Communication

Oxazolines as Dual Function Traceless Chromophores and Chiral Auxiliaries: Enantioselective Photoassisted Synthesis of Polyheterocyclic Ketones

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Oxazolines as Dual Function Traceless Chromophores and Chiral Auxiliaries: Enantioselective Photoassisted Synthesis of Polyheterocyclic Ketones.

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Supporting Information Placeholder

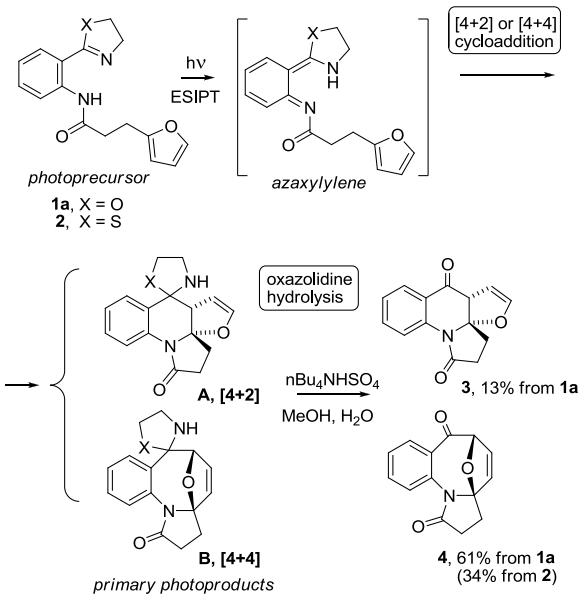
ABSTRACT: 2-(*o*-Amidophenyl)-oxa- and thiazolines undergo excited state intramolecular proton transfer (ESIPT), generating aza-*o*-xylylenes capable of intramolecular [4+2] and [4+4] cycloadditions with tethered unsaturated pendants. Facile hydrolysis of the primary photoproducts, spiro-oxazolidines and thiazolidines, under mild conditions unmasks a phenone functionality. Variations in linkers allow for access to diverse core scaffolds in the primary photoproducts, rendering the approach compatible with the philosophy of diversity-oriented synthesis. Chiral oxazolines, readily available from the corresponding amino alcohols, yield enantioenriched keto-polyheterocycles of complex topologies with *ee's* up to 90%.

There has been significant progress in chiral photochemistry,[1] yet its scope is largely limited to enantioselective Paternò-Büchi reactions[2] and other [2+2] cycloadditions,[3] with modest forays into [4+2] and [4+4] cycloadditions, as well as electrocyclic reactions and photorearrangements[4]. This may be partially attributable to the limited variety of chiral catalysts or chiral auxiliaries traditionally used in photochemical reactions (mostly esters or acetals), although recent advances in enantioselective photoredox chemistry help fill the void either with chiral auxiliaries adopted from the ground state radical chemistry or novel chiral photoredox catalysts.[5]

Recently we developed a novel photoassisted synthetic methodology involving excited state intramolecular proton transfer (ESIPT) to generate reactive aza-*o*-xylylenes from aromatic amino ketones[6] or imines.[7] It allows for rapid access to complex polyheterocyclic molecular architectures in a very few simple synthetic steps. We rationalized that such reactions with structurally not dissimilar chromophores, 2-*aryloxazolines*, could be a valuable addition to the synthetic applications of this methodology as the generated aza-*o*-xylylenes in this case would have the carbon terminus substituted with two heteroatoms, N and O, Scheme 1. Their primary photoproducts possess readily hydrolysable aminals, rendering these oxazoline chromophores *traceless*. We aimed to augment them with a chiral auxiliary to devise a dual-purpose traceless chromophore/auxiliary, especially in view of the fact that in the ground state chemistry – ever since the pioneering work of A. Meyers[8] – *oxazolines* are universally recognized as versatile chiral auxiliaries in asymmetric C-C bond formations, ligands for chiral catalysts[9] and as building blocks for organocatalysts[10].

In this communication we demonstrate that (i) 2-(*o*-aminophenyl)oxazolines undergo excited state intramolecular proton transfer leading to cycloaddition-competent pull-push aza-*o*-xylylene intermediates, and (ii) that chiral oxazolines indeed serve as effective dual function traceless chromophores/chiral auxiliaries.

