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COMMUNICATION

Asymmetric synthesis of Cyclic β -Amino Carbonyl Derivatives by a Formal [3+2] Photocycloaddition

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Herein, a visible-light mediated strategy unlocking a family of cyclic β -amino carbonyl derivatives bearing three contiguous stereogenic centres is introduced. The overall reactivity relies on the performance of the substrate-catalyst complex to assist both the enantiocontrol and the photoredox tasks. This transformation is translated to an enantioselective [3+2] photocycloaddition between coordinated α,β -unsaturated acyl imidazoles and cyclopropylamine derivatives.

Observing the plethora of biological active compounds known so far, cyclic β -amino carbonyl derivatives have recently raised on the stage of the synthetic chemist theatre. Especially, five and six membered ring species result very attractive due to their antifungal or antiviral properties (Figure 1a).¹ Hence, significant efforts have been devoted on the achievement of similar scaffolds in an enantioselective manner.² Concomitantly, asymmetric catalytic processes, driven by visible light, have been enriching the synthetic methodology toolbox of organic chemists on the last years.³ Examining the vast number of protocols described so far, dual catalytic systems represent the most employed strategy accomplishing this task.⁴ These systems are characterized by the use of an achiral photocatalyst that generates the reactive intermediate and a chiral catalyst that induces stereoselectivity in the process. Despite the considerable results obtained in this regard, such strategies reckon the high difficulty of fully suppressing racemic background pathways without the use of any artifice. A different perspective is introduced by visible light reactions promoted by dual functional catalysts.⁵ In this scenario, the interaction substrate-catalyst affords an intermediate responsible for the photoredox activation as well as the stereocontrol, promoting highly enantioselective reactions, and avoiding any possible racemic pathways. Among the systems described so far, Meggers' group developed a family of chiral-at-metal rhodium catalysts that purveyed excellent results.^{5a-5e}

Despite the latent ability of chiral-at-metal rhodium catalysis on promoting SET oxidative reactions, this reactivity has not received enough attention yet, and only few examples have been described so far. In relation with α -amino radicals addition, in 2017, Kang's group reported an enantioselective conjugate addition to α,β -unsaturated ketones triggered by SET oxidation induced by the coordinated catalyst-substrate species (Scheme 1b).^{5d}

a) Relevant amino carbonyl derivatives

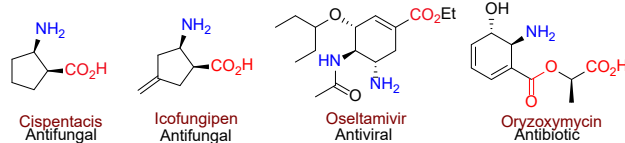
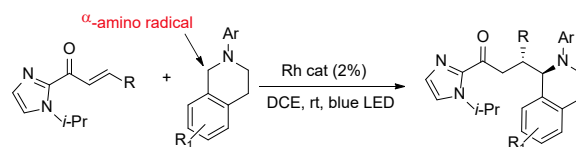
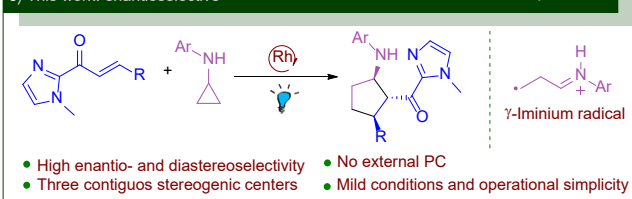
b) Previous enantioselective α -amino radical additionc) This work: enantioselective γ -iminium radical addition/intramolecular cyclization

Figure 1. a) Relevant amino carbonyl derivatives b) Previous enantioselective α -amino radical addition. c) This work: enantioselective γ -iminium radical addition.

Considering the importance of nitrogen compounds, cyclopropylamine derivatives are valuable building blocks for the synthesis of cyclopentanes presenting an amino motif. In 2012, Zheng's group disclosed the first racemic [3+2] cycloaddition promoted by visible-light employing this family of substrates.⁶ Since then, several efforts were combined on this topic, nevertheless, the first enantiocontrolled protocols were recently published in conjunction by the groups of Ooi and Jiang.⁷ These elegant methods employ a dual catalytic system formed by a photocatalyst responsible for the oxidation of the

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amine, and a chiral hydrogen bonding catalyst ruling the enantioselectivity of the process. However, they required the use of low temperature to afford good enantiocontrol, and it is limited to the construction of no more than two chiral centres in the final molecule. In this context, considering our revived interest in chiral-at-rhodium catalysis,⁸ we wondered, whether it would be possible, to unlock an enantioselective [3+2] cycloaddition directly promoted by the substrate-catalyst complex species to access a family of cyclic β -aminocarbonyl derivatives.

