JOC The Journal of Organic Chemistry

Note

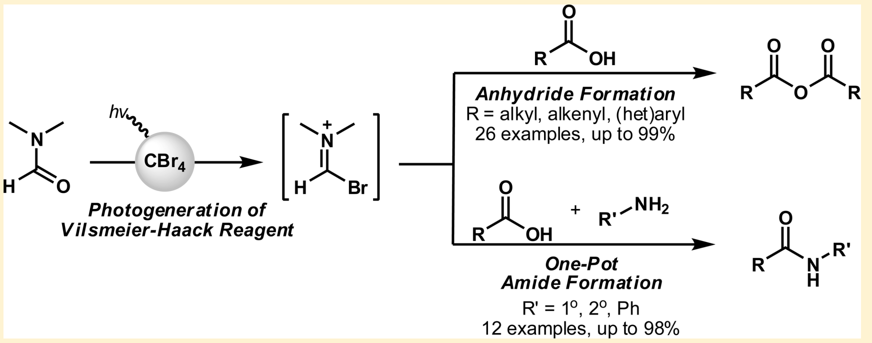
pubs.acs.org/joc

Light-Enabled Synthesis of Anhydrides and Amides

Terry McCallum and Louis Barriault*

Centre for Catalysis, Research and Innovation, Department of Chemistry, University of Ottawa, Ottawa, Ontario K1N 6N5, Canada

Supporting Information



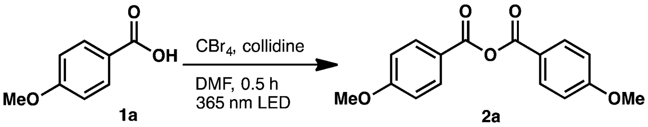
ABSTRACT: Recently, we have demonstrated that the photogeneration of Vilsmeier–Haack reagents is possible using only dimethylformamide (DMF) and tetrabromomethane (CBr_4) in the bromination of alcohols. Extending these findings to carboxylic acid substrates has produced a mild and facile approach to the in situ formation of symmetric anhydrides, which were conveniently converted to amide derivatives in a one-pot process. The efficient protocols discussed herein are marked by use of UVA LEDs (365 nm), which have reduced the reaction times and come with a low setup cost.

The activation of carboxylic acids has been paramount to the synthesis of peptides in coupling reactions with amines.[1] A variety of methods make carboxylic acids more electrophilic either by transforming the carboxylic acid into the corresponding acyl halide or through the addition of coupling agents.[2] Symmetric anhydrides have also seen great use in peptide chemistry because they provide electrophilic activation of the carboxylic moiety without forming coupling byproducts, as both electrophilic sites are identical. However, these anhydrides are often formed through the same procedures that apply to amide couplings[3] (acyl halide formation and then addition of carboxylates). New protocols offering the formation of anhydrides directly from the corresponding carboxylic acids along with the direct formation of amides in a one-pot process are of interest for development.[4]

Photoredox catalysis has emerged as a powerful tool in the development of new organic transformations, especially in forming C–C, C–N, and C–O bonds.[5] Vilsmeier–Haack reagents for useful organic transformations can be generated with photoredox catalysis;[6,7] however, studies among our group found that generation of the Vilsmeier–Haack reagent without use of a photocatalyst is possible from the irradiation of CBr_4 with UVA light (365 nm LED) in DMF under an air atmosphere.[8] Notably, visible light, in comparison, was unable to achieve this transformation. This was used as a synthetically facile route to bromoalkanes from alcohols, which was applicable to a one-pot deoxygenation protocol.[8b,9] Taking this into consideration, we sought to apply the photogeneration of Vilsmeier–Haack reagents from UVA and CBr_4 in a one-pot protocol for the synthesis of amides from readily available carboxylic acids and amines.

