Acyl Radicals

Deutsche Ausgabe: DOI: 10.1002/ange.201506432
Internationale Ausgabe: DOI: 10.1002/anie.201506432

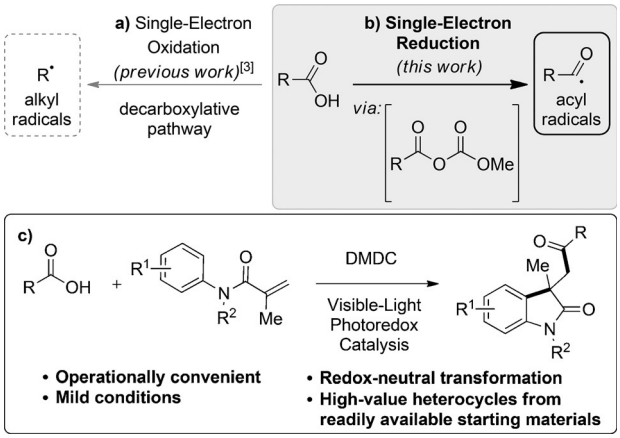
Acyl Radicals from Aromatic Carboxylic Acids by Means of Visible-Light Photoredox Catalysis

*Giulia Bergonzini, Carlo Cassani, and Carl-Johan Wallentin**

Abstract: *Simple and abundant carboxylic acids have been used as acyl radical precursor by means of visible-light photoredox catalysis. By the transient generation of a reactive anhydride intermediate, this redox-neutral approach offers a mild and rapid entry to high-value heterocyclic compounds without the need of UV irradiation, high temperature, high CO pressure, tin reagents, or peroxides.*

Carboxylic acids are abundant and inexpensive starting materials readily available in great structural diversity. For this reason, continuous efforts have been made to engage this class of compounds in novel catalytic organic transformations.[1] In more recent years, visible-light photoredox catalysis has emerged as a benign and powerful tool in organic synthesis, and novel strategies targeting carboxylic acids as building blocks have been developed.[2] Those methods rely on photo-induced oxidation of carboxylates to generate, after CO_2 extrusion, reactive alkyl radical intermediates (Scheme 1 a).[3] Capitalizing upon the high synthetic potential of visible-light photoredox catalysis, we questioned whether carboxylic acids might be used for the generation of acyl radicals by single-electron reduction (Scheme 1 b).[4] This would offer an unprecedented synthetic method that extends beyond the existing routes to access acyl radicals, which are often characterized by harsh conditions (UV irradiation, high temperature, high CO pressure, tin reagents, or peroxides) or the need of pre-generated acyl radical precursors such as telluroesters, selenoesters, and thioesters.[3j,5]

We envisioned that transient mixed anhydride intermediates, obtained from simple carboxylic acids in the presence of dimethyl dicarbonate (DMDC),[6] could be engaged as oxidative quenchers of a photocatalyst to generate the desired acyl radical species, along with CO_2 and methanoate as the only byproducts.[7,8] This would provide carboxylic acids with orthogonal redox reactivity under mild photocatalytic conditions and a novel entry to a broader spectrum of accessible products.



Scheme 1. a,b) Generation of reactive radical species from simple carboxylic acids by means of visible-light photoredox catalysis. c) Photocatalyzed redox-neutral acylarylation of methacrylamides using benzoic acids as starting material. DMDC = dimethyl dicarbonate.

At the onset of our investigation, we tested our idea for the formation of 3,3-disubstituted 2-oxindoles by 1,2-acylarylation of alkenes (Scheme 1 c). The 3,3-disubstituted 2-oxindoles containing the carbonyl functionality are common structural motifs in pharmaceutical and bioactive natural products, and represent versatile intermediates in organic synthesis.[9]

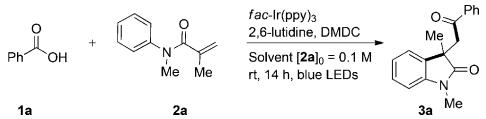
Consequently, in the last few years, the development of efficient synthetic methods for the synthesis of 3,3-disubstituted 2-oxindoles has received increased interest. Among these, 1,2-acylarylation of methacrylamides has emerged as a particularly interesting approach.[10] However, the use of stoichiometric amounts of external oxidants, high temperature, or high-energy UV light represent considerable disadvantages of the procedures.

