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Photocatalytic Reaction of Diazo Compounds with Aldehydes

K. Rybicka-Jasińska,[a] Ł. W. Ciszewski,[a,b] and D. Gryko[a,*]

[a] Institute of Organic Chemistry, Polish Academy of Sciences, Kasprzaka 44/52, 01-224 Warsaw, Poland
E-mail: dorota.gryko@icho.edu.pl
[b] Department of Chemistry, Warsaw University of Technology, Noakowskiego 3, 00-664 Warsaw, Poland

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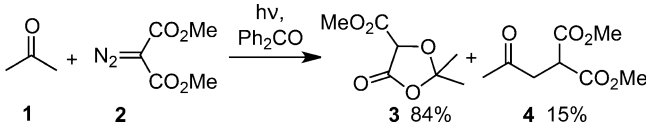
Abstract: Photocatalytic reactions of diazoacetates with aldehydes led to α-alkylated carbonyl compounds instead of the expected cyclopropane derivatives. The reaction requires a dual catalytic system – photocatalysis merged with enamine-iminium catalysis. NMR, EPR, UV/Vis, and ESI-MS analyses provided sufficient data to corroborate the proposed radical mechanism – enamine catalysis merged with photocatalysis.

Keywords: aldehydes; diazo compounds; organocatalysis; photocatalysis; radicals

Introduction

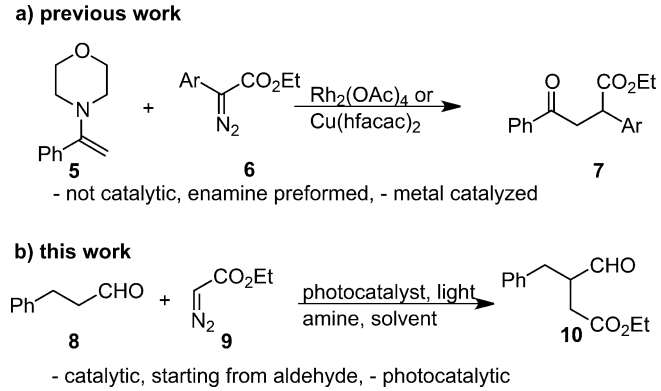
The chemistry of diazo compounds has been extensively investigated over the past decades and a variety of practical reactions such as C–H and heteroatom–H insertion,[1,2] cyclopropanation,[3,4] addition,[5,6] polymerization,[7] nucleophilic olefination,[8,9] etc. has been developed.[10–15] *However, little is known about their reactivity under light irradiation*. Light is a very powerful source of energy, a fact nature has exploited since the beginning.[16] But organic chemists have only recently started to realize the potential of light-induced transformations with effective photocycloadditions, rearrangements, cyclization, alkylation, photooxidation, and photooxygenation reactions being already developed.[17–23]

In this regard, it has been already reported that the reaction of a diazo compound with a carbonyl starting material, depending on the conditions used, follows different pathways.[24a–c] In the presence of light diazo compounds furnish carbenes in a singlet ground state *via* direct photolysis while less reactive triplet carbenes are formed in the presence of triplet-sensitizers. In this respect, Jones showed that irradiation of dimethyl diazomalonate in acetaldehyde, in the presence of benzophenone as a photosensitizer, led primarily to hydrogen abstraction giving dimethyl malonate in 83% yield.[24d] But, when the same experiment was conducted in acetone (**1**), product **3** predominated and the apparent C–H insertion also occurred giving alkylated malonate **4** in 15% yield (Scheme 1). Formation of compound **3** resulted from the ylide that demands the singlet carbene as a primary reacting species.



Scheme 1. Photoinduced reaction of dimethyl diazomalonate with acetone.

We wondered whether the reactivity of diazo compounds could be shifted towards functionalization of aldehydes at the α-position under visible light irradiation. MacMillan and co-workers have shown that under light irradiation, in the presence $Ru(bpy)_3Cl_2$ aldehydes, in fact enamines, reacted with bromomalonate furnishing alkylated derivatives.[25] This approach was subsequently used for iridium-catalyzed benzylation[26] and trifluoromethylation.[27] Zeitler[28] and Melchiorre[29,30] have advanced this methodology by showing that organic dyes were also efficient photoredox catalysts for this reaction and, what was more, in certain cases no photoredox catalyst was required. On the other hand, it has been also shown that aryldiazoacetates reacted with enamines in the presence of copper and rhodium complexes giving keto esters in moderate yields (Scheme 2a).[31,32] But the reported transformation was limited to acetophenones and required preformed enamines. *We have found that under visible light irradiation diazo compounds react with aldehydes giving α-alkylated carbonyl compounds instead of the expected cyclopropanes* (Scheme 2b).



Scheme 2. α-Alkylation of carbonyl compounds with diazo reagents.

Results and Discussion

Model Studies

In our initial experiment, 3-phenylpropanal (**8**) was reacted with ethyl diazoacetate (EDA, **9**) in the presence of morpholine and the common, in diazo compounds chemistry, catalysts $Cu(CH_3CN)BF_4$ or $Rh(CF_3CH_2CH_2CO_2)_2$.[32] Contrary to the reported reactions with keto enamines, no product formed. In the benzophenone-photocatalyzed reaction under light irradiation no extrusion of nitrogen was observed and GC analysis confirmed the recovery of starting material **8**. Hence, we speculated that benzophenone was not a suitable photocatalyst for this transformation. Other organic dyes: eosin Y, Rose Bengal, fluorescein, PDI, and methylene blue, and $Ir(ppy)_3$, upon irradiation with white light from LEDs as well as TiO_2 upon irradiation with UV failed to promote the reaction in CH_3CN. However, among Ru complexes tested, in the presence of $Ru(bpy)_3Cl_2$ the model reaction gave the desired product **10** in 55% yield.[33] Control experiments revealed that the exclusion of any of the reaction components: morpholine, light, or the photocatalyst stopped the reaction completely. This suggested a dual mode of activation, organocatalysis merged with photoredox or photocatalysis. We assumed that aldehyde **8** transformed into a more reactive enamine while $Ru(bpy)_3Cl_2$ in the presence of light facilitated carbenoid or carbene formation. As it is known that this reactive species may be also generated from diazo compounds using heat, aldehyde **8** was reacted with EDA (**9**) at elevated temperature with no photocatalyst added and shielded from light. Surprisingly, the reaction failed to afford functionalized aldehyde **10** suggesting that another mechanism operates.

Next, we performed a series of experiments in an effort to optimize the reaction conditions. Firstly, various amines were tested (Table 1). Pyrrolidine-catalyzed reaction furnished product **10** in a very low yield, opposite to most enamine-iminium catalyzed reactions (entry 1).[34] However, less basic secondary, cyclic amines were quite effective (entries 3–8). The superiority of six-membered, secondary amines over pyrrolidine suggests that nucleophilicity of the nitrogen could play a role, as the highest yields were obtained for amines with extra heteroatoms (oxygen or nitrogen).[35] These heteroatoms through an inductive effect, withdraw electron density from the nitrogen, making it less nucleophilic. Primary amines failed in catalyzing our model reaction (entry 9).