Initially we examined the reactions of achiral photoprecursors **1** and **2** containing unsubstituted oxa- and thiazolines, Scheme 1, which were prepared from readily accessible 2-(4,5-dihydrooxazol-2-yl)aniline and 2-(4,5-dihydrothiazol-2-yl)aniline (see SI for synthetic details). Compounds **1** and **2** have broad UV absorption with the maximum around 320-330 nm. Irradiations at ambient temperature were carried out in a broadband 300-400 nm Rayonet photoreactor (12 × 16 W) with dichloromethane as a solvent, resulting in the clean formation of both [4+2] and [4+4] photoproducts. The primary photoproducts, spiro oxazolidines or thiazolidines **A** and **B,** were hydrolyzed without isolation in aqueous methanol with PPTS or n-Bu_4NHSO_4 to corresponding ketones **3** and **4**.



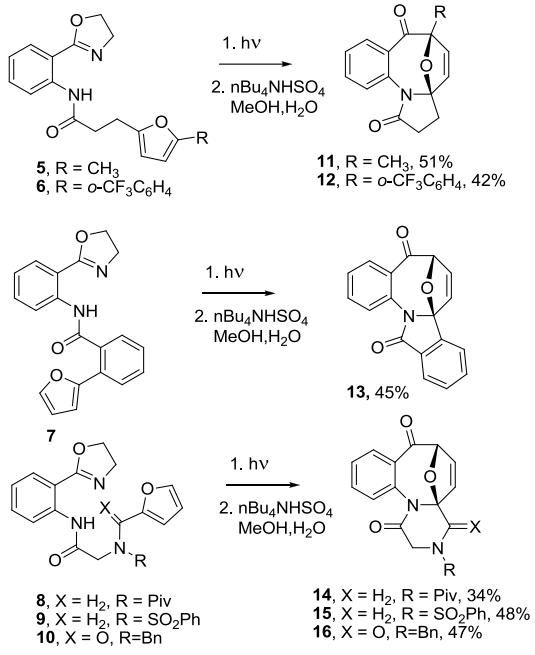
Scheme 1. Model photocycloaddition reactions with oxazoline and thiazoline photoprecursors **1a** and **2** (isolated yields over two steps are shown).

Instructively, the quantum yield of the photocyclization with the oxazoline chromophore was three times higher than that with thiazoline, which decided the further use of *oxa*- and not *thia*-zolines in the subsequent studies.

Photophysics of the close relatives of oxazolines – benzoxazoles, benzothiazoles, and benzimidazoles – was documented in the literature[11], and 2-(2'-hydroxyphenyl)benzoxazoles and -thiazoles found use in biosensors[12] and sensitizers.[13] However, to the best of our knowledge no synthetic applications of these processes have been reported and, further, no experimental data is available on ESIPT in oxazolines or thiazolines.

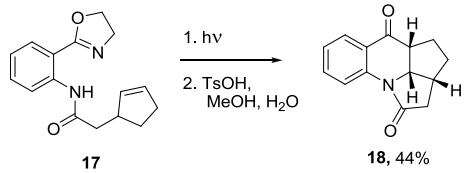
We also synthesized a *benzo*thiazole-based photoprecursor, because of benzothiazole's ready availability and a strong red-shifted absorption band. Although ESIPT in o-benzothiazolyl-anilines is known,[14] the benzothiazole-based photoprecursor failed to cyclize. Since it cannot serve as a dual function *chiral* chromophore anyway, its lack of photoreactivity was not disappointing.

The scope of the reaction was probed by varying the length and the nature of the linker between the 2-(*o*-aminophenyl)-4,5-dihydrooxazole photoactive core and the unsaturated pendant (i.e. the furan moiety), which also allowed for assessing the reaction tolerance to the functional groups in the potential diversity inputs. All photoprecursors were synthesized by amide coupling of 2-(4,5-dihydrooxazol-2-yl)aniline with the corresponding acid.[15]



Scheme 2. Scope of photocycloadditions with furanoyl and furanyl pendants tethered via aliphatic or aromatic linkers.