Herein we report the first redox-neutral approach for the mild visible-light-mediated tandem acylarylation of olefines using carboxylic acids as an acyl radical source. We first explored the proposed acylarylation reaction using benzoic acid **1a** and *N*-methyl-*N*-phenylmethacrylamide **2a** as the model substrates in the presence of the photocatalyst, DMDC, and 2,6-lutidine under visible-light irradiation (Table 1). We were pleased to find that the strongly reducing *fac*-$Ir(ppy)_3$ provided the desired product **3a** in excellent yield (entry 1). In contrast, much weaker reductants such as $[Ir(ppy)_2(dtbbpy)]^+$ and $[Ru(bpy)_3]^{2+}$ were unable to promote the reaction (Supporting Information, Table S1, entries 1 and

[*] Dr. G. Bergonzini,[+] Dr. C. Cassani,[+] Dr. C.-J. Wallentin
Department of Chemistry and Molecular Biology,
Gothenburg University
41258 Gothenburg (Sweden)
E-mail: carl.wallentin@chem.gu.se
[+] These authors contributed equally to this work.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201506432.

Table 1: Selected optimization studies.[a]



1a 2a 3a

Entry	*fac*-Ir(ppy)$_3$ [mol%]	DMDC [equiv]	2,6-lutidine [equiv]	Solvent	Yield [%][b]
1	1	4	2	DMA	>95
2[c,d]	**0.5**	**3**	**0.5**	**DMF**	**>95**
3[c,e]	0.5	3	0.5	DMF	<5
4[c,e,f]	0.5	3	0.5	DMF	88

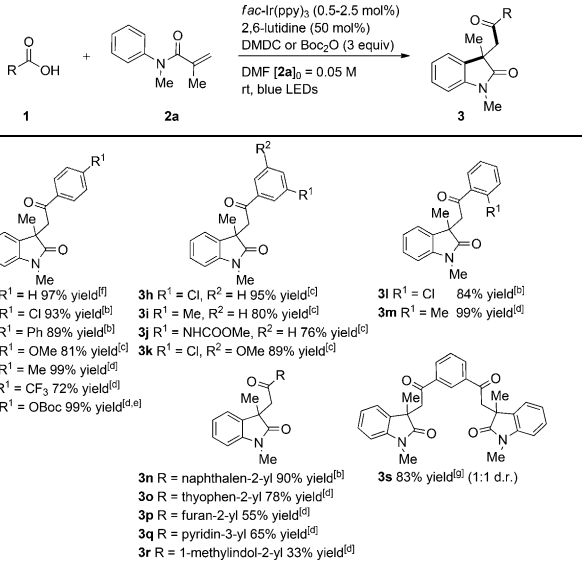
[a] Reactions performed on 0.1 mmol scale using 2 equiv of **1a**. [b] Determined by ^{1}H NMR using 2,5-dimethylfuran as internal standard. [c] Performed with 1.5 equiv of **1a**; $[\mathbf{2a}]_0 = 0.05$ M. [d] Reaction time = 6 h; [e] Reaction performed with 3 equiv of Boc_2O instead of DMDC; [f] Addition of 1 equiv of $MgCl_2$. DMA = *N*,*N*-dimethylacetamide; DMF = *N*,*N*-dimethylformamide.

2). Control experiments performed in the absence of the photocatalyst, the dicarbonate or the light source completely impeded any reactivity (Supporting Information, Table S1, entries 4–6). Fine tuning of the reaction conditions provided the desired product quantitatively while also decreasing reaction time and catalyst loading (Table 1, entry 2, Method A). When di-*tert*-butyl dicarbonate (Boc_2O) was used instead of DMDC to generate the corresponding mixed anhydride, only traces of product **3a** were found (entry 3). However, upon Lewis acid activation of Boc_2O with the addition of $MgCl_2$ the product was obtained in high yield (entry 4).[11]

With the optimized conditions in hand (Method A), we examined the scope of the acid component.