Table 1. Choice of an organocatalyst for the model reaction of 3-phenylpropanal (**8**) with EDA (**9**) catalyzed by $Ru(bpy)_3Cl_2$.[a]

Entry	Amine	pK_b[36]	Time [h]	Yield [%][b]
1	pyrrolidine	2.89	3	18
2	piperidine	2.73	3	31
3	piperazine	4.19	3	65
4	piperazine	4.19	5	62
5	*N*-methylpiperazine	4.87	3	42
6	*N*-methylpiperazine	4.87	5	62
7	morpholine	5.6	3	55
8	morpholine	5.6	5	61
9	1-phenypropan-1-amine	–	3	0
10	dicyclohexylamine	–	4	4

[a] *Reaction conditions:* aldehyde **8** (1 equiv.), morpholine (0.4 equiv.), $Ru(bpy)_3Cl_2$ (2 mol%), EDA (**9**, 1 equiv.), CH_3CN, 4 'household' LEDs, 39 °C.
[b] Yields were determined by GC.

The yield also depended on the light intensity and the reaction time. Irradiation with 4 'household' LEDs, for 5 h proved the most effective and the use of a CFL bulb did not alter the reaction outcome significantly (for details see the Supporting Information).

It has been reported that the base-catalyzed addition of EDA (**9**) to enamines affording cyclopropanes was very slow in CH_3CN. Hence, to avoid the undesired side reaction (cyclopropanation), we thought it to be a suitable solvent for our model reaction but other media, commonly used in organocatalyzed reactions, were also tested (Table 2). An increase in yield was observed when the reaction was performed in DMSO (entry 6). The use of dry solvents was not beneficial for the reaction outcome (entries 2 and 5); presumably traces of water were crucial for the enamine hydrolysis, hence for the recovery of morpholine in the catalytic cycle. The alkylation could be also performed in a mixture of CH_3CN/buffer (entry 9).

Furthermore, in enamine-iminium catalysis, the use of an acidic co-catalyst usually influences hydrolysis of an iminium salt, facilitating the recovery of a catalyst in a catalytic cycle.[38,39] A series of acids was

Table 2. Solvent screening for the α-alkylation of aldehyde (**9**).[a]

Entry	Solvent	Dielectric constant [ε_r][37]	Yield [%][b]
1	CH_3CN	37.5	61
2	CH_3CN_{dry}	37.5	62
3	DMF	36.7	25
4	DMA	37.8	25
5	$DMSO_{dry}$	46.7	48
6	***DMSO***	***46.7***	***75***
7	DMSO[c]	46.7	57
8	CH_2Cl_2	8.9	0
9	CH_3CN/H_2O[d]	–	55

[a] *Reaction conditions:* aldehyde **8** (1 equiv.), morpholine (0.4 equiv.), $Ru(bpy)_3Cl_2$ (2 mol%), EDA (**9**, 1 equiv.), solvent (5 mL), 5 h, 4 'household' LEDs.
[b] Yields were determined by GC.
[c] $Ru(bpy)_3Cl_2$ (2.5 mol%).
[d] 9:1 mixture.

therefore tested as additives with the goal of finding a probable relationship between pK_a of the acid and the outcome of the α-alkylation of aldehydes. Careful analysis of the data included in Table 3 led to interesting observations and generalizations. With an increase in pK_a of an acid added the yield increased reaching 83% for AcOH with a dissociation constant of 4.73 (entry 12). The addition of strong acids halted the reaction almost completely (entries 1 and 2), while other acids did have an influence albeit less pronounced.

Table 3. Co-catalyst influence.[a]

Entry	Additive	pK_a[40]	Yield [%][b]
1	TsOH	−1.34	0
2	TFA	0.26	6
3	F_2CHCO_2H	1.24	37
4	2,4-dinitrobenzoic acid	1.43	0
5	2-bromobenzoic acid	2.85	51
6	ICH_2CO_2H	3.12	3
7	2,4-dihydroxybenzoic acid	3.29	44
8	HCO_2H	3.75	58
9	$PhCO_2H$	4.20	61
10	4-methylbenzoic acid	4.37	79
11	4-hydroxybenzoic acid	4.54	70
12	***AcOH***	***4.76***	***83***
13	$AcOH/LiBF_4$	–	83
14	phenol	9.99	63
15	K_3PO_4	–	16
16	H_2O	–	59
17	2,6-lutidine	–	56

[a] *Reaction conditions:* aldehyde **8** (0.5 mmol), morpholine (0.4 equiv.), $Ru(bpy)_3Cl_2$ (2 mol%), EDA (**9**, 1 equiv.), additive (0.4 equiv.), 5 h, DMSO (5 mL), 4 'household' LEDs.
[b] Yields were determined by GC.

Table 4. Effect of the pH of a buffer on the α-alkylation of aldehydes.[a]

Entry	Solvent	Yield [%]	Entry	Buffer in DMSO [%]	Yield [%][b]
1	CH_3CN/H_2O[a]	55	10	2	70
2	DMSO/buf. pH 3.0	67	11	4	71
3	DMSO/buf. pH 3.5	67	12	6	71
4	***DMSO/buf. pH 4.0***	***83***	13	8	69
5	DMSO/buf. pH 4.5	74	14	10	83[c]
6	DMSO/buf. pH 5.0	70	15	12	75
7	DMSO/buf. pH 6.0	70	16	50	0
8	DMSO/buf. pH 7.0	67	17[d]	10	59
9	DMSO/buf. pH 8.0	36	19[e]	10	23
			20[f]	***10***	***88***[c]

[a] *Reaction conditions:* aldehyde (**8**, 0.5 mmol), morpholine (0.4 equiv.), $Ru(bpy)_3Cl_2$ (2 mol%), EDA (**9**, 1 equiv.), additive (0.4 equiv.), 5 h, DMSO, 4 'household' LEDs; entries 1–9 solvent/buffer (5 mL, 9:1 mixture), for entries 10–19 DMSO/buffer mixtures (5 mL, buffer pH 4, $c = 0.1$ M).
[b] Yields were determined by GC.
[c] Isolated yield.
[d] Reaction was performed in CH_3CN/buffer
[e] $Ru(bpm)_3Cl_2$ (2 mol%) was used.
[f] $LiBF_4$ (20 mol%) was added.

Reactions carried out in wet DMSO turned out to be pH dependent and the highest yield was obtained in a 9:1 mixture with the buffer of pH 4 containing $LiBF_4$ as an additive (Table 4, entries 4 and 20). Our data suggest that at pH ~ 4 EDA (**9**) is stable, and at the same time the organocatalytic cycle, requiring acidic conditions, is effective.

