Advanced Synthesis & Catalysis

Accepted Article

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To be cited as: *Adv. Synth. Catal.* 10.1002/adsc.201801413

Link to VoR: http://dx.doi.org/10.1002/adsc.201801413

10.1002/adsc.201801413

UPDATE

DOI: 10.1002/adsc.201((will be filled in by the editorial staff))

Visible Light-Mediated Synthesis of Enantiopure γ-Cyclobutane Amino and 3-(Aminomethyl)-5-phenylpentanoic Acids

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Received: ((will be filled in by the editorial staff))

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Abstract. A visible light-mediated [2+2] photocycloaddition of amide-linked dienes using [Ir(dtbbpy)(dF(CF$_3$)ppy)$_2$]PF$_6$ as triplet sensitizer was applied to generate a variety of *N*-*tert*-butyl, *N*-benzyl- and *N*-*tert*-butoxycarbonyl-protected 3-azabicyclo[3.2.0]heptan-2-ones in good yields and with good diastereoselectivity. Density functional theory calculations shed light on the conformational prerequisites for the [2+2] photocycloaddition. The bicyclic key structures could be readily transformed into γ-cyclobutane amino acids.
For the obtained racemic 3-phenyl-2-aminocyclobutane-1-carboxylic acid the resolution with chiral oxazolidin-2-one is demonstrated to allow access to both enantiomers. Alternatively, a chiral auxiliary approach led as well to the enantiomerically pure target compound. Finally, the synthesis of either enantiomer of 3-(aminomethyl)-5-phenylpentanoic acid, the racemate being described as an anticonvulsant, is described.

Keywords: amino acids, cycloaddition, energy transfer, green chemistry, photocatalysis

γ-Amino acids play an important role in the clinical treatment of diseases related to the central nervous system such as epilepsy, neuropathic pain or anxiety.[1] The most prominent representative of this family is γ-aminobutyric acid (GABA), which is the major inhibitory neurotransmitter in the mammalian central nervous system.[2] A wide variety of GABA derivatives have been synthesized and investigated over recent years.[3] Amongst these, cyclic GABA analogues have proven to be of significant therapeutic value, as exemplary shown with the commercial therapeutic gabapentin.[4] Besides their inherent biological activity, γ-amino acids have been in the focus due to their potential for application in the design of oligopeptides with well-defined secondary structures.[5] Especially, cyclic γ-amino acids are promising building blocks for such peptides due to the limitation of their backbone torsional mobility with potential applications in medicinal and material chemistry.[6]

Herein, we demonstrate a "green" synthesis towards new γ-amino-cyclobutane-carboxylic acid derivatives. Established procedures for the installation of the cyclobutane moiety in amino acid derivatives have made use of a UV-mediated [2+2] photocycloaddition as key step.[7] More recently, a variety of [2+2] photocycloaddition using visible light have been established.[8] These cycloadditions are either promoted by an electron transfer[9] or based on an energy-transfer-mechanism.[10] In 2012, an intramolecular energy transfer-mediated [2+2] photocycloaddition of tethered bisstyrenes whose oxidation potential has precluded its ability to participate in a radical cation cycloaddition was developed by Yoon and coworkers.[11] The iridium-based catalyst, Ir[(dtbbpy)(dF(CF$_3$)ppy)$_2$]PF$_6$ was a suitable triplet sensitizer for this [2+2] photocycloaddition via visible light. This method could also be applied to 1,3-dienes.[12] The intramolecular variant afforded mostly carbocycles or oxygen-containing heterocycles **2** (Scheme 1). In contrast to this metal-based photocatalytic process, also flavin derivatives can serve as triplet sensitizer for this reaction type,[13] being demonstrated for the cyclization of nitrogen- and sulfur-containing aryl dienes to the corresponding aryl-bicyclo[3.2.0]-heptanes **4**.[14] Already in 1976, Oppolzer *et al.*[15] have observed in the thermolysis of *N*-benzyl-substituted cinnamyl cinnamide the corresponding aza-bicyclo-[3.2.0]-heptanone as byproduct, whose generation was confirmed afterwards by an UV-mediated [2+2] photocycloaddition. An elegant example of utilizing UV light for the triplet-sensitized intramolecular [2+2] photocycloaddition was later reported by Bach *et al.*, who described the stereoselective preparation of 3-azabicyclo[3.2.0]heptanes from *N*,*N*-diallylamines with acetophenone as the sensitizer.[16] More recently, Mykhailiuk and coworkers irradiated *N*-benzyl-substituted amide-linked dienes at 366 nm in the presence of acetophenone as photosensitizer in order to build up 3-azabicylo[3.2.0]heptanes, which are attractive building blocks for drug discovery.[17]