The investigation began by selecting the α,β -unsaturated acyl imidazole **1a** and the cyclopropylamine **2a** as the model substrates (Table 1) and the Δ -Rh(S) as catalyst. Their choice was mindfully evaluated; indeed, the success of the global reaction depends on three factors: 1) the ability of the photoexcited Rh complex **I** in oxidizing the cyclopropylamine (right-top, Figure 2), 2) the fast formation of the distonic ion through the exergonic reaction in contrast to the back-electron transfer (BET) (right -bottom Figure 2), 3) the potential of the chiral catalyst to control the stereo induction during the overall reaction. The excited-state electron-properties of Rh complex **I** were described by Meggers' group ($E_{[Rh]^+ / [Rh]} = +1.38$ V vs SCE) (Figure 2),⁹ which theoretically is able to perform the single-electron oxidation of **2a** ($E_{1/2}^{red} = +0.92$ V vs SCE in MeCN).⁶ On the other side, a report by Ingold *et al.* described the rate constant for ring opening of a cyclopropyl-*n*-propylaminyl radical on the order of $1 \times 10^{-7} \text{ s}^{-1}$, accessing the distonic ion.¹⁰

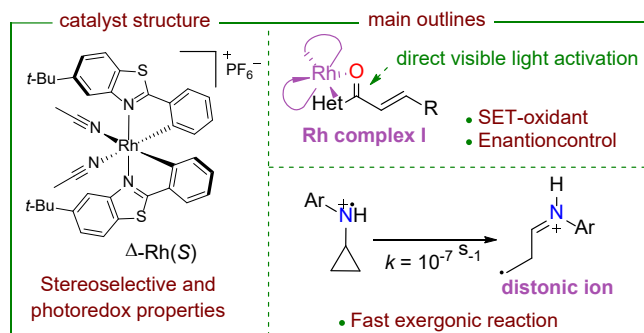


Figure 2. Design considerations for the [3+2] cycloaddition.

Our first attempt was using blue LEDs ($\lambda = 460$ nm) in MeCN at room temperature for 16 hours (Table 1, entry 1). Unlikely, a mixture of two diastereomers was obtained (d.r.: 1.3:1), one of them with good enantioselectivity (**3aa**) and the other one (**3'aa**)¹¹ as racemic mixture. The use of an external photocatalyst (entry 2) increased the amount of the undesired diastereomer (d.r.: 1.1:1). Then, different control experiments were carried out. Thus, in absence of catalyst Δ -Rh, the product **3a** was still formed as a mixture (d.r.: 1:5), observing no enantioselectivity in both diastereomers. This could be explained because, at this concentration, the amine is able to absorb light and, from the excited state, undergo the cycloaddition reaction in a racemic manner (see ESI). Moreover, the photochemical nature of the reaction was confirmed when no reactivity was observed in absence of light (entry 4). In order to avoid the uncontrolled background photoreaction that

affords the uncatalyzed amine product **3'aa**, catalyst loading was increased to 5 mol% (entry 5), achieving a higher d.r. and *ee*. Further optimization of the reaction conditions disclosed that 0.33M was the optimal concentration, finding worse results for more concentrated or diluted conditions (entries 6–7). A screening of different solvents was performed (entries 8–11), being acetone the best one (entry 11). Finally, a reaction with higher catalyst loading (8 mol%) was executed, but no evident improvements were achieved (entry 12).¹²