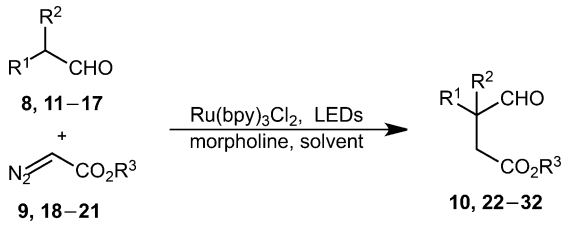
In the last step, the organocatalyst loading was optimized. A decrease in the amount of morpholine led to a decrease in yield although the use of 20 mol% was still sufficient for the activation of the aldehyde (73%).

Scope and Limitation Studies

Under optimal conditions: aldehyde (1 mmol.), morpholine (0.4 equiv.), $Ru(bpy)_3Cl_2$ (2 mol%), $LiBF_4$ (20 mol%), EDA (**9**, 1 equiv.), a mixture of DMSO/buffer (9:1, 10 mL, buffer pH 4, $c = 0.1$ M), 5 h, 4 'household' LEDs, the scope and limitation of the α-functionalization of aldehydes with diazo esters were explored (Table 5).

The C–H alkylation was applicable to various aldehydes giving the desired products **10**, **22**–**32** in decent yields, although the generation of quaternary centers proved difficult under the developed conditions. The results indicate that various functional groups are well tolerated: OMe and even Cl (compounds **22** and **25**). The list of aldehydes is not exhaustive but it is definitely representative. Furthermore, it is noteworthy

Table 5. Scope and limitations of the α-functionalization of aldehydes.



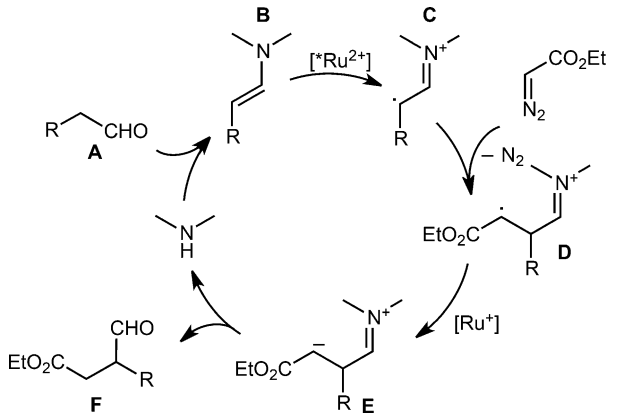
Aldehyde	Diazo ester	R^1, R^2, R^3	Product	Yield [%]
8	**9**	CH_2Ph, H, Et	**10**	88
11	**9**	CH_2-4-$CH_3OC_6H_4$, H, Et	**22**	80
12	**9**	$CH_2(CH)_6CH_3$, H, Et	**23**	76
13	**9**	Ph, H, Et	**24**	44
14	**9**	CH_2-3-ClC_6H_4, H, Et	**25**	71
15	**9**	$CH(CH_3)_2$, H, Et	**26**	63
16	**9**	Ph, CH_3, Et	**27**	0
17	**9**	CH_2CH_3, CH_3, Et	**28**	0
8	**18**	CH_2Ph, H, *t*-Bu	**29**	67
8	**19**[a]	CH_2Ph, H, CH_2Ph	**30**	78
8	**20**[a]	CH_2Ph, H, $CH_2CH_2CH_2Ph$	**31**	80
8	**21**[a]	CH_2Ph, H, *N*-Boc-Pro	**32**	71

[a] Prepared according to the literature procedure.[41]

that sterically hindered diazo esters **18** and **21** reacted equally well. The reaction with diazoacetate **21** consisting of an L-proline moiety afforded the desired compound in 71% yield as a mixture of diastereoisomers (3:2).

Mechanistic Consideration

The proposed mechanism for the functionalization of aldehydes is shown in Scheme 3. We assumed that the reaction proceeds mainly *via* a radical pathway but the formation of cyclopropane with subsequent ring-opening may also operate. We proved that each component of the reaction: amine, photocatalyst, and light is required for the reaction to take place and to validate the proposed mechanism, several experiments were conducted.



Scheme 3. Plausible mechanism for photocatalytic reaction of aldehydes with EDA (**9**).

Firstly, the reaction proceeds *via* enamine-iminium catalysis as in the presence of NEt_3 and DABCO instead of secondary amines recovery of the starting material only was observed. The generated enamine **B** was detected by ESI-MS and ^{1}H NMR analyses. In MS the corresponding peak at 204.14 Da $[M]^+$ was observed not only when aldehyde **8** was treated with morpholine but also in the reaction mixture. Moreover, the ^{1}H NMR spectrum clearly shows characteristic proton resonances for enamine **B** at 5.95 and 4.56 ppm (Figure 1).

Secondly, the composition of the reaction mixture was monitored using LR ESI-MS, GC, and ^{1}H NMR techniques after 0, 30, 90, 150, 210 min under light irradiation (for details see the Supporting Information). One of the main features of the ^{1}H NMR spectra was the progressive disappearance of the aldehyde proton resonance at 9.74 ppm (triplet) and concurrent occurrence of the signals corresponding to product **10** (CHO protons at 9.72 ppm, doublet, Figure 2).

GC and NMR analyses also clearly denoted the presence of aldehyde **8**, EDA (**9**), and the respective enamine of type **B** (Figure 1), while LR ESI-MS analysis showed a more complex picture presumably due to additional reactions taking place in the gas phase. Nevertheless, peaks at $m/z = 204.14$, 407.27, 579.36 Da corresponding, respectively, to the iminium (formed from aldehyde **8** and morpholine) $[M]^+$, $[2M+H]^+$ and product **10** in the form of enamine $[2M+H]^+$ were present in all spectra corroborating the enamine mechanism.

Thirdly, it was not clear whether an Ru-carbenoid is involved in the C–C bond formation step. Hogsten and Angrish found that the Ru complex has the ability to dimerize EDA.[42] In our case, ESI MS analyses, neither of the reaction mixture nor of the mixture of Ru complex with EDA, showed the peak corresponding to the EDA dimer. Moreover, the control analysis of $Ru(bpy)_3Cl_2$ in CH_3CN showed the base peak at 285.05 corresponding to $[Ru(bpy)_3Cl_2]^{2+}$. As the spectra of Ru complex and the mixture of Ru complex + EDA, and Ru complex + EDA + morpholine were almost identical, we could rule out the possible formation of an Ru carbenoid.