The formation of symmetric anhydrides was first optimized in order to minimize the reagents used (Table 1). Treating *p*-anisic acid with 1 equiv of CBr_4 and 2 equiv of 2,4,6-trimethylpyridine (collidine) in DMF were the conditions that gave anhydride product in the most reagent-minimizing protocol with among the best yields (entries 1–3). The reaction was found to occur quickly, within 30 min, as indicated

Table 1. Optimization of Symmetric Anhydrides



entry	CBr_4 (equiv)	collidine (equiv)	(%)[a]
1	1.0	5.0	95
2	0.5	5.0	78
3	1.0	2.0	91
4	0.5		9
5	1.0	2.0	n.r.[b]
6	1.0	2.0	n.r.[c]
7		2.0	n.r.

[a] ^{1}H NMR yield with mesitylene as internal standard. [b] Without irradiation; 80 °C overnight. n.r. = no reaction. [c] Using visible light.

Received: January 1, 2015
Published: February 17, 2015

DOI: 10.1021/acs.joc.5b00003
J. Org. Chem. 2015, 80, 2874–2878

by the precipitation of collidine hydrobromide. Removal of collidine resulted in little product formation (entry 4). Control experiments were performed that demonstrated that no reaction occurred upon heating at 80 °C without light irradiation in the presence of CBr_4 (entry 5) or UVA irradiation in the absence of CBr_4 (entry 7). Notably, the transformation does not react under visible light irradiation (410 nm LED, entry 6).

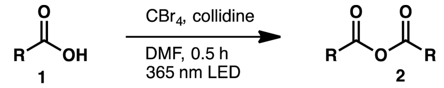
Having these conditions in hand, we established the scope of the transformation using a wide array of carboxylic acids (Table 2). Nonaromatic carboxylic acids including long chains, primary, secondary, and tertiary *α*-centers were converted in nearly quantitative yields, forming stable anhydrides **2b−d** and **2h** (entries 1−3 and 7). The reaction proved to be tolerant to alkenes and alkynes; the corresponding anhydrides **2d−f** were obtained in 75 to 98% yields (entries 4−6)

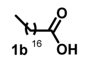
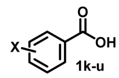
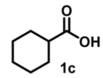
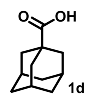
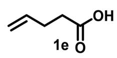
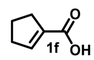
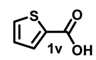
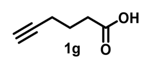
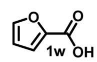
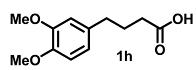
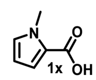
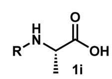
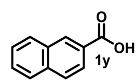
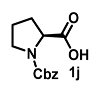
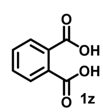
Interestingly, *N*-Boc and *N*-CBz protected L-alanine showed only degradation (entry 8); however, Cbz protected L-proline was fully converted to the corresponding anhydride **2j** (entry 9).[10] This may be attributed to instability of the anhydride formed. Various aromatic carboxylic acids were screened; a wide variety of functionality is tolerated in good yields, including OMe, *t*-Bu, halides, CF_3, naphthyl, and, to some extent, ortho and meta substitution (entries 10−20 and 24). 2-Carboxylic acid substituted heterocycles thiophene **2v**, furan **2w**, and *N*-methylpyrrole **2x** were also compatible with this method (entries 21−23). Phthalic acid also converted quantitatively to phthalic anhydride **2z** (entry 25), in an intramolecular version of this transformation.

The method showed a robust general applicability; however, isolation of many aromatic anhydrides resulted in some degradation or loss of product. Often, these compounds are used in amide couplings as the coupling partner for an amine. It was reasoned that a one-pot procedure for the coupling of these anhydrides to an amine should be developed to avoid degradation of the anhydride through work up steps. An optimization of the bases added to the reaction (Table 3) showed that 3 equiv of carboxylic acid, 5 equiv of collidine, and 1 equiv of DMAP furnished the best yield of amide formation (**3**) in the coupling of carboxylic acid **1c** and piperidine using CBr_4 with UVA LED light in DMF (entry 9). The analogous method using $[Ru(bpy)_3](PF_6)_2$ (5 mol %) with visible light (CFL light) gave little formation of either anhydride or amide product, 9% (entry 11). More importantly, the same reaction without $[Ru(bpy)_3](PF_6)_2$ gave a similar yield, 7% (entry 12). This may be due to the intensity of these lights being relatively weak compared to high-powered LED systems. A high-powered 410 nm LED was used, giving 12% yield with $[Ru(bpy)_3](PF_6)_2$, but it also yielded 8% without the photocatalyst (entries 13 and 14). One aspect of using more powerful lighting sources is that background activation (reaction with light source in the absence of photocatalyst, as shown in this study) may occur, which circumvents the need for photoredox catalysts. Also, the excited state of $[Ru(bpy)_3](PF_6)_2$ may be quenched by the amine in solution, which does not result in product forming pathways. For these reasons, a photomediated method for the combination of carboxylic acids with amines without a photocatalyst gives the best conditions for amide synthesis.