Table 1. Optimization of the reaction conditions.^a

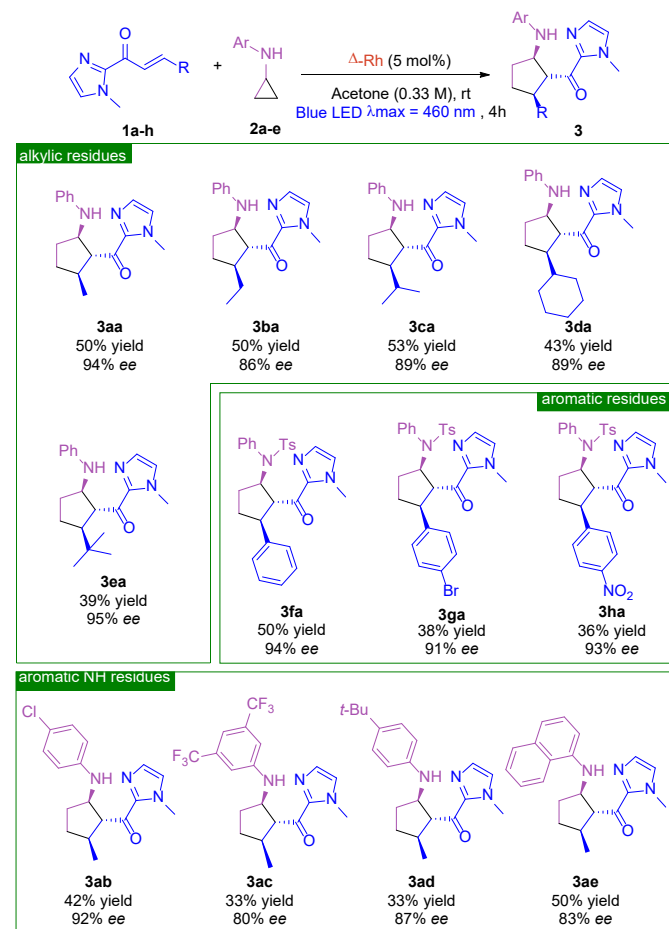
Entry	Rh	Solvent	Conversion [dr] ^b	Yield ^c [<i>ee</i>] ^d
1	2%	MeCN (0.2 M)	100% [1.3:1]	37% [79%]
2 ^e	2%	MeCN (0.2 M)	100% [1.1:1]	33% [75%]
3	-	MeCN (0.2 M)	16% [1:5]	7% [0%]
4 ^f	2%	MeCN (0.2 M)	-	-
5	5%	MeCN (0.2 M)	100% [2:1]	40% [91%]
6	5%	MeCN (0.33 M)	100% [3:1]	47% [92%]
7	5%	MeCN (0.5 M)	100% [2.5:1]	43% [92%]
8	5%	MeOH (0.33 M)	-	-
9	5%	CH ₂ Cl ₂ (0.33 M)	100% [2.5:1]	43% [91%]
10	5%	Toluene (0.33 M)	100% [2.5:1]	38% [92%]
11	5%	Acetone (0.33 M)	100% [3.3:1]	50% [93%]
12	8%	Acetone (0.33 M)	100% [3.5:1]	53% [94%]

^a Reaction conditions: 0.05 mmol scale using 2 equiv. of amine **2a** during 16 h under blue LED. ^b Determined by ¹H-NMR. ^c Isolated yield after flash chromatography. ^d *ee* was determined by SFC. ^e The reaction was performed with 2.0 mol% of 1,2,3,5-Tetrakis(carbazol-9-yl)-4,6-dicyanobenzene, 2,4,5,6-Tetrakis(9H-carbazol-9-yl) isophthalonitrile. ^f Without light.

After the screening of the reaction, the scope of the α,β -unsaturated acyl imidazoles was studied (Scheme 1). Firstly, different aliphatic residues were tested. As expected, primary and secondary alkyl chain residue afforded the corresponding products with excellent results of enantioselectivity **3ba–da** (86–89% *ee*) and moderate yield. Delightfully, the presence of a tertiary alkyl substituent is not a limitation for the methodology. Indeed, compound **3ea** was obtained in a similar form than previous examples (95% *ee*), what represents an advantage in comparison to previous works,¹³ in which no reaction was observed in the radical addition to tertiary alkyl residues due to the steric hindrance exerted by this moiety. Then, evaluation of aryl substituents was performed, obtaining good enantioselectivities for phenyl, *p*-bromo and *p*-NO₂ substituents (**3ga–3ha**). Regrettably, the crude mixtures showed the presence of four diastereoisomers of which, the major one, could be isolated after an *in-situ* tosylation. Lastly, the aryl influence on the cyclopropylamine was analyzed (bottom Scheme 1). Thus, the photocatalytic systems worked well with *p*-chloro substituents (**3ab**), electron-poor (**3ac**) and electron-rich aromatic rings (**3ad**), as well as *ortho*-bulkier substituents as the