Fourthly, the addition of TEMPO, a radical scavenger, to the reaction mixture, rendered it inactive suggesting a radical mechanism. Hence, the model reaction was studied using EPR spectroscopy. The concentration of free radicals in the reaction mixture was too low to be detected directly, therefore phenyl-*N*-*tert*-butylnitrone (PBN) was added as a spin trap.[43,44] The EPR spectrum of the reaction mixture was mea-

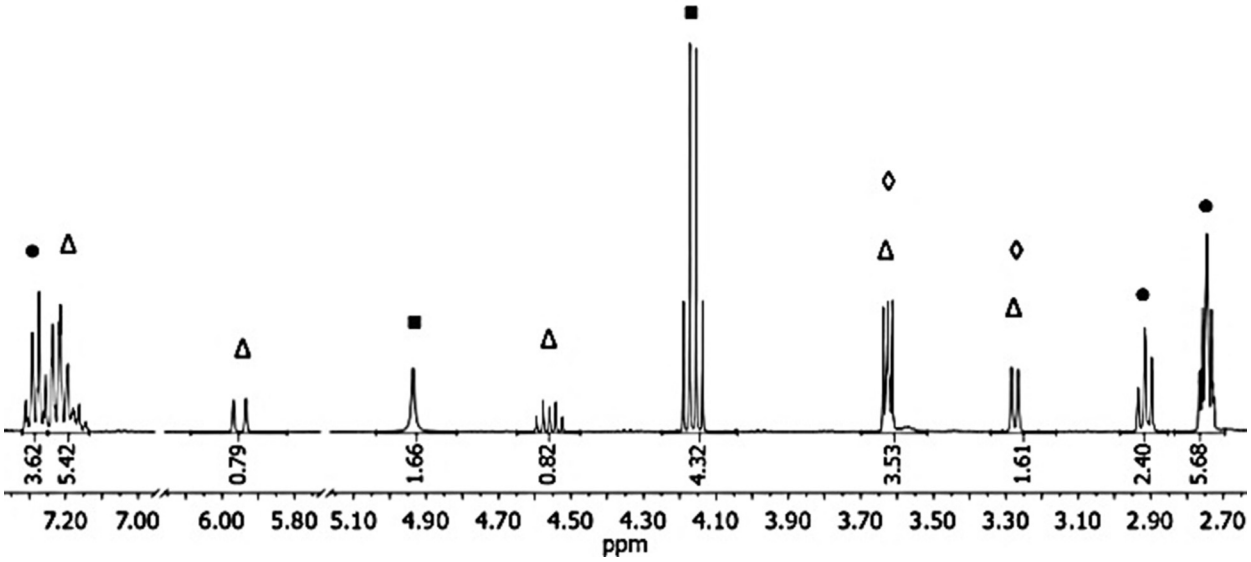


Figure 1. ^{1}H NMR spectrum of the reaction measured just after dissolution (● 3-phenylpropanal (**8**), ■ EDA (**9**), ◇ morpholine, and △ enamine).

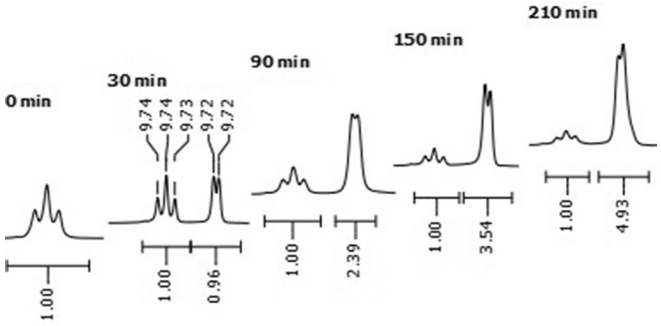


Figure 2. ^{1}H NMR spectra of the reaction mixture after 0, 30, 90, 150, 210 min under light irradiation.

sured after 10 min of irradiation (Figure 3). The formation of 'spin adducts' was ascertained thus supporting the radical mechanism. On the basis of these findings, we concluded that the C–H insertion at the α-position involves radicals.

Stern–Volmer analyses for each of the reaction components clearly showed that for enamine of type **B** very strong, in comparision to EDA and morpholine, quenching of $[Ru^*(bpy)_3Cl_2]^{3+}$ occurred thus confirming the proposed radical **C** being a reactive intermediate (Figure 4). In accord with the proposed mechanism the aldehyde resulted in minute Stern–Volmer quenching.

As an alternative pathway, cyclopropanation of enamine followed by ring-opening was considered. Kuehne and King reported that treatment of the preformed enamines with diazomethane in the presence of CuCl led to cyclopropylamines which after thermal hydrolysis gave alkylated carbonyl compounds as a mixture of regioisomeric products.[45] It was reported that in the presence of Rh(II) complex the reaction of α-diazo ketones with vinyl ethers afforded cyclopropane derivatives which underwent ring-opening leading to 1,4-diketones.[46] Such cyclopropanes bearing both electron-donating and electron-withdrawing

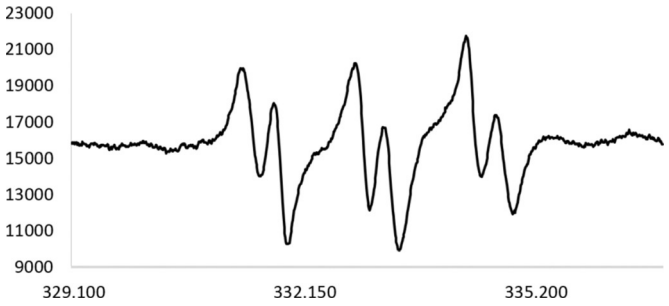


Figure 3. EPR of the reaction mixture: aldehyde **8** (1 equiv., 0.5 mmol), EDA (**9**, 1 equiv.), morpholine (0.4 equiv., 0.2 mmol), $Ru(bpy)_3Cl_2$ (2 mol%), CH_3CN (5 mL), spin trap PBN after 10 min of irradiation with LED.

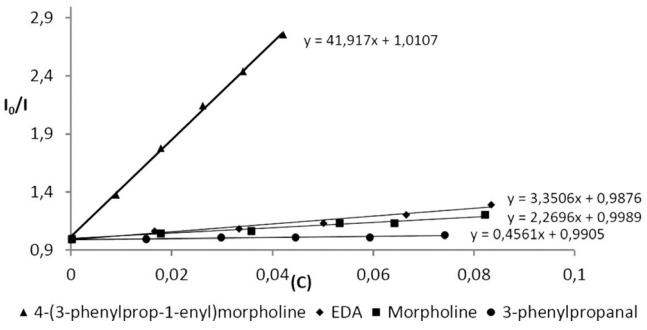
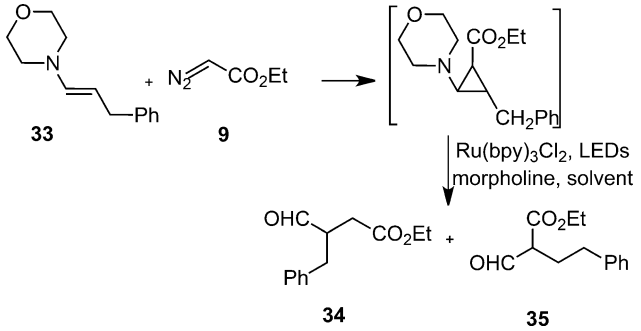


Figure 4. Stern–Volmer analyses for each of the reaction components.

groups were found to be easily cleaved.[45–49] We have prepared a cyclopropylamine derivative using a reported methodology and subjected it to the developed reaction conditions (Scheme 4).[24a]



Scheme 4. Ring-opening of cyclopropylamine.