As shown in Table 2, the reaction proceeds in good to excellent yield with a broad range of benzoic acids bearing different substituents in the *para*-, *meta*-, and *ortho*-position as well as carboxylic acids with extended aromatic systems (**3a**–**3n**). *Ortho*- and *para*-methyl, as well as *para*-hydroxy and *para*-trifluoromethyl benzoic acid, performed poorly under the optimized conditions, and fast conversion of these acids into the corresponding unreactive methyl esters was observed.[12] However, they could be efficiently employed (**3e**–**3g**, **3m**) by replacing DMDC with Boc_2O together with the use of 1 equiv of $MgCl_2$ and 2.5 mol% of *fac*-Ir(ppy)$_3$ over 48 h (Method B).[13] Electron-rich carboxylic acids, expected to be more difficult to reduce, can also serve to generate acyl radicals by simply increasing catalyst loading and reaction time (**3d**, **3i**–**k**). Notably, carboxylic acids bearing free hydroxy and amino groups smoothly furnished oxindoles **3g** and **3j** as carbonate and carbamate derivatives, providing an efficient and mild acylarylation/protection procedure in one-pot. Heteroaromatic substrates such as 2-thiophene, 2-furoic, nicotinic, and 1-methylindole-2-carboxylic acid proved to be valuable reaction partners, generating products **3o**–**3r** in moderate to good yields. Isophtalic acid could also be employed as a substrate furnishing product **3s** by a consecutive difunctionalization. Furthermore, the optimized method was successfully applied to five-fold scale-up of the reaction providing product **3a** in excellent yield (97%).[14] 2-Oxo-2-

Table 2: Carboxylic acid scope.[a]

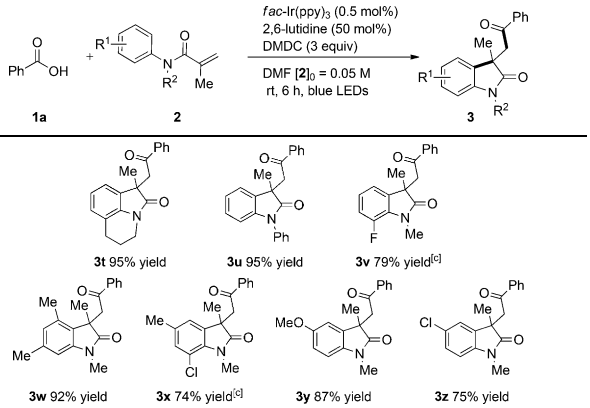


[a] Reactions performed on 0.2 mmol scale. Yield of isolated product. [b] Reaction performed using 0.5 mol% of *fac*-Ir(ppy)$_3$ and 3 equiv of DMDC over 6 h (Method A). [c] Method A using 2.5 mol% of *fac*-Ir(ppy)$_3$ over 14 h. [d] Reaction performed with 2.5 mol% of *fac*-Ir(ppy)$_3$, 3 equiv of Boc_2O and 1 equiv of $MgCl_2$ over 48 h (Method B). [e] 4 equiv of Boc_2O were used. [f] Reaction carried out with Method A on 1 mmol scale; reaction time = 10 h. [g] See the Supporting Information for details.

phenylacetic acid was also tolerated as a substrate, giving **3a** in 30% yield.[15] However, when aliphatic carboxylic acids such as 1-phenylcyclopentanecarboxylic acid, 2-methoxy-2-phenylacetic acid, and *N*-Boc-glycine were employed under the optimized conditions, no formation of the corresponding products was observed.[16]

We next turned to evaluate the scope of the olefin (Table 3). A range of methacrylates successfully gave access to the corresponding products in good to excellent yields (74–95%). Differently *N*-substituted phenylmethacrylamide could be used without loss of efficiency (**3t**, **3u**).