Simple cycloalkene pendants were also shown to react. Cyclopentenyl photoprecursor **17**, Scheme 3, underwent the [4+2] photocyclization, as the [4+4] channel is not available for alkenes. Oxazolidines initially formed from **17** proved to be somewhat more stable than their dihydrofuran-containing counterparts and required TsOH to hydrolyze.



Scheme 3. Photoreaction of cyclopentene-containing precursor **17**.

Encouraged by this success in the model achiral systems we then proceeded with synthesis of chiral oxazolines **1b**-**1f**, Figure 1, with the goal of accessing enantiopure photoproducts. In the context of ESIPT-generation of azaxylylenes, combining the roles of a chromophore and a chiral auxiliary in the same oxazoline moiety necessarily places its stereogenic center in the close proximity of the reaction center, which should arguably provide a greater control of the stereochemical outcome.

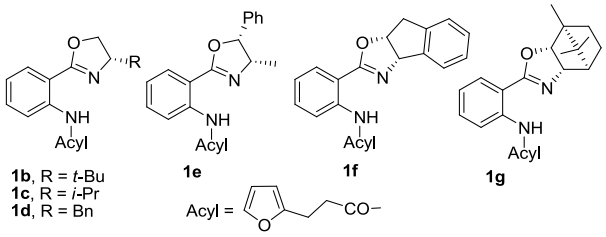


Figure 1. Chiral oxazoline-based photoprecursors **1b-g**.

Compounds **1b-1e** and **1g** can be readily prepared from commercially available 2-aminoalcohols,[16] camphor-based **1f** was obtained as described from camphorquinone.[17] The optimization runs (solvent/temperature/chiral auxiliary) are shown in Table 1 and Figure 2. At 20°C the *ee's* values in DMSO were slightly better than in DCM (dichloromethane) but low temperature clearly had an overriding advantage, making DCM the solvent of choice, as DMSO does not allow for any substantial cooling. Efficient temperature control was essential and therefore the photoinduced cycloadditions at low temperature were conducted in a Pyrex Dewar with a clear window, and a medium-pressure 200 W Hanovia lamp. Primary photoproducts – oxazolidines **A** and **B** – are formed as two diastereomers, distinguishable by NMR. This enabled calculation of diastereomeric excess prior to the workup of the reaction. After the completion of the irradiation as determined by NMR, hydrolysis was performed, and the mixture was analyzed by chiral HPLC (Chiracel AD) using compounds **3** and **4** as racemic chromatography standards. The results of this optimization are shown in Table 1.

Table 1. Optimization of reaction conditions for chiral photoprecursors

	T,°C/solv.	*de%* by NMR[a]		B:A ratio	*ee%* by HPLC[b]	
		[4+2]	[4+4]		**3**, [4+2]	**4**, [4+4]
1b	20/DCM	11%	72%	4.5	17%	54%
1b	20/DMSO	--[c]	--	--[c]	37%	68%
1b	0/DCM	51%	71%	4.5	41%	69%
1b	-20/DCM	48%	69%	3.7	37%	69%
1b	-40/DCM	38%	72%	3.4	51%	75%
1b	-78/DCM	57%	88%	2.9	60%	86%
1e	-78/DCM	36%	18%	2.3	43%	25%
1d	-78/DCM	12%	63%	2.1	8%	57%
1c	-78/DCM	61%	75%	3.0	65%	84%
1f	-78/DCM	34%	84%	3.7	30%	84%[d]
1g	-78/DCM	31%	96%	2.3	--	86%

[a]determined before hydrolysis; [b]determined by chiral HPLC after hydrolysis into ketones; [c]partial hydrolysis occurs during the photoreaction, calculation of de% or **B**:**A** ratios is not possible; [d]1-amino-2-hydroxyindanone-based auxiliary produced reversed ratio of enantiomers.

Figure 2 illustrates in a graph form the final *ee* values determined by chiral HPLC for the optimization runs in the [4+4] cycloadducts. Of commercially available amino-alcohols *tert*-leucinol-based photoprecursor **1b** (first six vertical bars) performed the best. Compounds **1f** and **1g** exhibited similar performance, but were not commercially available. We therefore selected the *tert*-leucinol-based photoactive cores. As follows from Table 1, the

de- values for the primary photoproducts of type **A** and **B** (columns 2 & 3 in Table 1) generally correlated with the final *ee* values for the hydrolyzed products **3** and **4**. One instructive observation (see Table 1) was that the [4+4] products generally exhibited higher *ee*'s than the [4+2] products. Our mechanistic rationale for this is presented in Figure 3.