Under light irradiation ring cleavage occurred and subsequent hydrolysis of the iminium moiety yielded the α-functionalized product. GC-MS analysis (see the Supporting Information) revealed the presence of two regioisomeric derivatives **34** and **35** (ratio 1: 4.5), hence the photocatalytic ring opening was not regioselective. As only one product formed in our model reaction, we postulate that the described α-alkylation proceeds mainly *via* the radical pathway but to some extent cyclopropanation followed by ring opening may also operate. In addition, chain propagation reactions may likely also be involved.[50]

Conclusions

We have found that a dual mode of activation – enamine converged with photocatalysis – changed the reaction pathway from the usual condensation of an aldehyde with EDA to the C–H insertion at the α-position. Specifically, the reaction of aldehydes with diazo reagents in the presence of morpholine as an organocatalyst and $Ru(bpy)_3Cl_2$ as a photoredox catalyst under visible light irradiation furnished exclusively α-alkylated aldehydes. The reported reaction proceeds *via* the carbene transfer pathway but the formation of the cyclopropane cannot be excluded definitely, a detailed mechanistic overview is needed for further exploration.

Our findings proved that the reactivity of diazo compounds can be altered under visible light irradiation thus opening new opportunities in the chemistry of diazo reagents.

Experimental Section

General Procedure for α-Functionalization of Aldehydes

Photocatalyst (2 mol%) was placed in a reaction tube and dissolved in DMSO and buffer pH 4 (mixture 9:1, 10 mL). Then aldehyde (1 mmol), morpholine (0.4 equiv., 0.4 mmol), EDA (1 equiv., 1 mmol) and $LiBF_4$ (20 mol%) were added to the solution. The reaction mixture was stirred at 39 °C under irradiation (4 × LED, 1200 lumens) for 5 h. The light was turned off and the reaction mixture was diluted with AcOEt, and extracted with 1 N HCl. The aqueous phase was separated and then extracted with AcOEt three times. Combined organic phases were washed with $NaHCO_3$, brine and dried over Na_2SO_4, filtered and concentrated. The crude product was purified by flash chromatography using silica gel (hexanes/AcOEt) to afford the corresponding product.

Ethyl 3-benzyl-4-oxobutanoate (10): yield: 194 mg (88%); ^{1}H NMR ($CDCl_3$, 500 MHz): $\delta = 9.79$ (s, 1H, CHO), 7.31–7.17 (m, 5H, Ph), 4.11 (q, $J = 7.1$ Hz, 2H, $COCH_2CH_3$), 3.14–3.08 (m, 2H, CH_2), 2.77–2.71 (m, 1H, CH), 2.65 (dd, $J = 7.6$ Hz, 1H, CH), 1.40 (dd, $J = 4.8$ Hz, 1H, CH), 1.23 (t, $J = 7.0$ Hz, 3H, $COCH_2CH_3$); ^{13}C NMR ($CDCl_3$, 125 MHz): $\delta = 202.2$, 171.6, 137.7, 129.0, 128.6, 126.7, 60.7, 49.2, 34.6, 32.7, 14.1; IR: $\nu = 3029$, 2982, 2934, 2725, 1733 (CO), 1496, 1454 (CHO), 1375, 1199, 1161, 1031, 750, 702 cm^{-1}; HR-MS (ESI): $m/z = 243.0993$, calcd. for $C_{13}H_{16}O_3$ $[M+Na]^+$: 243.0997; elemental analysis; calcd. (%) for $C_{13}H_{16}O_3$: C 70.89, H, 7.32; found: C 70.74, H, 7.40.

Ethyl 3-formyl-4-(4-methoxyphenyl)butanoate (22): yield: 200 mg (80%); ^{1}H NMR ($CDCl_3$, 500 MHz): $\delta = 9.78$ (s, 1H, CHO), 7.09–7.07 (m, 2H, Ph), 6.84–6.83 (m, 2H, Ph), 4.10 (q, $J = 7.0$ Hz, 2H, $COCH_2CH_3$), 3.78 (s, 3H, OCH_3), 3.08–3.01 (m, 2H, CH_2), 2.71–2.60 (m, 2H, CH_2), 2.40 dd, $J = 5.5$ Hz, (1H, CH), 1.23 (t, $J = 7.0$ Hz, 3H, $COCH_2CH_3$); ^{13}C NMR ($CDCl_3$, 125 MHz): $\delta = 202.5$, 171.7, 158.3, 129.9, 129.5, 114.0, 60.7, 55.2, 49.4, 33.7, 32.6, 14.1; IR: $\nu = 2982$, 2958, 2935, 2837, 1731 (CO), 1612, 1514 (CHO), 1249 (OCH_3), 1179, 1034, 838 cm^{-1}; HR-MS (ESI): $m/z = 273.1102$, calcd. for $C_{14}H_{18}O_4$ $[M+Na]^+$: 273.11032; elemental analysis calcd. (%) for $C_{14}H_{18}O_4$: C 67.18, H 7.25; found: C 67.24, H 7.10.

Ethyl 3-formylundecanoate (23): yield: 184 mg (76%); ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 9.71$ (s, 1H, CHO), 4.15 (q, $J = 4$ Hz, 2H, $COCH_2CH_3$), 2.83–2.79 (m, 1H, CH), 2.70–2.64 (m, 1H, CH), 3.39 (dd, $J = 4$ Hz, 1H, CH), 1.72–1.68 (m, 1H, CH), 1.49–1.43 (m, 1H, CH), 1.35- 1.23 (m, 15H, CH_2), 0.87 (t, $J = 4$ Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 202.9$, 171.9, 60.7, 47.7, 33.1, 31.8, 29.5, 29.3, 29.1, 28.6, 26.7, 22.6, 14.1, 14.0; IR: $\nu = 2927$, 2856, 1737 (CO), 1466 (CHO), 1374, 1185, 1032, 723 cm^{-1}; HR-MS (ESI): $m/z = 265.1779$, calcd. for $C_{14}H_{26}O_3$ $[M+Na]^+$: 265.1780; elemental analysis calcd. (%) for $C_{14}H_{26}O_3$: C 69.38, H 10.81; found: C 69.30, H 10.85.