Table 3: Olefin scope.[a,b]

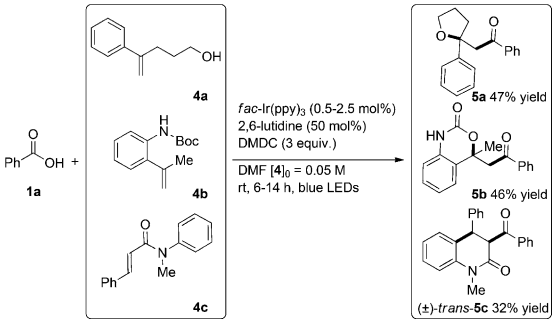


[a] Reactions performed on 0.2 mmol using Method A. [b] Yield of isolated product. [c] Reaction performed using 2.5 mol% of *fac*-Ir(ppy)$_3$ over 14 h.

Substrates bearing electron-donating groups reacted smoothly and furnished the products in excellent yields (**3w**, **3y**). Electron poor substrates reacted slower under the optimized conditions, and higher catalyst loading and reaction times were needed to obtain good yields (**3v**, **3x**).

To showcase the generality and synthetic utility of this method, we sought to employ a range of olefins beyond methacrylamides (Scheme 2).

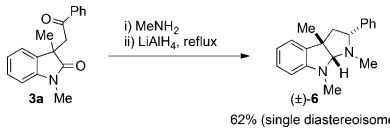
Pleasantly, we found that the procedure can be applied to styrene-type substrates **4a–c** to readily build high molecular complexity accessing diverse heterocyclic motifs **5a–c** in promising yields (Scheme 2).



Scheme 2. Acylarylation of styrene-type olefins for the generation of diverse heterocyclic scaffolds.

A further demonstration of the synthetic value of the method is given by the straightforward preparation of compound **6**, which features the hexahydropyrrolo[2,3-*b*]indole unit found in many natural products (Scheme 3).[17]

A plausible reaction mechanism (Figure 1 a) begins with the photoexcitation of *fac*-$Ir^{III}(ppy)_3$ (depicted as Ir^{III} in



Scheme 3. Preparation of derivative **6** bearing the hexahydropyrrolo-[2,3-*b*]indole core.

Figure 1 a) under visible light, to generate *fac*-$*Ir^{III}(ppy)_3$, which is a strong reductant ($E_{1/2}$ $[Ir^{IV}/*Ir^{III}] = -1.73$ V vs SCE).[2] Single-electron reduction of mixed anhydride **I** (generated in situ from carboxylic acid **1** in the presence of DMDC under basic conditions) by *fac*-$*Ir^{III}(ppy)_3$ provides *fac*-$Ir^{IV}(ppy)_3$ and radical anion **II** that, after fragmentation, delivers acyl radical **III** along with CO_2 and methanoate. Subsequently, acyl radical **III** undergoes selective radical addition to olefin **2** giving radical intermediate **IV**.[10b–g] Upon intramolecular cyclization, intermediate **V** is oxidized by *fac*-$Ir^{IV}(ppy)_3$ providing final product **3** along with the ground-state of the photocatalyst. To verify the proposed role of **I** in the catalytic cycle, we reacted isolated mixed anhydride **7** ($E_{1/2}^{red} = -1.74$ V vs SCE)[15] with olefin **2a** in the presence of the photocatalyst under visible-light (Figure 1 b) and as expected, smooth conversion into product **3a** was observed. Furthermore, a series of Stern–Volmer fluorescence quench-

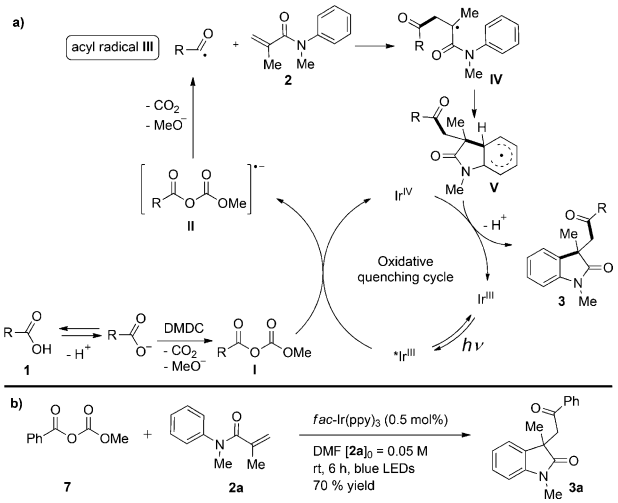


Figure 1. a) Proposed mechanism. b) Reaction performed using 0.1 mmol of **2a** and 1.5 equiv of **7**. Yield determined by ^1H NMR using 2,5-dimethylfuran as internal standard.