An extension of the amide protocol also showed promising results, (Table 4). Carboxylic acids functionalized with cyclohexane, phenyl, and 4-CF_3-phenyl were chosen to represent alkyl, aryl, and electron-withdrawing functionalities. These were matched with *n*-butylamine, piperidine, and aniline

Table 2. Formation of Symmetric Anhydrides from Carboxylic Acids[a]



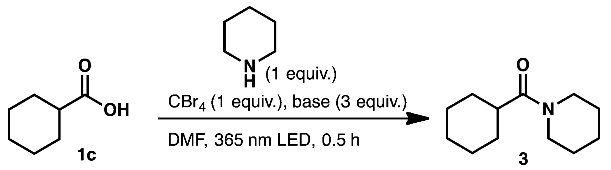
Entry	Subs.	(%)[b]	Entry	Subs.	(%)[b]
	Non-Aromatic			Aromatic	
1	 1b	99		 1k-u	
			10	X = H	88, 68[c]
			11	4-tBu	70
			12	4-F	54
2	 1c	99	13	4-Br	95
			14	4-CF_3	42
3	 1d	99	15	3-Br	53
			16	2-OMe	81
4	 1e	75	17	2-Br	54
			18	3,4,5-OMe	65
			19	3,5-CF_3	59
			20	2,4,6-Me	45
5	 1f	98	21	 1v	85
6	 1g	78	22	 1w	62
7	 1h	80	23	 1x	45
8	 1i, R = Boc, CBz	Deg.	24	 1y	63
9	 1j	99	25	 1z	99

[a]General conditions: carboxylic acid (1 equiv), DMF (0.2 M), collidine (2 equiv), and, lastly, CBr_4 (1 equiv) were added to screw top vial, sealed, and irradiated for 0.5 h with a 365 nm LED. [b]^{1}H NMR yield with mesitylene as standard. [c]1.0 g scale of benzoic acid in a 150 mL cylindrical Pyrex vessel.

to represent primary, secondary, and aromatic amines. Couplings of these compounds all proceeded in yields ranging from 34 to 98%. Interestingly, the examples using 4-CF_3-benzoic acid for amide couplings obtained much higher yields of the amide products **4f−h** (entries 6−8) as compared to isolation of the corresponding anhydride **2n** (cf. Table 2, entry 14). Benzoic acid was coupled with L-ala-OMe, which showed that amino acid derivatives **4i** retain their configuration throughout the reaction with 99:1 e.r. (entry 9), where racemization plagues many protocols.[11] Using *N*-Cbz-L-ala as carboxylic acid coupled with *n*-butylamine, conservation of

DOI: 10.1021/acs.joc.5b00003
J. Org. Chem. 2015, 80, 2874−2878

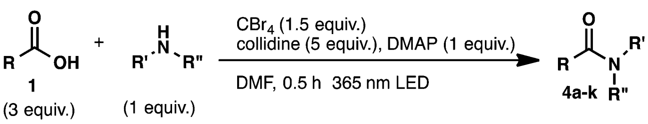
Table 3. Optimization of One-Pot Amide Formation



entry	base	(%)[a]
1	collidine	22
2	DMAP	22
3	DABCO	16
4	imidazole	6
5	pyridine	10
6	DBU	5
7	DIPEA	11
8	collidine	27[b]
9	collidine	61[b,c], 38[d]
10	collidine	11[b,e]
11	2,6-lutidine	9[f]
12	2,6-lutidine	7[g]
13	2,6-lutidine	12[h]
14	2,6-lutidine	8[i]