Ethyl 4-oxo-3-phenylbutanoate (24):[51] yield: 103 mg (44%); ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 9.70$ (s, 1H, CHO), 7.40–7.32 (m, 3H, Ph), 7.21–7.19 (m, 2H, Ph), 4.17–4.10 (m, 3H, $COCH_2CH_3$, CH), 3.14 (dd, $J = 8.0$ Hz, 1H, CH), 2.61 (dd, $J = 8$ Hz, 1H, CH), 1.22 (t, $J = 8$ Hz, 3H, $COCH_2CH_3$); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 198.5$, 171.5, 134.8, 129.2, 128.8, 128.0, 60.7, 54.6, 34.6, 14.0.

Ethyl 3-(3-chlorobenzyl)-4-oxobutanoate (25): yield: 180 mg (71%); ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 9.78 (s, 1H, CHO), 7.26–7.18 (m, 3H, Ph), 7.07–7.06 (m, 1H, Ph), 4.12 (q, J = 7.2 Hz, 2H, $COCH_2CH_3$), 3.12–3.07 (m, 2H, CH_2), 2.74–2.69 (m, 1H, CH), 2.65 (dd, J = 7.1 Hz, 1H, CH), 2.40 (dd, J = 5.1 Hz, 1H, CH), 1.24 (t, J = 7.1 Hz, 3H, $COCH_2CH_3$); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 201.7, 171.4, 139.9, 134.5, 129.9, 129.1, 127.2, 127.0, 60.9, 49.0, 34.1, 32.7, 14.1; IR: ν = 2982, 2934, 1730 (CO), 1598, 1574, 1476, 1374 (CHO), 1198, 1157, 1027, 878, 783, 703, 684, 443 cm^{-1}; HR-MS (ESI): m/z = 309.0867, calcd. for $C_{13}H_{15}ClO_3$ [M + CH_3OH + Na]$^+$: 309.0870; elemental analysis calcd. (%) for $C_{13}H_{15}ClO_3$: C 61.30, H, 5.94, Cl 13.92; found: C 61.27, H 5.91, Cl 13.86.

Ethyl 2-formyl-3-methylbutanoate (26);[52] (yield: 117 mg (63%); ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 9.74 (s, 1H, CHO), 4.12 (q, J = 8.0 Hz, 2H, $COCH_2CH_3$), 2.81–2.64 (m, 2H, CH), 2.42–2.28 (ddd, J = 4.0 Hz, 1H, CH), 2.19–2.01 (m, 1H, CH), 1.25–1.21 (td, J = 8.0 Hz, J = 4 Hz, 3H, $COCH_2CH_3$), 1.01–0.92 (m, 6H, 2CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 203.3, 179.8, 172.2, 60.7, 60.6, 53.5, 47.2, 32.6, 29.8, 27.7, 20.1, 19.9, 19.3, 19.1, 14.0, 14.0; residual peaks from AcOEt, hexane and CH_2Cl_2 – product is very volatile and difficult to dry.

***tert*-Butyl 3-benzyl-4-oxobutanoate (29):** yield: 166 mg (67%); ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 9.78 (s, 1H, CHO), 7.30–7.16 (m, 5H, Ph), 3.10–3.04 (m, 2H, CH_2), 2.74–2.2.72 (m, 1H, CH), 2.56 (dd, J = 7.6 Hz, 1H, CH), 2.35 (dd, J = 5.1 Hz, 1H, CH), 1.42 (s, 9H, *t*-Bu); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 202.5, 170.8, 137.9, 129.0, 128.6, 126.6, 81.1, 49.4, 34.5, 34.1, 28.0; IR: ν = 2979, 2931, 1728 (CO), 1455, 1368 (CHO), 1255, 1150, 751, 701 cm^{-1}; HR-MS (ESI): m/z = 303.1562, calcd. for $C_{15}H_{20}O_3$ [M + CH_3OH + Na]$^+$: 303.1572; elemental analysis calcd. (%) for $C_{15}H_{20}O_3$: C 72.55; H 8.12; found: C 72.31, H 8.29.

Benzyl 3-benzyl-4-oxobutanoate (30): yield: 219 mg (78%); ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 9.79 (s, 1H, CHO), 7.36–7.28 (m, 6H, Ph), 7.27–7.22 (m, 2H, Ph), 7.15–7.13 (m, 2H, Ph), 5.08 (s, 2H, CH_2Ph), 3.14–3.07 (m, 2H, CH_2), 2.76–2.67 (m, 2H, CH_2), 2.42 (dd, J = 4.0 Hz, 1H, CH); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 202.1, 171.5, 137.5, 135.5, 129.0, 128.7, 128.5, 128.3, 128.2, 126.7, 66.6, 49.2, 34.5, 32.6; IR: ν = 3087, 3063, 3030, 2925, 2828, 2724, 1732 (CO), 1496, 1455, 1383 (CHO), 1352, 1189, 1160, 748, 700, 491 cm^{-1}; HR-MS (ESI): m/z = 337.1413, calcd. for $C_{18}H_{18}O_3$ [M + CH_3OH + Na]$^+$: 337.1416; elemental analysis calcd. (%) for $C_{18}H_{18}O_3$: C 76.57, H 6.43; found: C 76.48, H 6.24.

3-Phenylpropyl 3-benzyl-4-oxobutanoate (31): yield: 248 mg (80%); ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 9.79 (s, 1H, CHO), 7.31–7.25 (m, 5H, Ph), 7.19–7.16 (m, 5H, Ph), 4.06 (td, J = 4.0 Hz, 2H, CH_2), 3.12–3.10 (m, 2H, CH_2), 2.75 (d, J = 4.0 Hz, 1H, CH), 2.68–2.62 (m, 3H, CH_2 + CH), 2.39 (dd, J = 4.0 Hz, 1H, CH), 1.95–1.91 (m, 2H, CH_2); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 202.2, 171.7, 141.0, 137.6, 129.0, 128.7, 128.4, 128.3, 126.7, 126.0, 64.2, 49.2, 34.6, 32.6, 32.1, 30.1; IR: ν = 3085, 3061, 3027, 2952, 2925, 2858, 1731 (CO), 1603, 1496, 1453 (CHO), 1192, 1163, 1030, 748, 701, 492 cm^{-1}; HR-MS (ESI): m/z = 333.1461, calcd. for $C_{20}H_{22}O_3$ [M + Na]$^+$: 333.1467; elemental analysis calcd. (%) for $C_{20}H_{22}O_3$: C 77.39, H 7.14; found: C 77.36, H 7.01.