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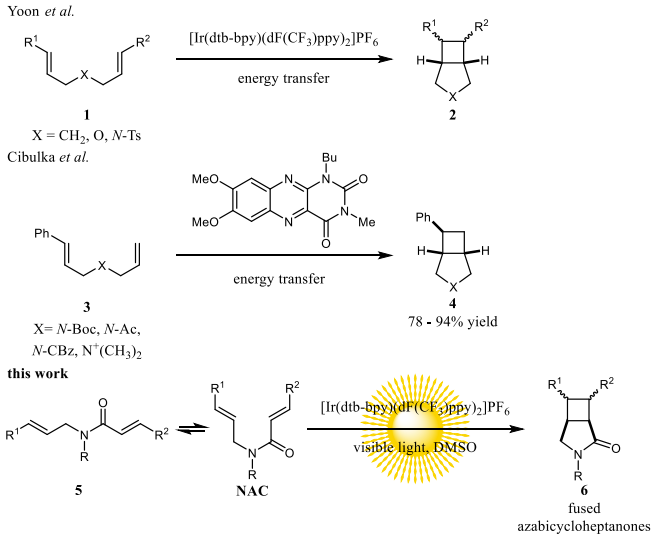
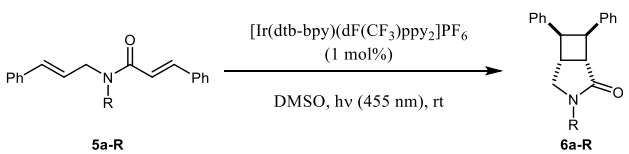
Having the synthesis of novel cyclobutane containing amino acids in mind, we investigated the extension of the iridium-based triplet sensitized reaction to amide linked dienes **5** (Scheme 1).



Scheme 1. Visible light-mediated synthesis of bicyclo[3.2.0] cores.

The seemingly small change from substrate of type **1** to **5** poses a challenge since a near attack conformation (NAC) favorable for cyclization has to be adopted that involves the rotation around an amide bond (Scheme 1). Our study therefore focused initially on screening different substituents R (Table 1), which indeed proved to be crucial for the success of the desired photocyclization. While hydrogen, methyl or phenyl (**5a-H, 5a-Me, 5a-Ph**) did not result in any cyclization product even after 48 h of irradiation, a *tert*-butyl substituent allowed the smooth conversion of **5a-*t*Bu**, giving rise to **6a-*t*Bu** in 79% yield after only 3 h. **6a-*t*Bu** was obtained as a 4:1 diastereomeric mixture in favor for *exo*-diastereomer, having the phenyl groups oriented on the sterically favored convex face of the bicycle.

Table 1. Screening of substituents R on the amide bond.



entry	R	time [h]	yield [%]
1	H	48	-
2	Me	48	-
3	Ph	48	-
4	*t*Bu	3	79 (*dr* 81/19)[a]

[a] Diastereomeric ratio was estimated by crude ^{1}H-NMR, major diastereomer shown.

Two aspects were addressed by computational chemistry to understand the different reactivity of **5a-H** and **5a-*t*Bu**: Stability of the reactive ground state conformation **NAC** and barriers and reaction free energies associated with its reactive triplet state after the energy transfer by the excited photocatalyst (Table 2, Figure 1). To cover for expected dispersion interactions the D3-corrected (u)B3lYP hybrid functional[18a-c] was applied with a 6-311+G** basis set[18d,e] (see SI for further details).