ing studies clearly revealed that **7** is the only molecular entity in the reaction mixture that efficiently quenches *fac*-$*Ir^{III}(ppy)_3$.[15] Together, these experiments strongly support the proposed mechanism delineated in Figure 1 a.

In conclusion, we have developed an operationally convenient visible-light photocatalytic tandem acylarylation of olefins using available aromatic carboxylic acids as starting material. The protocol presents a mild and energy-efficient system which offers a viable method for the generation of acyl radicals and their employment in C–C bonding reactions.

Acknowledgements

The Olle Engkvist Byggmästare foundation, the Wilhelm and Martina Lundgren research foundation, the Ollie and Elof foundation, the Magnus Bergvall foundation, the Adlerbertska foundation, and the Swedish Research Council are gratefully acknowledged for financial support. C.C. is grateful to the European Commission for a Marie Skłodowska-Curie fellowship (H2020-MSCA-IF-2014 n: 660668). The authors thank Pegah Sadat Nabavi Zadeh and Dr. Gert Göransson for their generous assistance with fluorescence and cyclic voltammetry experiments. The Swedish NMR Centre at the University of Gothenburg is acknowledged for instrument access and support.

Keywords: acyl radicals · acylarylation · carboxylic acids · oxindoles · photoredox catalysis

How to cite: *Angew. Chem. Int. Ed.* **2015**, *54*, 14066–14069
Angew. Chem. **2015**, *127*, 14272–14275

[1] For recent reviews, see: a) W. I. Dzik, P. P. Lange, L. J. Gooßen, *Chem. Sci.* **2012**, *3*, 2671–2678; b) T. Li, L. Huoa, C. Pulleya, A. Liu, *Bioorg. Chem.* **2012**, *43*, 2–14; c) N. Rodríguez, L. J. Gooßen, *Chem. Soc. Rev.* **2011**, *40*, 5030–5048; d) L. J. Gooßen, N. Rodríguez, K. Gooßen, *Angew. Chem. Int. Ed.* **2008**, *47*, 3100–3120; *Angew. Chem.* **2008**, *120*, 3144–3164.

[2] For recent reviews, see: a) T. Koike, M. Akita, *Inorg. Chem. Front.* **2014**, *1*, 562 – 576; b) D. A. Nicewicz, T. M. Nguyen, *ACS Catal.* **2014**, *4*, 355 – 360; c) S. Fukuzumi, K. Ohkubo, *Org. Biomol. Chem.* **2014**, *12*, 6059 – 6071; d) D. M. Schultz, T. P. Yoon, *Science* **2014**, *343*, 985; e) D. P. Hari, B. König, *Chem. Commun.* **2014**, *50*, 6688 – 6699; f) C. K. Prier, D. A. Rankic, D. W. C. MacMillan, *Chem. Rev.* **2013**, *113*, 5322 – 5363; g) D. Ravelli, M. Fagnoni, A. Albini, *Chem. Soc. Rev.* **2013**, *42*, 97 – 113; h) Y. Xi, H. Yi, A. Lei, *Org. Biomol. Chem.* **2013**, *11*, 2387 – 2403; i) M. Reckenthaeler, A. G. Griesbeck, *Adv. Synth. Catal.* **2013**, *355*, 2727 – 2744; j) M. A. Ischay, T. P. Yoon, *Eur. J. Org. Chem.* **2012**, 3359 – 3372; k) L. Shi, W. Xia, *Chem. Soc. Rev.* **2012**, *41*, 7687 – 7697; l) J. Xuan, W.-J. Xiao, *Angew. Chem. Int. Ed.* **2012**, *51*, 6828 – 6838; *Angew. Chem.* **2012**, *124*, 6934 – 6944; m) F. Teplý, *Collect. Czech. Chem. Commun.* **2011**, *76*, 859 – 917; n) J. M. Narayanam, C. R. J. Stephenson, *Chem. Soc. Rev.* **2011**, *40*, 102 – 113.