[a] ^{1}H NMR yield with mesitylene as standard, based on amine. [b] 1 equiv of DMAP added. [c] 3 equiv of **1c**, 5 equiv of collidine, 1.5 equiv of CBr_4. [d] 1.0 g scale of piperidine in a 150 mL cylindrical Pyrex vessel using same equivalents as those in entry 9. [e] 3 equiv of piperidine and 5 equiv of collidine; yield based on carboxylic acid. [f] $[Ru(bpy)_3](PF_6)_2$ 5 mol %, Ar degas, CFL light 97 h. [g] No photocatalyst, Ar degas, CFL light 97 h. [h] $[Ru(bpy)_3](PF_6)_2$ 5 mol %, Ar degas, 410 nm LED, 0.5 h. [i] No photocatalyst, Ar degas, 410 nm LED, 0.5 h.

Table 4. One-Pot Amidation Protocol



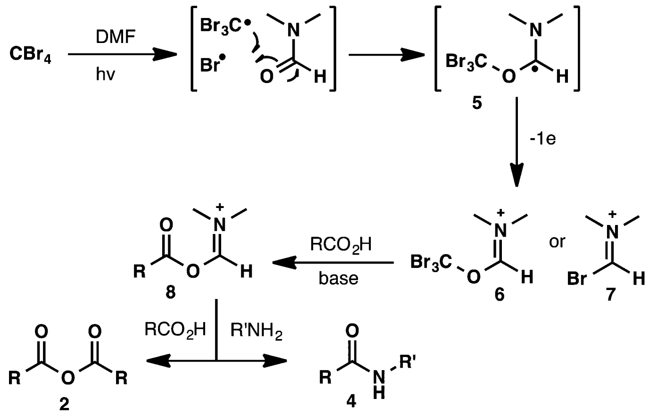
entry	R	N(R′)R″	product (yield %)[a]
1	Cy	n-BuNH$_2$	**4a** (98)
2	Cy	PhNH$_2$	**4b** (63)
3	Ph	piperidine	**4c** (80)
4	Ph	n-BuNH$_2$	**4d** (86)
5	Ph	PhNH$_2$	**4e** (75)
6	4-CF$_3$Ph	piperidine	**4f** (90)
7	4-CF$_3$Ph	n-BuNH$_2$	**4g** (98)
8	4-CF$_3$Ph	PhNH$_2$	**4h** (94)
9	Ph	L-ala-OMe	**4i** (34)[b]
10	*N*-Cbz-L-ala	n-BuNH$_2$	**4j** (92)[b]
11	*N*-Cbz-L-ala	L-ala-OMe	**4k** (94)[c]

[a] Isolated yield, based on amine. [b] e.r. = 99:1. [c] d.r. > 20:1, determined by ^{1}H NMR analysis.

enantiopurity was also observed with e.r. = 99:1, in 92% yield (entry 10). Coupling of L-ala-OMe and *N*-Cbz-L-ala as carboxylic acid demonstrated that the chirality of both centers is retained, with d.r. > 20:1 and in 94% yield.

Mechanistic consideration of this transformation is described in Scheme 1. Irradiation of CBr_4 produces an electrophilic radical, $^{\bullet}CBr_3$, which, upon addition to DMF, generates the radical intermediate **5**. Under these reaction conditions, **5** is readily oxidized to produce the Vilsmeier−Haack reagents **6** or **7**.[6−8] In the presence of carboxylic acid, the latter is converted to intermediate **8**. At this point, intermediate **8** can be converted to corresponding anhydride **2** or amide **4**. The formation of amide **4** through a transient anhydride intermediate **2** could be also considered.