This analysis is based on the assumption that the conformational changes of the substrate are occurring prior to the bimolecular activation step (energy transfer) as indicated by the computed activation barriers associated with conformational changes and bond reorganizations (Figure 1). Hence, the concentration of the reactive conformation of **5**, the so-called near-attack conformation (**NAC**), plays a key role in understanding why **5a-*t*Bu** gives rise to **6a-*t*Bu** via a formal [2+2] cyclization and **5a-H** does prefer the competitive quenching path of the excited state via double bond isomerization. From the excited triplet state of the substrate in principle two chemical quenching pathways can be envisioned: The desired cyclization and the double bond isomerization. The latter is known for stilbenes to proceed via conical intersections (CoI), hence a very efficient and quick reaction path.[19] Therefore, if the linear substrate is activated it probably will not undergo conformational changes in order to allow a cyclization, but rather will follow the CoI path of the double bond isomerization.

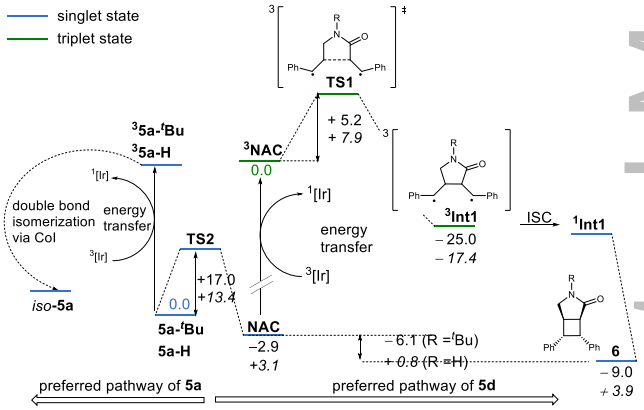
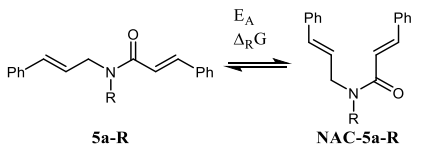


Figure 1. Reaction coordinate diagram of the key-elemental steps describing the cyclisation of **NAC-5a-H** (italic numbers) and **NAC-5a-*t*Bu** and in its triplet state (B3LYP-D3/6-311+G**) on the contrary there is the preferred pathway of **5a-H** featuring the double bond isomerization after energy transfer.

In case of **5a-*t*Bu** it was expected that in analogy to the Thorpe-Ingold effect the formation of the near-attack conformation (**NAC**) is facilitated by the *tert*-butyl group.[20] Although the comparison of both **NAC** (**5a-H, 5a-*t*Bu**) conformers did not show any significant differences in their geometries (see SI) the higher stability of **NAC-5a-*t*Bu** by 6 kcal/mol compared to **NAC-5a-H** (Table 1) supports this hypothesis. Barriers of interconverting the linear **5** to the **NAC** conformation were estimated based on a relaxed PES scan (Table 2, see SI for details) indicating a facile

population of the **NAC** conformer at room temperature with barriers of 17.0 kcal/mol (**5a-*t*Bu**) and 13.4 kcal/mol (**5a-H**). The interconversion of **NAC** back to the linear conformer (19.9 kcal/mol **NAC-5a-*t*Bu** to **5a-*t*Bu**; 16.5 kcal/mol **NAC-5a-H** to **5a-H**) indicate that the **NAC-5a-*t*Bu** has a 300-fold longer life-time than **NAC-5a-H**. In combination with the thermodynamic preference of **NAC-5a-*t*Bu** over its linear conformer, it is **NAC-5a-*t*Bu** that will almost exclusively take part in the energy transfer activation by ^{3}[Ir] than **5a-*t*Bu** and the reversed situation would be true for **5a-H** and **NAC-5a-H**.

Table 2. Overview of the calculated energy values.