[3] a) J. Xie, P. Xu, H. Li, Q. Xue, H. Jin, Y. Cheng, C. Zhu, *Chem. Commun.* **2013**, *49*, 5672 – 5674; b) Z. Zuo, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2014**, *136*, 5257 – 5260; c) A. Noble, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2014**, *136*, 11602 – 11605; d) L. Chu, C. Ohta, Z. Zuo, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2014**, *136*, 10886 – 10889; e) Z. Zuo, D. T. Ahneman, L. Chu, J. A. Terrett, A. G. Doyle, D. W. C. MacMillan, *Science* **2014**, *345*, 437 – 440; f) C. Cassani, G. Bergonzini, C.-J. Wallentin, *Org. Lett.* **2014**, *16*, 4228 – 4231; g) A. Noble, S. J. McCarver, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2015**, *137*, 624 – 627; h) T. Chinzei, K. Miyazawa, Y. Yasu, T. Koike, M. Akita, *RSC Adv.* **2015**, *5*, 21297 – 21300; i) S. Ventre, F. R. Petronijevic, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2015**, *137*, 5654 – 5657; j) X. Wu, C. Meng, X. Yuan, X. Jia, X. Qian, J. Ye, *Chem. Commun.* **2015**, *51*, 11864 – 11867; k) Q.-Q. Zhou, W. Guo, W. Ding, X. Wu, X. Chen, L.-Q. Lu, W.-J. Xiao, *Angew. Chem.* **2015**, DOI: 10.1002/ange.201504559; *Angew. Chem. Int. Ed.* **2015**, DOI: 10.1002/anie.201504559; l) J. D. Griffin, M. A. Zeller, D. A. Nicewicz, *J. Am. Chem. Soc.* **2015**, DOI: 10.1021/jacs.5b07770.

[4] An example on the use of visible-light photoredox and nickel catalysis for the decarboxylative coupling of α-oxo acids by single-electron oxidation has been reported: L. Chu, J. M. Lipshultz, D. W. C. MacMillan, *Angew. Chem. Int. Ed.* **2015**, *54*, 7929 – 7933; *Angew. Chem.* **2015**, *127*, 8040 – 8044.

[5] For selected examples, see: a) C. Chatgilialoglu, D. Crich, M. Komatsu, I. Ryu, *Chem. Rev.* **1999**, *99*, 1991 – 2096; b) S. Esposti, D. Dondi, M. Fagnoni, A. Albini, *Angew. Chem. Int. Ed.* **2007**, *46*, 2531 – 2534; *Angew. Chem.* **2007**, *119*, 2583 – 2586; c) S. Bath, N. M. Laso, H. Lopez-Ruiz, B. Quiclet-Sire, S. Z. Zard, *Chem. Commun.* **2003**, 204 – 205; d) I. Ryu, A. Tani, T. Fukuyama, D. Ravelli, M. Fagnoni, A. Albini, *Angew. Chem. Int. Ed.* **2011**, *50*, 1869 – 1872; *Angew. Chem.* **2011**, *123*, 1909 – 1912; e) L. Lv, S. Lu, Q. Guo, B. Shen, Z. Li, *J. Org. Chem.* **2015**, *80*, 698 – 704; f) L. Benati, G. Calestani, R. Leardini, M. Minozzi, D. Nanni, P. Spagnolo, S. Strazzari, *Org. Lett.* **2003**, *5*, 1313 – 1316; g) M. Majek, A. Jacobi von Wangelin, *Angew. Chem. Int. Ed.* **2015**, *54*, 2270 – 2274; *Angew. Chem.* **2015**, *127*, 2298 – 2302; h) W. Guo, L.-Q. Lu, Y. Wang, Y.-N. Wang, J.-R. Chen, W.-J. Xiao, *Angew. Chem. Int. Ed.* **2015**, *54*, 2265 – 2269; *Angew. Chem.* **2015**, *127*, 2293 – 2297.