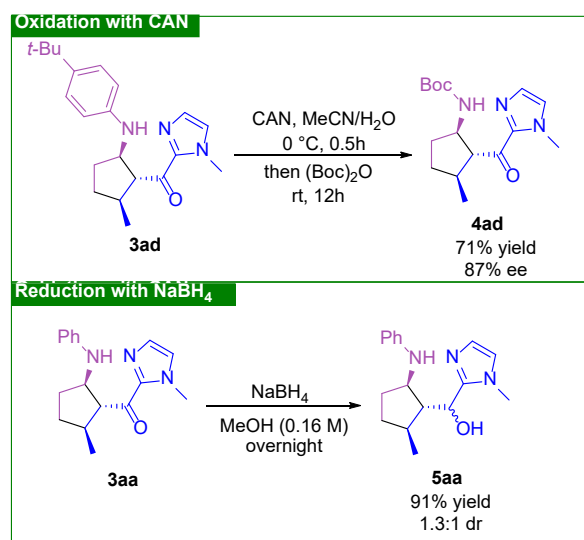
naphthyl group (**3ae**). To our convenience, suitable crystals of compound **3ab** were obtained, allowing the determination of the absolute configuration of the new stereogenic centers generated (**1R**, **2S**, **5S**).¹⁴

Scheme 1. Reaction scope for Michael acceptor **1** and cyclopropylamines **2**.^a



^a Reaction conditions: **1** (0.05 mmol), **2** (2 equiv.), Δ -Rh (5 mol%), acetone (150 μ L), blue LED, 4h. Isolated yield after flash column chromatography. ee was determined by SFC.

In order to showcase the utility of the method, synthetic transformations were performed (Scheme 2). Firstly, compound **3ad** was treated with CAN (cerium nitrate IV) to access a primary amine as intermediate, which successively is functionalized as Boc-derivative **4ad**. Delightfully, the stereochemistry of the chiral centers is maintained during the overall process. Then, the carbonyl moiety was subjected to a reductive reaction with a common agent as NaBH₄. Regrettably, the internal architecture of compound **3aa** did not unlock any diastere-differentiation, observing the final alcohol **5aa** as a mixture of two diastereoisomers (dr 1.3:1).



Scheme 2. Derivatizations: a) Oxidation with CAN to free the amine. b) Reduction with Sodium Borohydride to unlock β -amino alcohols

Finally, we have proposed a mechanism based on previous studies from literature^{5e} and absorption properties of every component of the reaction (Figure 3 and see ESI). Although the amine presents a strong absorption at 455 nm, this absorption is stronger in the case of the Rh complex **I**. Therefore, it can be assumed that the Rh complex **I** is the photoactive species in the system. Thus, after coordination of **1** with the initial rhodium complex, intermediate **I** is formed, and upon LED irradiation, it reaches the excited state whose electronic properties ($E[\text{Rh}^{\text{III}*}/\text{Rh}^{\text{II}}] = +1.38$ V vs. SCE)⁹ allow the oxidation of the cyclopropylamine ($E_{1/2}^{\text{red}} = +0.92$ V vs. SCE)⁶, affording intermediate **II** and the radical cation of the amine. Considering the susceptibility of cyclopropyl systems to undergo ring-opening reaction, the amine species is in equilibrium with its distonic ion. Thus, it can evolve in two different pathways. On one hand (path A), it can react with the radical **II**, following a fast radical-radical recombination due to the proximity of the two intermediates, to afford the enolate **III**. At this point, a polar cyclisation can take place, which generates intermediate **IV** that upon de-coordination from Δ -Rh afford the final product **3**. On the other hand (path B), if the previous radical-radical recombination is not fast enough, the distonic ion can escape the solvent cage, and then reacts directly with complex **I** that is in larger amount than **II**, yielding the radical **VI** that is consecutively reduced by the radical intermediate **II**. Again, de-coordination of the final product **3** renews the catalytic cycle. In addition, a low quantum yield ($\phi = 0.031$) was determined, discarding any possible radical chain pathways.