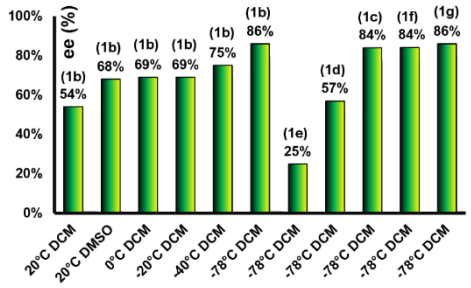


Figure 2. Optimization of *ee*'s for the [4+4] ketone product.

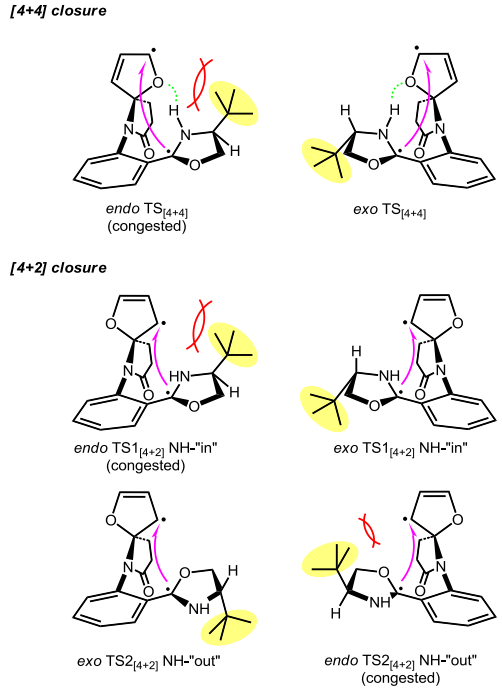
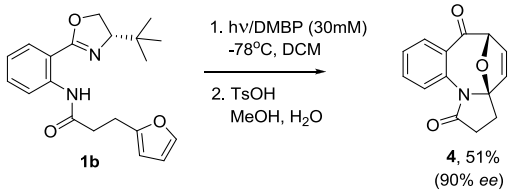


Figure 3. Plausible mechanistic rationale for tighter stereocontrol in the TS leading to [4+4] photoproducts.

We hypothesize that the stereodifferentiation either does not occur at all or occurs only to a minor extent at the initial attack of the N-radical center of the triplet aza-*o*-xylylene on the tethered furan moiety. Rather, the stereochemical outcome is controlled at the recombination step (after the intersystem crossing, ISC, to the singlet ground state) in the diradical species produced by this initial attack, Figure 3. For the [4+4] closure, the hydrogen bond (green dotted line) between the furan oxygen and the NH moiety locks the rotation of oxazolidinyl radical limiting the conformational space to only one rotamer – either *endo* $TS_{[4+4]}$ or *exo* $TS_{[4+4]}$. In the *endo* $TS_{[4+4]}$, the collapse of the diradical species after ISC is obstructed by the *t*-butyl group while there is no such steric clash in the *exo* $TS_{[4+4]}$ – hence, the higher *ee* values.

The [4+2] cycloadducts are formed via a similar radical recombination, but at the other terminus of the allylic radical (the alternative *resonance* structure for the dihydrofuryl radicals illustrates this in Figure 3). The rotamers leading to the [4+2] closure lack the hydrogen bond with furan's oxygen, so the NH moiety is free to assume both "in" and "out" conformation in the aryl-conjugated oxazolidinyl radical. This implies that all four combinations, *exo/endo* and *NH-in/NH-out*, are feasible, thus lowering the *ee* values for the [4+2] products. The fact that the [4+2] reaction is still stereoselective may point to a weak hydrogen bond between the NH and the γ-lactam moiety, which biases the system toward the NH-"in" rotamer, *exo* $TS1_{[4+2]}$. The overall regioselectivity of the addition, i.e. [4+4] *vs* [4+2], is conceivably governed by the intrinsic differences of spin density in the allylic radical and the average distance between the radical centers, which is slightly greater for the [4+4] recombination. The better orbital overlap for the [4+2] channel and the fact that the [4+4] to [4+2] ratio decreases at lower temperatures (Table 1, *tert*-leucinol-based **1b**) indicates that [4+2] is a kinetic product.