[6] Dimethyl dicarbonate is regarded as a benign additive since it hydrolyzes in water giving methanol and CO_2. It is currently utilized as food additive (in Europe it is listed with the E number E 242).

[7] For the generation of acyl radicals from symmetric anhydrides, see: D. Occhialini, K. Daasbjerg, H. Lund, *Acta Chem. Scand.* **1993**, *47*, 1100 – 1106.

[8] For cobalt-catalyzed addition of acyl radicals generated from symmetric anhydrides by electrochemical or chemical reduction to activated olefins, see: R. Scheffold, R. Orlinski, *J. Am. Chem. Soc.* **1983**, *105*, 7200 – 7202.

[9] a) N. R. Ball-Jones, J. J. Badillo, A. K. Franz, *Org. Biomol. Chem.* **2012**, *10*, 5165 – 5181; b) J. J. Badillo, N. V. Hanhan, A. K. Franz, *Curr. Opin. Drug Discovery Dev.* **2010**, *13*, 758 – 776; c) F. Zhou, Y.-L. Liu, J. Zhou, *Adv. Synth. Catal.* **2010**, *352*, 1381 – 1407.

[10] a) J. E. M. N. Klein, R. J. K. Taylor, *Eur. J. Org. Chem.* **2011**, 6821 – 6841; b) M.-B. Zhou, R.-J. Song, X.-H. Ouyang, Y. Liu, W.-T. Wei, G.-B. Deng, J.-H. Li, *Chem. Sci.* **2013**, *4*, 2690 – 2694; c) H. Wang, L.-N. Guo, X.-H. Duan, *Adv. Synth. Catal.* **2013**, *355*, 2222 – 2226; d) X.-H. Ouyang, R.-J. Song, J.-H. Li, *Eur. J. Org. Chem.* **2014**, 3395 – 3401; e) B. Niu, P. Xie, W. Zhao, Y. Zhou, Z. Bian, C. U. Pittman, Jr., A. Zhou, *RSC Adv.* **2014**, *4*, 43525 – 43528; f) L. Zheng, H. Huang, C. Yang, W. Xia, *Org. Lett.* **2015**, *17*, 1034 – 1037; g) R.-J. Song, Y. Liu, Y.-X. Xie, J.-H. Li, *Synthesis* **2015**, 1195 – 1209.

[11] For selected examples of Lewis acid activation of di-*tert*-butyl dicarbonate with $MgCl_2$, see: a) C. Robert, F. de Montigny, C. M. Thomas, *ASC Catal.* **2014**, *4*, 3586 – 3589; b) H. Yin, C. Zhao, H. You, K. Lin, H. Gong, *Chem. Commun.* **2012**, *48*, 7034 – 7036.

[12] For an example of decarboxylative esterification using DMDC and other dialkyl dicarbonates, see: L. Gooßen, A. Döhring, *Adv. Synth. Catal.* **2003**, *345*, 943 – 947.

[13] This behavior can be rationalized by a much slower alcoholysis of the resulting mixed anhydride intermediate.

[14] For a discussion on issues associated to the scale-up of photochemical reactions, see: J. W. Tucker, Y. Zhang, T. F. Jamison, C. R. J. Stephenson, *Angew. Chem. Int. Ed.* **2012**, *51*, 4144 – 4147; *Angew. Chem.* **2012**, *124*, 4220 – 4223.

[15] See the Supporting Information for experimental details.

[16] Lack of conjugation and thus an accompanying increased threshold for the reduction of these substrates provide a reasonable explanation for the observed absence of reactivity.

[17] a) P. Ruiz-Sanchis, S. A. Savina, F. Albericio, M. Álvarez, *Chem. Eur. J.* **2011**, *17*, 1388 – 1408; b) D. Crich, A. Banerjee, *Acc. Chem. Res.* **2007**, *40*, 151 – 161.

Received: July 13, 2015
Revised: August 26, 2015
Published online: September 25, 2015