(2*S*)-*tert*-Butyl-2-{[(3-benzyl-4-oxobutanoyl)oxy]methyl}-pyrrolidine-1-carboxylate (32): yield: 266 mg (71%); ^{1}H NMR ($CDCl_3$, 600 MHz): δ = 9.78 (s, 1H, CHO), 7.33–7.30 (m, 2H, Ph), 7.27 (m, 1H, Ph), 7.19–7.17 (m, 2H, Ph), 4.17–3.99 (m, 3H, CH_2, CH), 3.34–3.32 (m, 2H, CH_2), 3.16–3.09 (m, 2H, CH_2), 2.79–2.72 (m, 1H, CH), 2.69–2.61 (m, 1H, CH), 2.40 (dd, J = 6 Hz, 1H, CH), 2.01–1.70 (m, 4H, 2CH_2), 1.46 (s, 9H, *t*-Bu); ^{13}C NMR ($CDCl_3$, 150 MHz): δ = 202.1, 171.5, 154.4, 137.5, 129.9, 128.7, 126.7, 79.7, 79.3, 64.9, 55.4, 49.1, 46.4, 34.5, 32.5, 28.7, 28.4, 27.8, 23.7, 22.9; ^{1}H NMR [$(CD_3)_2SO$, 80 °C, 500 MHz]: δ = 9.70 (s, 1H, CHO), 7.31–7.27 (m, 2H, Ph), 7.23–7.18 (m, 3H, Ph), 4.11–4.06 (m, 1H, CH), 4.05–3.99 (m, 1H, CH), 3.92–3.86 (m, 1H, CH), 3.33–3.27 (m, 1H, CH), 3.10–3.02 (m, 3H, CH_2 + CH), 2.80–2.73 (m, 1H, CH), 2.63–2.57 (dd, J = 6 Hz, 1H, CH), 2.49–2.41 (m, 1H, CH), 1.97–168 (m, 4H, 2CH_2), 1.41 (s, 9H, *t*-Bu); ^{13}C NMR [$(CD_3)_2SO$, 80 °C, 125 MHz]: δ = 203.1, 171.4, 171.4, 154.0, 138.7, 129.3, 128.7, 126.7, 79.0, 64.9, 55.7, 55.7, 49.1, 46.7, 40.8, 40.7, 40.5, 40.3, 40.2, 40.0, 39.8, 34.2, 32.8, 28.6, 28.5, 28.3, 23.3. IR: ν = 2975, 2932, 2880, 1736 (CO), 1693 (CO), 1394 (CHO), 1366, 1167, 1109, 702 cm^{-1}; HR-MS (ESI): m/z = 430,2208, calcd. for $C_{20}H_{22}O_3$ [M + CH_3OH + Na]$^+$: 430.2206; elemental analysis calcd. (%) for $C_{21}H_{29}NO_5$: C 67.18, H 7.79, N 3.73; found: C 67.22, H 7.72, N 3.69.

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References

[1] F. Hu, Y. Xia, C. Ma, Y. Zhang, J. Wang, *Chem. Commun.* **2015**, *51*, 7986–7995.
[2] H. M. L. Davies, D. Morton, *Chem. Soc. Rev.* **2011**, *40*, 1857–1869.
[3] W. I. Dzik, X. Xu, X. P. Zhang, J. N. H. Reek, B. de Bruin, *J. Am. Chem. Soc.* **2010**, *132*, 10891–10902.
[4] X. Cui, X. Xu, H. Lu, S. Zhu, L. Wojtas, X. P. Zhang, *J. Am. Chem. Soc.* **2011**, *133*, 3304–3307.
[5] T. Hashimoto, K. Maruoka, *Bull. Chem. Soc. Jpn.* **2013**, *86*, 1217–1230.
[6] R. Bates, *Organic Synthesis Using Transition Metals*, 2nd edn., Wiley, **2012**, chap. 8, pp 312–320.
[7] E. Jellema, A. L. Jongerius, J. N. H. Reek, B. de Bruin, *Chem. Soc. Rev.* **2010**, *39*, 1706–1723.
[8] O. Fujimura, T. Honma, *Tetrahedron Lett.* **1998**, *39*, 625–626.
[9] G. A. Mirafzal, G. Cheng, L. K. Woo, *J. Am. Chem. Soc.* **2002**, *124*, 176–177.
[10] Y. Xi, Y. Su, Z. Yu, B. Dong, E. J. McClain, Y. Lan, X. Shi, *Angew. Chem.* **2014**, *126*, 9975–9979; *Angew. Chem. Int. Ed.* **2014**, *53*, 9817–9821.
[11] a) H. M. L. Davies, S. J. Hedley, *Chem. Soc. Rev.* **2007**, *36*, 1109–1119; b) A. Ford, H. Miel, A. ring, C. N. Slattery, A. R. Maguire, M. A. McKervey, *Chem. Rev.* **2015**, *115*, 9981–10080.
[12] Z. Zhang, J. Wang, *Tetrahedron* **2008**, *64*, 6577–6605.
[13] A. C. B. Burtoloso, R. M. P. Dias, B. Bernardim, *Acc. Chem. Res.* **2015**, *48*, 921–934.