Scheme 1. Proposed Mechanism



In summary, the photogeneration of Vilsmeier−Haack reagents from irradiation of CBr_4 with UVA light in DMF has been shown to be a useful method for the generation of symmetric anhydrides. This process is conveniently applicable to a one-pot synthesis of amides from readily available carboxylic acids and amines, without need of a photoredox catalyst. These studies not only exhibit the importance of photochemical transformations in the synthesis of amide bonds but also the power of conducting control reactions and light-source optimization in developing fast, efficient, and reagent-minimizing methods in organic synthesis.

■ EXPERIMENTAL SECTION

General Information. All reactions were performed under atmospheric air (unless otherwise noted) in Pyrex glassware equipped with a magnetic stir bar, capped with a septum. DMF was filtered using a purification system. Commercial reagents were used without further purification. Reactions were monitored by thin-layer chromatography (TLC) analysis. TLC plates were viewed under UV light and stained with potassium permanganate or *p*-anisaldehyde staining solution. ^{1}H NMR spectra were recorded on 300 or 400 MHz in chloroform-*d*, and chemical shifts are reported in ppm referenced to residual undeuterated solvent. Data are reported as follows: chemical shift, multiplicity, coupling, integration. ^{13}C NMR spectra were recorded on 75 or 101 MHz. Optical rotations were recorded at 589 nm with 0.1 dm/2 mL sample cell. Retention of configuration was determined by running an analogous reaction with racemic mixtures of either amine or acid with respect to the amide couplings, with workup in the usual way. Samples were diluted with 5% *i*-PrOH in hexane and run on a chiral HPLC; chromatographs are available in the Supporting Information (column: AD-H, 5% *i*-PrOH/hexanes, 1.0 mL/min, over 60 min).

General Procedure 1 (GP1). *Preparation of Symmetric Anhydrides from Carboxylic Acids.* To an 8 mL Pyrex screw-top reaction vessel were added substrate (0.3 mmol, 1.0 equiv) and dimethylformamide (1.5 mL, 0.2 M) and then 2,4,6-trimethylpyridine (0.6 mmol, 2.0 equiv) and carbontetrabromide (0.3 mmol, 1.0 equiv). The reaction mixture was capped and irradiated with a UVA (365 nm) LED at a distance of 1 cm for 30 min. The resulting mixture was poured into a separatory funnel containing 25 mL of a 3:1 mixture of diethyl ether and hexanes (ethyl acetate was added for compounds that needed further solubility). This was washed with water, where the combined aqueous fractions were re-extracted with 25 mL of diethyl ether. The combined organic portions were washed with saturated sodium bicarbonate and brine and dried over sodium sulfate. The solution was concentrated in vacuo, and products were weighed for

DOI: 10.1021/acs.joc.5b00003
J. Org. Chem. 2015, 80, 2874−2878

crude yields and then were added an internal standard (mesitylene), where yields were determined with proton NMR by comparison to literature precedence.

General Procedure 2 (GP2). *Preparation of Amides from Carboxylic Acids and Amines.* To an 8 mL Pyrex screw-top reaction vessel were added carboxylic acid (0.6 mmol, 3.0 equiv), amine (0.2 mmol, 1.0 equiv), and dimethylformamide (1.0 mL, 0.2 M) and then 2,4,6-trimethylpyridine (1.0 mmol, 5.0 equiv), DMAP (0.2 mmol, 1.0 equiv), and carbontetrabromide (0.3 mmol, 1.5 equiv). The reaction mixture was capped and irradiated with a UVA (365 nm) LED at a distance of 1 cm for 30 min. The resulting mixture was poured into a separatory funnel containing 25 mL of ethyl acetate. This was washed with 1 M HCl, where the combined aqueous fractions were re-extracted with 25 mL of ethyl acetate. The combined organic portions were washed with saturated sodium bicarbonate and brine and dried over sodium sulfate. Products were further purified by column chromatography (0−100% EtOAc/Hex), and the relevant fractions were combined, concentrated in vacuo, and characterized by NMR by comparison to literature precedence.