Preparative scale low temperature irradiations always present additional challenge as the Hanovia medium pressure mercury lamps deposit considerable amount of energy into the reaction flask. UV LEDs offer well-conditioned "cool" UV light, but currently only 360nm (and higher) LEDs are powerful enough to be practical for the preparative runs. Yet the absorption maximum of oxazolines **1b-g** is blue shifted to 320-330 nm as compared with 350-360 nm absorption of the corresponding *o*-aminoketones. Our earlier mechanistic studies in the ketone series indicated that these cycloadditions occur in the triplet manifold.[18] Therefore, our solution to this challenge was to employ a triplet sensitizer, which allowed for the utilization of a linear array of 365nm UV-LEDs (4 × 250 mW). Several sensitizers were tested (aminobenzonitrile, methyl anthranilate, benzophenone, 4-methoxybenzophenone, 4,4'-dimethylbenzophenone, 4,4'-difluorobenzophenone, 4,4'-dimethoxybenzophenone, thioxanthone), and 4,4'-dimethoxybenzophenone (DMBP) was identified as the sensitizer of choice. The preparative scale (~100 mg) irradiation at -78 °C with a 10 mol % sensitizer proceeded smoothly and, after hydrolysis and chromatographic purification, gave [4+4] cycloadduct **4** with the isolated yield of 51% and *ee* of 90% (average of two experiments), Scheme 4.



Scheme 4. Preparative scale photolysis for *tert*-leucinol-based photoprecursor **1b**.

In conclusion, we report the first example of the photoinduced intramolecular cycloadditions of 2-(2-amidophenyl)oxazolines via ESIPT. The photoprecursors are amenable to modular assembly rendering the method compatible with the philosophy of diversity-oriented synthesis. The reaction is tolerant to a variety of linkers and proceeds smoothly with both furyl and alkenyl unsaturated pendants. The facile hydrolysis of the primary photoproducts, spiro-oxazolidines, cleanly unmasks a ketone functionality. The use of readily accessible chiral oxazolines results in the formation of enantioenriched heterocyclic ketones with high *ee*'s. Given a variety of postphotochemical transformations available to further grow complexity of the primary photoproducts of azaxylylene cyclizations,[6,7] one can readily envision how rather complex polyheterocyclic molecular architectures could be obtained in an enantiopure form.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectra (100 pages). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interests.

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REFERENCES

(1) For reviews, see (a) Rau, H. *Chem. Rev.*, **1983**, *83*, 535-547. (b) Inoue, Y.; Ramamurthy, V., Ed. Chiral Photochemistry, Marcel Dekker, New York, **2004**, 665 p. (c) Grosch, B.; Bach, T. Enantioselective Photocycloaddition Reactions in Solution CRC Handbook on Photochemistry and Photobiology 2nd edition Ed. Horspool, W.; Lenci, F. CRC Press, **2003**, p. 61-1 (d) Natarajan, A.; Kaanumalle L.S.; Ramamurthy, V. Manipulating Photochemical Reactions CRC Handbook on Photochemistry and Photobiology 2nd edition Ed. Horspool, W.; Lenci, F. CRC Press, **2003**, p. 107-1 (e) Bach, T. *Synthesis* **1998**, 683-703. (f) Namyslo, J. C.; Kaufmann, D. E. *Chem. Rev.* **2003**, *103*, 1485-1538. (g) Lee-Ruff, E.; Mladenova, G. *Chem. Rev.* **2003**, *103*, 1449-1483. (h) R. Brimioulle, D. Lenhart, M. M. Maturi, T. Bach, *Angew. Chem. Int. Ed.* **2015**, *54*, 3872-3890.

