproducts **2**−**4**. Photoproducts **2** and **4** are expected to be a mixture of enantiomers as the N−C(Aryl) bond was shown to rotate freely due to the reduced C−N−C bond angle.[9]

$$\ln(k_R/k_S) = \ln[(100 + \%\text{ee})/(100 - \%\text{ee})] \quad (1)$$

$$\ln(k_R/k_S) = \Delta\Delta G^{\ddagger} = \Delta\Delta S^{\ddagger}_{R-S}/R - \Delta\Delta H^{\ddagger}_{R-S}/RT \quad (2)$$

Photoirradiation of optically pure atropisomers of **1** (Scheme 1) was preformed using a 450 W medium pressure Hg lamp with a Pyrex cutoff and a cooling jacket under a constant flow of nitrogen at various temperatures (+40 to −40 °C). The reaction was found to be clean and efficient with >95% conversion after 3 h at 30 °C.[8] At low temperatures, the reaction was slow and longer irradiation times were necessary to achieve higher conversions. The photoproducts were purified by chromatography and characterized by NMR and CD spectroscopy, optical rotation, and single crystal XRD.[8] HPLC analysis of the photolysate on a chiral stationary phase gave the enantiomeric ratio (e.r.) in the β-lactam **2** (Table 1). The optical antipodes of **1** gave opposite enantiomers in the β-lactam **2** as expected. Additionally, the e.r. values in **2** were found to be dependent on the reaction temperature (Figure 1). For example, in the case of **1a**, e.r. values increased (with the same enantiomer) from ∼74:26 to ∼90:10 upon changing the temperature from +40 °C to −40 °C.

Scheme 1. γ-Hydrogen Abstraction Involving Axially Chiral **1a**−**b**

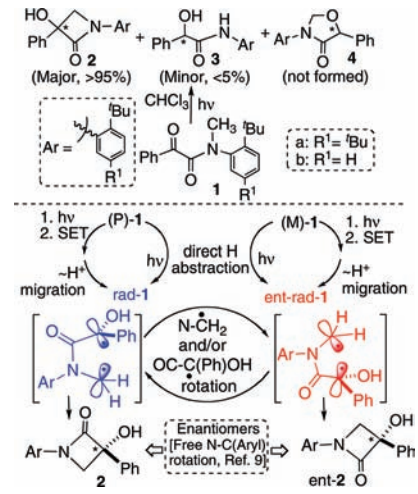

Table 1. Enantiomeric Ratios and Activation Parameters ($\Delta\Delta H^{\ddagger}$ and $\Delta\Delta S^{\ddagger}$) for γ-Hydrogen Abstraction of **1** in $CHCl_3$[a−c]

entry	*T* (°C)	time (min)	(−)-**1a**	(+)-**1a**	(−)-**1b**	(+)-**1b**
1	40	30	74:26 (A)	26:74 (B)	70:30 (A)	30:70 (B)
2	30	30	76:24 (A)	23:77 (B)	72:28 (A)	27:73 (B)
3	20	30	79:21 (A)	21:79 (B)	74:26 (A)	25:75 (B)
4	10	30	82:18 (A)	18:82 (B)	78:22 (A)	22:78 (B)
5	0	60	85:15 (A)	15:85 (B)	81:19 (A)	20:80 (B)
6	−20	120	89:11 (A)	11:89 (B)	84:16 (A)	15:85 (B)
7	−40	360	90:10 (A)	11:89 (B)	86:14 (A)	14:86 (B)
8	$\Delta\Delta H^{\ddagger}$ (kcal/mol)		−2.11	2.14	−1.80	1.60
9	$\Delta\Delta S^{\ddagger}$ (cal/mol/K)		−4.50	4.65	−3.93	3.26

[a] Values are an average of 3 runs (±2% error). [b] A and B refer to the first and second peaks that elute in the HPLC on a chiral stationary phase. [c] $\Delta\Delta H^{\ddagger}$, $\Delta\Delta S^{\ddagger}$ were computed from Eyring plots (eqs 1 and 2, refs 2a and 8).