Compounds **2a**−**g** and **2k**−**z** were synthesized according to GP1 and characterized by NMR comparison.[12] Compounds **3** and **4a**−**k** were synthesized according to GP2 and characterized by NMR comparison.[12]

*4-(3,4-Dimethoxyphenyl)Butanoic Anhydride (**2h**): Synthesized According to GP1.* IR (neat, cm^{-1}): 2933(m), 2836(w), 1813(s), 1745(s), 1648(m), 1591(s), 1514(vs), 1450(s), 1416(s). ^1H NMR (300 MHz, $CDCl_3$): δ 6.82−6.75 (m, 2 H), 6.75−6.65 (m, 4 H), 3.87 (s, 6 H), 3.85 (s, 6 H), 2.63 (t, J = 7.5 Hz, 4 H), 2.44 (t, J = 7.3 Hz, 4 H), 1.97 (quint, J = 7.4 Hz, 4 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.2 (2 × C), 148.8 (2 × C), 147.3 (2 × C), 133.4 (2 × C), 120.2 (2 × CH), 111.6 (2 × CH), 111.2 (2 × CH), 55.8 (2 × CH_3), 55.7 (2 × CH_3), 34.2 (2 × CH_2), 34.2 (2 × CH_2), 25.8 (2 × CH_2) ppm. HRMS (EI) m/z calcd for $C_{24}H_{30}O_7$ [M^+], 430.1992; found, 430.1993.

*(R)-1-((Benzyloxy)carbonyl)pyrrolidine-2-carboxylic Anhydride (**2j**): Synthesized According to GP1.* IR (neat, cm^{-1}): 2995(m), 2882(w), 1827(s), 1745(s), 1697(vs) (overlapping), 1411(s), 1352(vs). ^1H NMR (400 MHz, $CDCl_3$): δ 7.45−7.23 (m, 10 H), 5.25−5.03 (m, 4 H), 4.51−4.28 (m, 2 H), 3.72−3.42 (m, 4 H), 2.22−1.84 (m, 8 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ 167.7, 167.6, 167.5, 167.4 (2 × C, rotamers), 155.9, 154.8, 154.6, 153.9 (2 × C, rotamers), 136.8, 136.6, 136.4, 136.2 (2 × C, rotamers), 128.4, 128.4, 128.2, 128.0, 128.0, 127.9, 127.9, 127.8, 127.7, 127.5, 127.4 (10 × CH, rotamers), 67.3, 67.3, 67.2, 67.1 (2 × CH_2, rotamers), 59.7, 59.6, 59.3, 59.2 (2 × CH, rotamers), 46.9, 46.9, 46.4, 46.3 (2 × CH_2, rotamers), 31.0, 30.2, 30.2, 30.1, 29.6, 29.5, 29.0, 28.9 (2 × CH_2, rotamers), 24.2, 24.2, 23.4, 23.3 (2 × CH_2, rotamers) ppm. HRMS (EI) m/z calcd for $C_{26}H_{28}N_2O_7$ [M^+], 480.1897; found, product was unstable. $[\alpha]_D^{20}$ = −32.1° (c 1.0, EtOH).

*Methyl Benzoyl-L-alaninate (**4i**).* Synthesized according to GP2 and characterized according to NMR comparison.[12] $[\alpha]_D^{20}$ = +30.2° (c 1.0, $CHCl_3$).

*Benzyl (S)-(1-(Butylamino)-1-oxopropan-2-yl)carbamate (**4j**).* Synthesized according to GP2 and characterized according to NMR comparison.[12] $[\alpha]_D^{20}$ = −6.8° (c 1.0, EtOH).

*Z-L-ala-L-ala-OMe (**4k**).* Synthesized according to GP2 and characterized according to NMR comparison.[12] $[\alpha]_D^{20}$ = −49.0° (c 1.0, MeOH).

■ ASSOCIATED CONTENT

Supporting Information

Chiral-HPLC data for hydrolysis of **2j** yielding *Z*-L-proline and compounds **4i**−**k** along with ^1H and ^{13}C NMR for compounds **2h**, **2j**, **3**, and **4a**−**k**. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: lbarriau@uottawa.ca.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the Natural Sciences and Engineering Research Council (for Accelerator, Discovery and CREATE grants to L.B.) and the University of Ottawa (for a University Research Chair to L.B.) for support of this research. Acknowledgement is also made to the donor of the American Chemical Society Petroleum Research Fund for support of this research. T.M. thanks NSERC (CREATE on medicinal chemistry and biopharmaceutical development).