(2) (a) Terao, K.; Nishiyama, Y.; Kakiuchi, K. *J. Flow Chem.* **2014**, *4*, 35-39. (b) Bach, T.; Bergmann, H.; Grosch, B.; Harms, K. *J. Am. Chem. Soc.* **2002**, *124*, 7982-7990. (c) Bach, T.; Bergmann, H.; Harms, K. *J. Am. Chem. Soc.*, **1999**, *121*, 10650-10651. (d) Bach, T.; Bergmann, H.; Brummerhop, H.; Lewis, W.; Harms, K. *Chem. Eur. J.*, **2001**, *7*, 4512-4521.

(3) For recent examples, see (a) Vallavoju, N.; Selvakumar, S.; Jockusch, S.; Sibi, M.P.; Sivaguru, J. *Angew. Chem. Int. Ed.* **2014**, *53*, 5604-5608. (b) Coote, S.C.; Pöthig, A.; Bach, T. *Chem. Eur. J.* **2015**, *21*, 6906-6912. (c) Brimoulle, R.; Bauer, A.; Bach, T. *J. Am. Chem. Soc.*, **2015**, *137*, 5170-5176. (d) Yanagisawa, Y.; Nishiyama, Y.; Tanimoto, H.; Morimoto, T. Kakiuchi, K. *Tetrahedron Lett.*, **2014**, *55*, 2123-2126. (e) Zhao, G.; Yang, C.; Sun, H.; Lin, R.; Xia, W. *Org. Lett.*, **2012**, *14*, 776-779. (f) Faure, S.; Piva-Le-Blanc, S.; Bertrand, C.; Pete, J.-P.; Faure, R.; Piva, O. *J. Org. Chem.* **2002**, *67*, 1061-1070.

(4) [4+2] cycloadditions: (a) Grosch, B.; Orlebar, C.N.; Herdtweck, E.; Kaneda, M.; Wada, T.; Inoue, Y.; Bach, T. *Chem. Eur. J.* **2004**, *10*, 2179-2189. (b) Kim, J.-I.; Schuster, G.B. *J. Am. Chem. Soc.*, **1992**, *114*, 9309-9317. (c) Asaoka, S.; Ooi, M.; Jiang, P.; Wada, T.; Inoue, Y. *J. Chem. Soc., Perkin Trans. 2*, **2000**, 77-84. [3+2] Cycloadditions: (d) Lajkiewicz, N. J.; Roche, S.P.; Gerard, B.; Porco, J.A. *J. Am. Chem. Soc.*, **2012**, *134*, 13108-13113. (e) Sugimura, T.; Nishiyama, N.; Tai, A.; Hakushi, T. *Tetrahedron: Asymmetry* **1994**, *5*, 1163-1166. [4+4] Cycloadditions: (f) Bach, T.; Bergmann, H.; Grosch, B.; Harms, K. *Org. Lett.*, **2001**, *3*, 601-603. Photodeconjugation reactions: (g) Henin, F.; Letinois, S.; Muzart, J. *Tetrahedron: Asymmetry*, **2000**, *11*, 2037-2044. Electrocyclizations: (h) Naito, Y.; Tada, Y.; Ninomiya, I. *Heterocycles*, **1984**, *22*, 237-240. (i) Bach, T.; Grosch, B.; Strassner, T.; Herdtweck, E. *J. Org. Chem.* **2003**, *68*, 1107-1116.