[14] T. Ye, M. A. McKervey, *Chem. Rev.* **1994**, *94*, 1091–1160.
[15] M. P. Doyle, R. Duffy, M. Ratnikov, L. Zhou, *Chem. Rev.* **2010**, *110*, 704–724.
[16] M. Fontecave, *Angew. Chem.* **2015**, *127*, 7050-7051; *Angew. Chem. Int. Ed.* **2015**, *54*, 6946–6947.
[17] a) D. A. Nicewicz, T. M. Nguyen, *ACS Catal.* **2014**, *4*, 355–360; b) J. M. R. Narayanam, C. R. J. Stephenson, *Chem. Soc. Rev.* **2011**, *40*, 102–113; c) D. Ravelli, S. Protti, P. Neri, M. Fagnoni, A. Albini, *Green Chem.* **2011**, *13*, 1876–1884; d) Sanofi-Aventis, WO Patent WO 2011/026865 A1C, **2011**; e) S. Liu, M. Tong, Y. Yu, H. Xie, H. Li, W. Wang, *Chem. Commun.* **2015**, *51*, 11221–11224; f) D. M. Hodgson, A. Charlton, *Tetrahedron* **2014**, *70*, 2207–2236; g) K. Fidaly, C. Ceballos, A. Falguières, M. Sylla-Iyarreta, A. Guy, C. Ferroud, *Green Chem.* **2012**, *14*, 1293–1297; h) E. R. Welin, A. A. Warkentin, J. C. Conrad, D. W. C. MacMillan, *Angew. Chem.* **2015**, *127*, 9804–9808; *Angew. Chem. Int. Ed.* **2015**, *54*, 9668–9672; i) P. Riente, A. M. Adams, J. Albero, E. Palomares, M. A. Pericàs, *Angew. Chem.* **2014**, *126*, 9767–9770; *Angew. Chem. Int. Ed.* **2014**, *53*, 9613–9616; j) Ł. Woźniak, J. J. Murphy, P. Melchiorre, *J. Am. Chem. Soc.* **2015**, *137*, 5678–6581; k) L. Caruana, F. Kniep, T. K. Johansen, P. H. Poulsen, K. A. Jörgensen, *J. Am. Chem. Soc.* **2014**, *136*, 15929–15932.
[18] a) D. Ravelli, M. Fagnoni, A. Albini, *Chem. Soc. Rev.* **2013**, *42*, 97–113; b) D. Ravelli, M. Fagnoni, *ChemCatChem* **2012**, *4*, 169–171.
[19] A. Nijland, S. R. Harutyunyan, *Catal. Sci. Technol.* **2013**, *3*, 1180–1189.
[20] J. W. Tucker, J. D. Nguyen, J. M. R. Narayanam, S. W. Krabbe, C. R. Stephenson, *Chem. Commun.* **2010**, *46*, 4985–4987.
[21] D. K. Prier, D. A. Rankic, D. W. C. MacMillan, *Chem. Rev.* **2013**, *113*, 5322–5363.
[22] R. Brimioulle, D. Lenhart, M. M. Maturi, T. Bach, *Angew. Chem.* **2015**, *127*, 3944–3963; *Angew. Chem. Int. Ed.* **2015**, *54*, 3872–3890.
[23] a) C. Müller, T. Bach, *Aust. J. Chem.* **2008**, *61*, 557–564; b) C. Müller, Ch. Bauer, T. Bach, *Angew. Chem.* **2009**, *121*, 6767–6769; *Angew. Chem. Int. Ed.* **2009**, *48*, 6640–6642.
[24] a) A. C. Lottes, J. A. Landgrebe, K. Larsen, *Tetrahedron Lett.* **1989**, *30*, 4093–4096; b) P. Yates, B. L. Shapiro, *J. Am. Chem. Soc.* **1963**, *85*, 1171–1176; c) E. Wenkert, C. A. McPherson, *J. Am. Chem. Soc.* **1972**, *94*, 8084–8090; d) R. P. L'Ësperance, T. M. Ford, M. Jones, *J. Am. Chem. Soc.* **1988**, *110*, 209–213.
[25] D. A. Nicewicz, D. W. C. MacMillan, *Science* **2008**, *322*, 77–80.
[26] H.-W. Shih, M. N. Vander Wal, R. L. Grange, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2010**, *132*, 13600–13603.
[27] D. A. Nagib, M. E. Scott, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2009**, *131*, 10875–10877.
[28] M. Neumann, S. Füldner, B. König, K. Zeitler, *Angew. Chem.* **2011**, *123*, 981–985; *Angew. Chem. Int. Ed.* **2011**, *50*, 951–954.
[29] E. Arceo, I. D. Jurberg, A. Álvarez-Fernández, P. Melchiorre, *Nat. Chem.* **2013**, *5*, 750–756.
[30] M. Silvi, E. Arceo, I. D. Jurberg, C. Cassni, P. Melchiorre, *J. Am. Chem. Soc.* **2015**, *137*, 6120–6123.
[31] C. R. Holmquist, E. J. Roskamp, *J. Org. Chem.* **1989**, *54*, 3258–3260.
[32] W.-J. Zhao, M. Yan, D. Huang, S.-J. Ji, *Tetrahedron* **2005**, *61*, 5585–5593.
[33] We have not studied eosin Y under the optimized conditions.
[34] D. Gryko, D. Walaszek, *Stereoselective Organocatalysis*, (Ed.: R. R. Torres), 1st edn., Wiley, **2013**, chap 2, pp 81–126.
[35] P. W. Hickmott, *Tetrahedron* **1982**, *38*, 1975–2050.
[36] S. Mukherjee, J. W. Yang, S. Hoffmann, B. List, *Chem. Rev.* **2007**, *107*, 5471–5569.
[37] Y. Cui, L. Zeng, Y. Fang, J. Zhu, C. H. Devillers, D. Lucas, N. Desbois, C. P. Gros, K. M. Kadish, *ChemElectroChem* **2016**, *3*, 110–121.
[38] A. Erkkilä, I. Majander, P. M. Pihko, *Chem. Rev.* **2007**, *107*, 5416–5470.
[39] A. G. Cook, M. L. Absi, V. K. Bowden, *J. Org. Chem.* **1995**, *60*, 3169–3171.
[40] F. Ramirez, J. F. Marecek, *Pure Appl. Chem.* **1980**, *52*, 1021–1045.
[41] T. Toma, J. Shimokawa, T. Fukuyama, *Org. Lett.* **2007**, *9*, 3195–3197.
[42] D. M. Hodgson, D. Angrish, *Chem. Commun.* **2005**, *39*, 4902–4904.
[43] J. Zhao, W. Wu, J. Sun, S. Guo, *Chem. Soc. Rev.* **2013**, *42*, 5323–5351.
[44] a) H. Tomioka, E. Iwamoto, H. Itakura, K. Hirai, *Nature* **2001**, *412*, 626–628; b) Tomioka, M. Itoh, S. Yamakawa, Y. Izawa, *J. Chem. Soc. Perkin Trans. 2* **1980**, 603–609.
[45] M. E. Kuehne, J. C. King, *J. Org. Chem.* **1973**, *38*, 304–311.
[46] K. Saigo, H. Kurihara, H. Miura, A. Hongu, N. Kubota, H. Nohira, M. Hasegawa, *Synth. Commun.* **1984**, *14*, 787–796.
[47] E. Wenkert. C. A. McPherson, E. L. Sanchez, R. L. Webb, *Synth. Commun.* **1973**, *3*, 255–258.
[48] E. Kunkel, I. Reichelt, H. U. Reiβig, *Liebigs Ann. Chem.* **1984**, 802–819.
[49] E. Wenkert, T. S. Arrhenius, B. Bookser, M. Guo, P, Mancini, *J. Org. Chem.* **1990**, *55*, 1185–1193.
[50] M. A. Cismesia, T. P. Yoon, *Chem. Sci.* **2015**, *6*, 5426–5434.
[51] P. Deslongchamps, A. Bélanger, D. J. F. Berney, H.-J. Borschberg, R. Brousseau, A. Doutheau, R. Durand, H. Katayama, R. Lapalme, D. M. Leturc, C.-C. Liao, F. N. MacLachlan, J.-P. Maffrand, F. Marazza, R. Martino, C. Moreau, L. Ruest, L. Saint-Laurent, R. Saintonge, P. Soucy, *Can. J. Chem.* **1990**, *68*, 127–152.
[52] L. Carman, L. D. Kwart, T. Hulicky, *Synth. Commun.* **1986**, *16*, 169–182.