■ REFERENCES

(1) (a) El-Faham, A.; Albericio, F. *Chem. Rev.* **2011**, *111*, 6557. (b) Pattabiraman, V. R.; Bode, J. W. *Nature* **2011**, *480*, 471.

(2) (a) Schotten, C. *Ber. Dtsch. Chem. Ges.* **1884**, *17*, 2544. (b) Baumann, E. *Ber. Dtsch. Chem. Ges.* **1886**, *19*, 3218. (c) Fischer, E. *Ber. Dtsch. Chem. Ges.* **1903**, *36*, 2982. (d) Zuffanti, S. *J. Chem. Educ.* **1948**, *25*, 481. (e) Valeur, E.; Bradley, M. *Chem. Soc. Rev.* **2009**, *38*, 606. (f) Joullie, M. M.; Lassen, K. M. *Arkivoc* **2010**, *VIII*, 189.

(3) (a) Rambacher, P.; Make, S. *Angew. Chem.* **1968**, *80*, 487. (b) Plusquellec, D.; Roulleau, F.; Lefeuvre, M.; Brown, E. *Tetrahedron* **1988**, *44*, 2471.

(4) (a) Ferris, A. F.; Emmons, W. D. *J. Am. Chem. Soc.* **1953**, *75*, 232. (b) Hata, T.; Tajima, K.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1968**, *41*, 2746. (c) Lee, J. C.; Cho, Y. H.; Lee, H. K.; Cho, S. H. *Synth. Commun.* **1995**, *25*, 2877. (d) Kaminski, Z. J.; Kolesinka, B.; Malgorzata, M. *Synth. Commun.* **2004**, *34*, 3349. (e) Liu, J.; West, K. R.; Bondy, C. R.; Sanders, J. K. M. *Org. Biomol. Chem.* **2007**, *5*, 778. (f) Bartoli, G.; Bosco, M.; Carlone, A.; Dalpozzo, R.; Marcantoni, E.; Melchiorre, P.; Sambri, L. *Synthesis* **2007**, *22*, 3489. (g) Strukil, V.; Bartolec, B.; Portada, T.; Dilovic, I.; Halasz, I.; Bargetic, D. *Chem. Commun.* **2012**, *48*, 12100. (h) Bai, J.; Zambron, B.; Vogel, P. *Org. Lett.* **2014**, *16*, 604 and references cited therein.

(5) For recent reviews, see (a) Prier, C. K.; Rankic, D. A.; MacMillan, D. W. C. *Chem. Rev.* **2013**, *113*, 5322. (b) Schultz, D. M.; Yoon, T. P. *Science* **2014**, *343*, 985.

(6) Dai, C.; Narayanam, J. M. R.; Stephenson, C. R. J. *Nat. Chem.* **2011**, *3*, 140.

(7) (a) Konieczynska, M. D.; Dai, C.; Stephenson, C. R. J. *Org. Biomol. Chem.* **2012**, *10*, 4509. (b) Srivastava, V. P.; Yadav, A. K.; Yadav, L. D. S. *Synlett* **2014**, *25*, 665. (c) Yadav, A. K.; Srivastava, V. P.; Yadav, L. D. S. *RSC Adv.* **2014**, *4*, 4181.

(8) (a) Nishina, Y.; Ohtani, B.; Kikushima, K. *Beilstein J. Org. Chem.* **2013**, *9*, 1663. (b) McCallum, T.; Slavko, E.; Morin, M.; Barriault, L. *Eur. J. Org. Chem.* **2015**, *1*, 81. Information on photochemical equipment and set-up can be obtained in the Supporting Information of this publication.

(9) For reduction of unactivated bromoalkanes, see Revol, G.; McCallum, T.; Morin, M.; Gagosz, F.; Barriault, L. *Angew. Chem., Int. Ed.* **2013**, *52*, 13342.