10.1021/ja9050586 CCC: $40.75

The differential activation parameters ($\Delta\Delta H^{\ddagger}$ and $\Delta\Delta S^{\ddagger}$) were computed using Eyring plots (eqs 1 and 2).[2a,8] The enantioselectivity ($\Delta\Delta G^{\ddagger}$) depends on both $\Delta\Delta H^{\ddagger}$ and $\Delta\Delta S^{\ddagger}$. The magnitude and more importantly the signs of $\Delta\Delta H^{\ddagger}$ and $\Delta\Delta S^{\ddagger}$ help explain the effect of temperature on e.r. values. Since the $\Delta\Delta H^{\ddagger}/RT$ term is proportional to the reciprocal temperature (eq 2), the $\ln(k_R/k_S)$, i.e., the $\Delta\Delta G^{\ddagger}$ value, is determined mostly by the enthalpic contribution at low temperatures; however, as the temperature increases, the relative contribution from the $\Delta\Delta S^{\ddagger}/R$ term increases and contributes substantially to $\ln(k_R/k_S)$ at higher temperatures. As both $\Delta\Delta H^{\ddagger}$ and $\Delta\Delta S^{\ddagger}$ have the same sign, the decrease in temperature enhances the same isomer as the magnitude of $\Delta\Delta G^{\ddagger}$ increases (eq 2). Hence the enantioselectivity (e.r. values) should increase upon lowering the temperature as observed. The opposite signs with similar magnitude of $\Delta\Delta H^{\ddagger}$ and $\Delta\Delta S^{\ddagger}$ for a given pair of axially chiral (*P* and *M*) α-oxoamides **1** are reflected in the optical antipodes of the enhanced β-lactam **2**. The activation parameters and its influence on e.r. values in **2** are indicative of conformational factors playing a pivotal role in the reaction pathway.[2a]

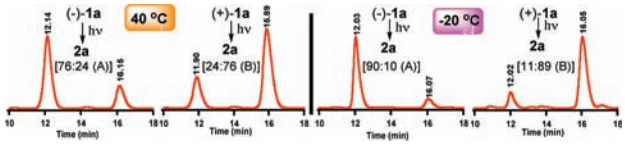

Figure 1. Enantiomeric ratios in **2a** at various temperatures in $CHCl_3$.

NMR analysis of **1** (pure *P* or *M*) showed that both *E* and *Z* N—CO rotamers exist in solution.[8] The dynamic nature of N—CO rotation in axially chiral amides is well established.[6,7] Analysis of the crystal structures of **1** reveals that the two carbonyl groups are at 90° to each other.[8] The free N—CO rotation in solution likely enables **1** to adopt a conformation ideal for photochemical γ-hydrogen abstraction defined by Scheffer and co-workers.[10] The established mechanism[5c] of photoreaction in α-oxoamides involves 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). Unlike aromatic ketones that undergo γ-hydrogen abstraction from the $n\pi^*$ triplet state,[5b] photochemical γ-hydrogen abstraction in α-oxoamides is mediated by the electron transfer pathway even if the lowest triplet excited state of the ketone is the otherwise unreactive $\pi\pi^*$ state.[5c] Depending on the axial chirality (*P* or *M*) in **1**, the torsion angle O=C—C_α—N_β could be positive or negative leading to the possibility of γ-hydrogen abstraction from one face of the carbonyl resulting in the 1,4-diradical (*rad*-**1** or *ent-rad*-**1**).

In general, the chirality of the β-lactam photoproduct **2** is decided at the stage of ring closure of the 1,4-diradical intermediate, i.e., which face of the benzylic radical center adds to the γ-carbon radical. The 1,4-diradical is free to rotate in solution, and the competition between bond rotations vs bond formation in the 1,4-diradical likely determines the extent of chiral induction in the photoproducts. In other words, the rate of interconversion between the two diradicals (*rad*-**1** and *ent-rad*-**1**) and the rate of ring closure leading to **2** impart a dynamic nature in the system as ascertained by the differential activation parameters ($\Delta\Delta H^{\ddagger}$ and $\Delta\Delta S^{\ddagger}$). We believe that, upon lowering the temperature, the rate of interconversion between the two 1,4-diradicals (*rad*-**1** and *ent-rad*-**1**) is lowered with respect to the rate of ring closure, as bond rotations are slower at lower temperatures resulting in efficient axial chirality transfer leading to high enantioselectivity (e.r. values) in β-lactam **2** as observed. This speculation can be ascertained based on indirect evidence from $\Delta G^{\ddagger}$ for enantiomerization. Molecular constraints based on restricted bond rotation are enhanced in **1a** ($k = 2.6 \times 10^{-6}$ s^{-1})[8] compared to **1b** ($k = 4.0 \times 10^{-6}$ s^{-1})[8] with respect to the rate of enantiomerization. This is reflected in the slower rate of enantiomerization[8] resulting in the more efficient chiral transfer in **1a** than in **1b**. A closer look at the e.r. values reveals that the selectivity in the di-*tert*-butyl derivative **1a** is slightly higher than the corresponding mono-*tert*-butyl derivative **1b** adding credibility to the above rationale. Thus this simple mechanistic model enables us to rationalize the observed temperature dependence of e.r. values in **2**.