(5) (a) Nicewicz, D.A.; MacMillan, D.W. C. *Science* **2008**, *322*, 77-80. (b) Nagib, D.A.; Scott, M.E.; MacMillan, D.W.C. *J. Am. Chem. Soc.*, **2009**, *131*, 10875-10877. (c) Cherevatskaya, M.; Neumann, M.; Füldner, S.; Harlander, C.; Kümmel, S.; Dankesreiter, S.; Pfitzner, A.; Zeitler, K.; König, B. *Angew. Chem., Int. Ed.* **2012**, *51*, 4062-4066. (d) DiRocco, D. A.; Rovis, T. *J. Am. Chem. Soc.* **2012**, *134*, 8094-8097. (e) Cecere, G.; König, C. M.; Alleva, J. L.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2013**, *135*, 11521-11524. (f) Rono, L. J.; Yayla, H. G.; Wang, D. Y.; Armstrong, M. F.; Knowles, R. R. *J. Am. Chem. Soc.* **2013**, *135*, 17735-17738. (g) Bergonzini, G.; Schindler, C. S.; Wallentin, C.-J.; Jacobsen, E. N.; Stephenson, C. R. *J. Chem. Sci.* **2014**, *5*, 112-116. (h) Du, J.; Skubi, K. L.; Schultz, D. M.; Yoon, T. P. *Science* **2014**, *344*, 392-396. (i) Tellis, J. C.; Primer, D. N.; Molander, G. A. *Science* **2014**, *345*, 433-436. (j) Zhu, Y.; Zhang, L.; Luo, S. *J. Am. Chem. Soc.* **2014**, *136*, 14642-14645. (k) Huo, H.; Shen, X.; Wang, C.; Zhang, L.; Röse, P.; Chen, L.-A.; Harms, K.; Marsch, M.; Hilt, G.; Meggers, E. *Nature* **2014**, *515*, 100-103. (l) Gutierrez, O.; Tellis, J. C.; Primer, D. N.; Molander, G. A.; Kozlowski, M. C. *J. Am. Chem. Soc.* **2015**, *137*, 4896-4899. (m) Huo, H.; Wang, C.; Harms, K.; Meggers E. *J. Am. Chem. Soc.*, **2015**, *137*, 9551-9554.

(6) (a) Mukhina, O. A.; Kumar, N. N. B.; Arisco, T. M.; Valiulin, R. A.; Metzel, G. A.; Kutateladze, A. G. *Angew. Chem., Int. Ed.* **2011**, *50*, 9423-9428. (b) Nandurkar, N. S.; Kumar, N. N. B.; Mukhina, O. A.; Kutateladze, A. G. *ACS Comb. Sci*. **2013**, *15*, 73-76. (c) Kumar, N. N. B.; Mukhina, O. A.; Kutateladze, A. G. *J. Am. Chem. Soc.*, **2013**, *135*, 9608-9611. (d) Cronk, W.C.; Mukhina, O.A.; Kutateladze, A.G. *J. Org. Chem.*, **2014**, *79*, 1235-1246. (e) Kumar, N.N.B.; Kuznetsov, D.M.; Kutateladze, A.G. *Org. Lett.*, **2015**, *17*, 438-441. (f) Mukhina, O.A.; Kumar, N.N.B.; Cowger, T.M.; Kutateladze, A.G. *J. Org. Chem.*, **2014**, *79*, 10956-10971. (g) Umstead, W.J.; Mukhina, O.A.; Kutateladze, A.G. *Eur. J. Org. Chem.*, **2015**, 2205-2213. (h) Umstead, W.J.; Mukhina, O.A.; Kutateladze, A.G. *Aust. J. Chem.* **2015**, *68*, 1672-1681.

(7) Mukhina, O.A.; Kuznetsov, D.M.; Cowger, T.M.; Kutateladze, A.G. *Angew. Chem. Int. Ed.*, **2015**, *39*, 11516-11520.

(8) For selected examples, see (a) Meyers, A.I.; Knaus, G.; Kamata, K.; Ford, M.E. *J. Am. Chem. Soc.*, **1976**, *98*, 567-576. (b) Meyers, A.I.; Whitten, C.E. *J. Am. Chem. Soc.* **1975**, *97*, 6266-6267. (c) Meyers, A.I.; Shipman, N. *J. Org. Chem*. **1991**, *56*, 7098-7102. (d) Michelon, F.; Pouihes, A.; van Bac, N.; Langlois, N. *Tetrahedron Lett.* **1992**, *33*, 1743-1746. (e) Dahuron, N.; Langlois, N. *Synlett*, **1996**, 51-52. (f) Johnson, J. A.; Li, N.; Sames, D. *J. Am. Chem. Soc.* **2002**, *124*, 6900-6903. (g) Giri, R.; Chen, X.; Yu, J.-Q. *Angew. Chem. Int. Ed.* **2005**, *44*, 2112-2115. For reviews, see (h) Meyers, A.I. *J. Org. Chem.* **2005**, *70*, 6137-6151. (i) Gnas, Y.; Glorius, F. *Synthesis*, **2006**, 1899-1930. (j) Ager, D.J.; Prakash, I.; Schaad, D.R. *Chem. Rev.*, **1996**, *96*, 835-876.