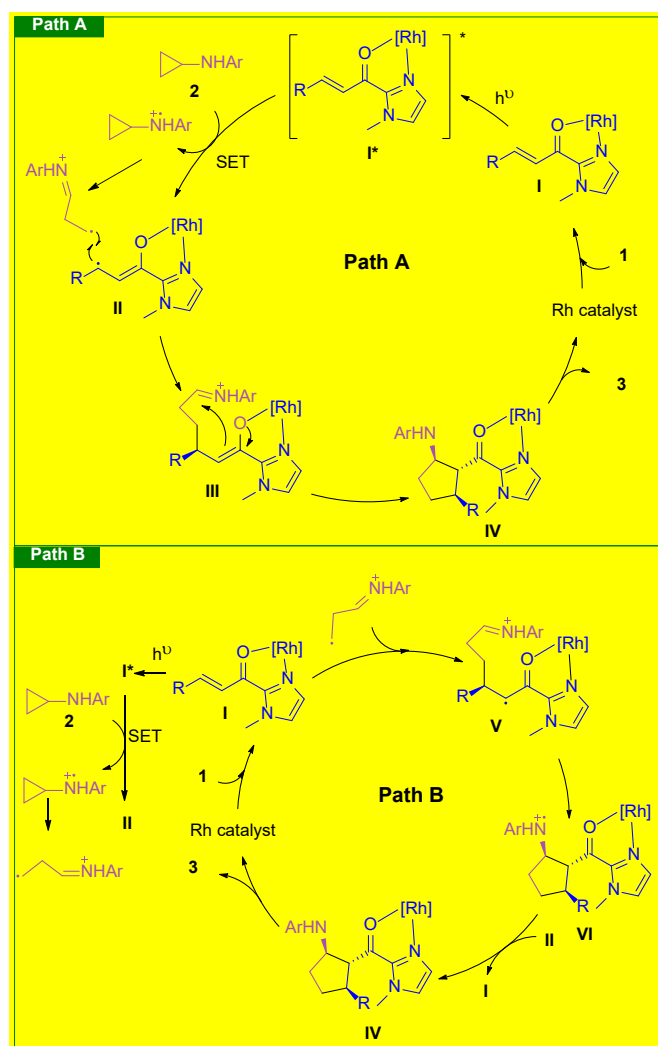


Figure 3. Mechanism proposal: a) radical-radical recombination between II and 2. b) radical addition of 2 to I.

In conclusion, a formal [3+2] cycloaddition directly promoted by visible-light excitation of the catalyst-substrate complex has been developed. This new synthetic strategy allowed the synthesis of a family of cyclic β -amino carbonyl compounds characterised by three contiguous stereogenic centres with excellent results in terms of enantioselectivity.

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Conflicts of interest

There are no conflicts to declare.