Our investigation has paved the way to employ a new class of nonbiaryl atropisomers, *viz*. axially chiral α-oxoamides **1**, for asymmetric photochemical transformations in solution. Irradiation of axially chiral chromophores that equilibrate very slowly in the ground state leads to very high enantioselectivity in the photoproducts. We are currently exploring this strategy for various asymmetric phototransformations in solution.

Acknowledgment. J.S. thanks the financial support of the NSF (CAREER: CHE-0748525). This paper is dedicated to Prof. K. K. Balasubramanian, Indian Institute of Technology—Madras (IIT Madras), an inspiring teacher on the occasion of his 70th birthday.

Supporting Information Available: Experimental procedures for synthesis and photoreactions, characterization of α-oxoamides **1** and β-lactam **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) (a) Miyashita, A.; Yasuda, A.; Takaya, H.; Toriumi, K.; Ito, T.; Souchi, T.; Noyori, R. *J. Am. Chem. Soc.* **1980**, *102*, 7932–7934. (b) Chen, Y.; Yekta, S.; Yudin, A. K. *Chem. Rev.* **2003**, *103*, 3155–3212.
(2) (a) Inoue, Y. In *Chiral Photochemistry*; Inoue, Y., Ramamurthy, V., Eds.; Marcel Dekker: New York, 2004; Vol. 11, pp 129—177. (b) Muller, C.; Bach, T. *Aust. J. Chem.* **2008**, *61*, 557–564. (c) Hammond, G. S.; Cole, R. S. *J. Am. Chem. Soc.* **1965**, *87*, 3256–3257.
(3) Sivaguru, J.; Natarajan, A.; Kaanumalle, L. S.; Shailaja, J.; Uppili, S.; Joy, A.; Ramamurthy, V. *Acc. Chem. Res.* **2003**, *36*, 509–521.
(4) Ayitou, A. J.-L.; Sivaguru, J. *J. Am. Chem. Soc.* **2009**, *131*, 5036–5037.
(5) (a) Aoyama, H.; Sakamoto, M.; Kuwabara, K.; Yoshida, K.; Omote, Y. *J. Am. Chem. Soc.* **1983**, *105*, 1958–1964. (b) Wagner, P. J.; Park, B.-S. *Org. Photochem.* **1991**, *11*, 227–366. (c) Chesta, C. A.; Whitten, D. G. *J. Am. Chem. Soc.* **1992**, *114*, 2188–2197. (d) Wang, R.; Chen, C.; Duesler, E.; Mariano, P. S. *J. Org. Chem.* **2004**, *69*, 1215–1220. (e) Natarajan, A.; Mague, J. T.; Ramamurthy, V. *J. Am. Chem. Soc.* **2005**, *127*, 3568–3576.
(6) Curran, D. P.; Hale, G. R.; Geib, S. J.; Balog, A.; Cass, Q. B.; Degani, A. L. G.; Hernandes, M. Z.; Freitas, L. C. G *Tetrahedron: Asymmetry* **1997**, *8*, 3955–3975.
(7) (a) Clayden, J. *Chem. Commun.* **2004**, 127–135. (b) Honda, A.; Waltz, K. M.; Carroll, P. J.; Walsh, P. J. *Chirality* **2003**, *15*, 615–621.
(8) Refer to Supporting Information.
(9) Kitagawa, O.; Fujita, M.; Kohriyama, M.; Hasegawa, H.; Taguchi, T. *Tetrahedron Lett.* **2000**, *41*, 8539–8544.
(10) Gudmundsdottir, A. D.; Lewis, T. J.; Randall, L. H.; Scheffer, J. R.; Rettig, S. J.; Trotter, J.; Wu, C.-H. *J. Am. Chem. Soc.* **1996**, *118*, 6167–6184.

JA9050586