(9) For reviews, see (a) Hargaden, G.C.; Guiry, P.J. *Chem. Rev.* **2009**, *109*, 2505-2550. (b) Gossage, R.A. *Dalton Trans.*, **2011**, *40*, 8755-8759. (c) Ward, B.D.; Gade, L.H. *Chem. Commun.*, **2012**, *48*, 10587-10599. For a recent example, see: (d) Chu, J.C.K.; Dalton, D.M.; Rovis, T. *J. Am. Chem. Soc.* **2015**, *137*, 4445-4452.

(10) (a) Rajaram, S.; Sigman, M. S. *Org. Lett.* **2002**, *4*, 3399-3401. (b) Rajaram, S.; Sigman, M.S. *Org. Lett.*, **2005**, *7*, 5473-5475. (c) Jensen, K. H.; Sigman, M. S. *Angew. Chem., Int. Ed.* **2007**, *46*, 4748-4750. (d) Harper, K.C.; Sigman, M.S. *J. Org. Chem.* **2013**, *78*, 2813-2818.

(11) (a) Henary, M.M., Wu, Y.; Cody, J.; Sumalekshmy, S.; Li, J.; Mandal, S.; Fahrni, C.J. *J. Org. Chem.* **2007**, *72*, 4784-4797. (b) Hsieh, C.-C.; Cheng, Y.-M.; Hsu, C.-J.; Chen, K.-Y.; Chou, P.T. *J. Phys.Chem. A* **2008**, *112*, 8323-8332. (c) Chen, W.-H., Pang, Y. *Tetrahedron Lett.*, **2010**, *51*, 1914-1918. (d) Santos, F.S.; Costa, T.M.H.; Stefani, W.; Gonçalves, P.F.B.; Descalzo, R.R.; Benvenutti. E.V.; Rodembusch, F.S. *J. Phys. Chem. A* **2011**, *115*, 13390-13398. (e) Patil, V.S.; Padalkar, V.S.; Tathe, A.B.; Gupta, V.D.; Sekar, N. *J. Fluoresc*, **2013**, *23*, 1019-1029.

(12) Chen, W.-H.; Xing, Y.; Pang, Y. *Org. Lett.* **2011**, *13*, 1362-1365.

(13) Yang, P.; Zhao, J.; Wu, W.; Yu, X.; Liu, Y. *J. Org. Chem.*, **2012**, *77*, 6166-6178.

(14) Tseng, H.W.; Liu,J.-Q.; Chen, Y.An.; Chao, C.-M.; Liu, K.-M.;Chen, C.-L.; Lin, T-C.; Hung, C.-H.; Chou, Y.-L.; Lin, T.-C.; Wang, T.-L.; Chou,P.-T. *Phys. Chem. Lett.* **2015**, *6*, 1477-1486.

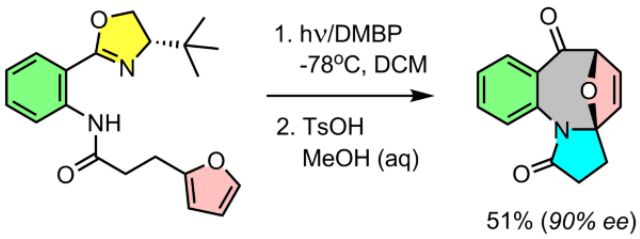
(15) In the reactions shown in Scheme 2 the minor [4+2] product was not isolated.

(16) (a) Zhang, Z.; Lippert, K. M.; Hausmann, H.; Kotke, M.; Schreiner, P. R. *J. Org. Chem.* **2011**, *76*, 9764-9776. (b) Kurosu, M.; Lin, M.-H.; Kishi, Y. *J. Am. Chem. Soc.*, **2004**, *126*, 12248-12249.

(17) Synthesized analogously to Thérien, M.-É.; Guilbault, A.-A.; Legault, C.Y. *Tetrahedron: Asymmetry*, **2013**, *24*, 1193-1197.

(18) Mukhina, O.A.; Cronk, W.C.; Kumar, N.N.B.; Sekhar, M.; Samanta, A.; Kutateladze, A.G. *J. Phys. Chem. A.*, **2014**, *118*, 10487-10496.

TOC GRAPHICS



51% (*90% ee*)