(10) Anhydride arising from *N*-Cbz protected L-proline was hydrolyzed, where the resulting acid was analyzed by chiral HPLC, showing retention of L configuration in 98.5:1.5 e.r. (L/D) (see the Supporting Information).

(11) Bodansky, M. *Principles of Peptide Synthesis*; Springer-Verlag: New York, 1984.

(12) Literature for NMR comparison of compounds **2b**,**k**,**r**, see 4d. For **2c**, see Tsang, W.; Ahmed, N.; Hemming, K.; Page, M. *Org. Biomol. Chem.* **2007**, *5*, 3993. For **2d**, see 3b. For **2e**, see Ellervik, U.; Magnusson, G. *Acta Chem. Scand.* **1993**, *47*, 826. For **2f**, see Trost, B. M.; Whitman, P. J. *J. Am. Chem. Soc.* **1974**, *96*, 7421. For **2g**, see Moody, C.; Shah, P. *J. Chem. Soc., Perkin Trans. 1* **1988**, 3249. For **2a**,**l**,**m**,**q**,**u**, see Li, Y.; Xue, D.; Wang, C.; Liu, Z.; Xiao, J. *Chem. Commun.* **2012**, *48*, 1320. For **2n**,**p**,**v**,**w**,**y**, see Cirriez, V.; Rasson, C.; Riant, O. *Adv. Synth. Catal.* **2013**, *355*, 3137. For **2o**,**t**, see Shiina, I.

DOI: 10.1021/acs.joc.5b00003
J. Org. Chem. 2015, 80, 2874−2878

Tetrahedron **2004**, *60*, 1587. For **2s**, see Daskiewicz, J.; Depeint, F.; Viornery, L.; Bayet, C.; Comte-Sarrazin, G.; Comte, G.; Gee, J. M.; Johnson, I. T.; Ndjoko, K.; Hostettmann, K.; Barron, D. *J. Med. Chem.* **2005**, *48*, 2790. For **2x**, see Robert, J. M. H.; Robert-Piessard, S.; Courant, J.; Le Baut, G.; Robert, B.; Lang, F.; Petit, J. Y.; Grimaud, N.; Welin, L. *Eur. J. Med. Chem.* **1995**, *30*, 915. For **2z**, see Hwang, J.; Prakash, G.; Olah, G. *Tetrahedron* **2000**, *56*, 7199. For **3**, see Wannberg, J.; Larhed, M. *J. Org. Chem.* **2003**, *68*, 5750. For **4a**,**d**, see Hans, J. J.; Driver, R. W.; Burke, S. D. *J. Org. Chem.* **2000**, *65*, 2114. For **4b**, see Liu, H.; Yan, N.; Dyson, P. J. *Chem. Commun.* **2014**, *50*, 7848. For **4c**, see Toledo, H.; Pisarevsky, E.; Abramovich, A.; Szpilman, A. M. *Chem. Commun.* **2013**, *49*, 4367. For **4e**, see Murthy, S. N.; Madhav, B.; Reddy, V. P.; Nageswar, Y. V. D. *Adv. Synth. Catal.* **2010**, *352*, 3241. For **4f**, see Khan, B. A.; Buba, A. E.; Gooßen, L. J. *Chem.—Eur. J.* **2012**, *18*, 1577. For **4g**, see Kaiser, N.-F. K.; Hallberg, A.; Larhed, M. *J. Comb. Chem.* **2002**, *4*, 109. For **4h**, see Perry, R. J.; Wilson, B. D. *J. Org. Chem.* **1996**, *61*, 7482. For **4i**, see Reddy, K. R.; Maheswari, C. U.; Venkateshwar, M.; Kantam, M. L. *Eur. J. Org. Chem.* **2008**, *2008*, 3619. For **4j**, see Kolesinska, B.; Kaminski, Z. J. *Org. Lett.* **2009**, *11*, 765. For **4k**, see Brown, D. W.; Campbell, M. M.; Walker, C. V. *Tetrahedron* **1983**, *39*, 1075.

DOI: 10.1021/acs.joc.5b00003
J. Org. Chem. 2015, 80, 2874−2878