Notes and references

- (a) F. Fülöp, *Chem. Rev.*, 2001, **101**, 2181; (b) L. Kiss and F. Fülöp, *Chem. Rev.*, 2014, **114**, 1116; (c) R. Singh, G. Bhasin, R. Srivastava, Geentanjali, *Mini Rev. Org. Chem.*, 2016, **13**, 143.
- (a) S. G. Davies, D. Diez, M. M. El Hammouni, A. C. Garner, N. M. Garrido, M. J. C. Long, R. M. Morrison, A. D. Smith, M. J. Sweet and J. M. Whitey, *Chem. Commun.*, 2003, **19**, 2410; (b) A. C. Garner, M. J. C. Long, A. D. Smith, M. J. Sweet, J. M. Whitey and S. G., Davies, *Org. Biomol. Chem.*, 2004, **2**, 3355; (c) A. M. Fletcher, P. M. Roberts, J. E. Thomson, C. Zammit and S. G. Davies, *Chem. Commun.*, 2013, **49**, 7037; (d) A. M. Fletcher, P. M. Roberts, J. E. Thomson, C. Zammit and S. G. Davies, *Tetrahedron: Asymmetry*, 2016, **27**, 208.
- (a) J. M. R. Narayanan and C. R. J. Stephenson, *Chem. Soc. Rev.*, 2011, **40**, 102; (b) C. K. Prier, D. A. Rankic and D. W. C. MacMillan, *Chem. Soc. Rev.*, 2013, **113**, 5322; (c) M. H. Shaw, J. Twilton and D. W. C. MacMillan, *J. Org. Chem.*, 2016, **81**, 6898; (d) N. A. Romero and D. A. Nicewicz, *Chem. Rev.*, 2016, **116**, 10075. (e) A. F. Garrido-Castro, M. C. Maestro and J. Aleman, *Tetrahedron Lett.*, 2018, **59**, 1286; (f) T. Rigotti and J. Aleman, *Chem. Commun.*, 2020, **56**, 11169.
- (a) M. N. Hopkins, B. Sahoo, J. -L. Li and F. Glorius, *Chem. Eur. J.*, 2014, **20**, 3874; (b) K. L. Skubi, T. R. Blum, T. P. Yoon, *Chem. Rev.*, 2016, **116**, 10035; (c) X. Lang, J. Zhao and X. Chen, *Chem. Soc. Rev.*, 2016, **45**, 3026.
- (a) X. Huang, T. R. Quinn, K. Harms, R. D. Webster, L. Zhang, O. Wiest and E. Meggers, *J. Am. Chem. Soc.*, 2017, **139**, 9120; (b) X. Huang, X. Li, X. Xie, K. Harms, R. Riedel and E. Meggers, *Nat. Commun.*, 2017, **8**, 2245; (c) N. Hu, H. Jung, Y. Zheng, J. Lee, L. Zhang, Z. Ullah, X. Xie, K. Harms, M. -H. Baik and E. Meggers, *Angew. Chem. Int. Ed.*, 2018, **57**, 6242; (d) S. -X. Lin, G. -J. Sun and Q. Kang, *Chem. Commun.*, 2017, **53**, 7665. (e) F. F. Assis, X. Huang, M. Akiyama, R. A. Pili and E. Meggers, *J. Org. Chem.*, 2018, **83**, 10922; (f) J. Zheng, W. B. Swords, H. Jung, K. L. Skubi, J. B. Kidd, G. J. Meyer, M. -H. Baik and T. P. Yoon, *J. Am. Chem. Soc.*, 2019, **141**, 136635.
- (a) S. Maity, M. Zhu, R. S. Shinabery and N. Zheng, *Angew. Chem. Int. Ed.*, 2012, **51**, 222; (b) Y. Cai, J. Wang, Y. Zhang, Z. Li, D. Hu, N. Zheng and H. Chen, *J. Am. Chem. Soc.*, 2017, **139**, 12259; (c) Y. Cai, J. Wang, Y. Zhang, Z. Li, D. Hu, N. Zheng, H. Chen, *Chem. Sci.*, 2019, **10**, 10716.
- (a) D. Uruguchi, Y. Kimura, F. Ueoka and T. Ooi, *J. Am. Chem. Soc.*, 2020, **142**, 19462; (b) Y. Yin, Y. Li, T. Goncalves, Q. Zhan, G. Wang, X. Zhao, B. Qiao, K. -W. Huang and Z. Jiang, *J. Am. Chem. Soc.*, 2020, **142**, 19451; (c) Y. Kimura, D. Uruguchi, T. Ooi, *Org. Biomol. Chem.*, 2021, **19**, 1744.
- (a) R. I. Rodriguez, L. Mollari and J. Aleman, *Angew. Chem. Int. Ed.*, 2021, **60**, 4555; (b) F. Aguilar-Galindo, R. I. Rodríguez, L. Mollari, J. Alemán, S. Díaz-Tendero, *Catalysts* **2021**, **11**, 922.
- H. Jung, M. Hong, M. Marchini, M. Villa, P. S. Steinhardt, X. Huang, M. Hemming, E. Meggers, P. Ceroni, J. Park and M. -H. Baik, *Chem. Sci.*, **2021**, **12**, 9673.
- Y. Maeda and K. U. Ingold, *J. Am. Chem. Soc.* 1980, **102**, 328.
- CDCC 2111056 contains the crystallographic data of compound **3aa** (www.ccdc.cam.ac.uk/data_request/cif).
- Other control experiments suggested that the best ratio between cyclopropylamine and Michael acceptor was 2:1 (see SI).
- (a) C. Wang, K. Harms, E. Meggers; *Angew. Chem. Int. Ed.*, 2016, **55**, 13495; (b) H. Huo, K. Harms, E. Meggers, *J. Am. Chem. Soc.*, 2016, **138**, 6936.
- CDCC 2095914 contains the crystallographic data of compound **3ab** (www.ccdc.cam.ac.uk/data_request/cif).