5a-R **NAC-5a-R**

entry	energies in [kcal/mol]	R= *tert*-butyl	R= H
1	$\Delta_R G_{(5\ to\ NAC)}$	-2.9	3.1
2	$\Delta E_{A(5\ to\ NAC)}$	17.0	13.4
3	$\Delta_R G_{(^3NAC\ to\ ^3Int)}$	-25.0	-17.4
4	$\Delta G^{\neq}_{(^3NAC\ to\ ^3Int)}$	5.2	7.9
5	$\Delta G^{\neq 0}_{(^3NAC\ to\ ^3Int)}$	15.1	15.6

Starting from the ^{3}**NAC** the barriers for a formal [2+2]-cycloaddition were calculated (Table 2, Figure 1).[21] This C-C bond formation is more favorable both in activation free energy and driving force for ^{3}**NAC-5a-*t*Bu** than for ^{3}**NAC-5a-H**, but still both processes are feasible and fast at room temperature. To close the cyclobutane a second C-C bond formation must take place. This is only possible if a quick ISC occurs between the two states ^{3}**Int** and ^{1}**Int**. As soon as ^{1}**Int** is populated it is believed to react without a barrier to the annulated cyclobutane **6**.[22] Interestingly, the overall reaction free energy **5** to **6** is slightly endergonic in case of **5a-H** (+ 3.9 kcal/mol) and considerably exergonic for **5a-*t*Bu** (– 9.0 kcal/mol).

In conclusion, the difference in reactivity and selectivity of **5a-H** and **5a-*t*Bu** is best explained to be a ground state phenomenon. Analysis of equilibria and lifetimes of reactive conformations are key to the understanding of the unexpected failure of substrates **5** with sterically undemanding R (= H, Me) to not undergo the desired cycloaddition reaction via energy transfer.

To gain insight into which part of the substrate is sensitized, we performed a Stern-Volmer emission quenching study (Figure 2). The fluorescence intensity of the excited-state photocatalyst was decreasing upon titration with substrates **5c-*t*Bu** and *N*-(tert-butyl)-*N*-cinnamylamine (I) in a linear fashion. On the contrary, the emission intensity of photocatalyst stayed constant upon titration with ethyl acrylate (II). These results show that styrene part of the substrate interacts with the excited-state photocatalyst and quenches its luminescence.

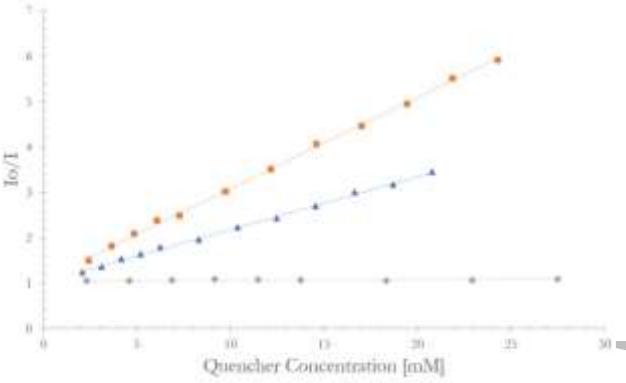


Figure 2. Stern-Volmer plot for the fluorescence quenching of photocatalyst [Ir(dtb-bpy)(dF(CF$_3$)ppy)$_2$]PF$_6$ with **5c-*t*Bu** (▲, *N*-(tert-butyl)-*N*-cinnamylamine (■), and ethyl acrylate (●).

The triplet excited state energy of an amide-linked diene **5a-*t*Bu** was attempted to be experimentally determined from its phosphorescence spectrum, but the substrate is not emissive, thus no information about the triplet energy was obtained. To exclude a single-electron transfer mechanism of the reaction, the redox potential of starting material **5c-*t*Bu** ($E_{1/2}$ = + 1.57 V vs SCE; see SI for further details) was measured and compared with the redox potential of photocatalyst (E = + 1.21 V vs SCE)[23]. Additionally, from the comparison of triplet state energy of the photocatalyst used (E_T = 61 kcal/mol) [23] and the calculated triplet energy of starting material **NAC-5a-*t*Bu** (E_T = 57.8 kcal/mol), it can be concluded that the reaction proceeds through energy transfer.

Variation of the catalyst, light source and reaction temperature the optimized reaction conditions were established: 1 mol% [Ir(dtb-bpy)(dF(CF$_3$)ppy)$_2$]PF$_6$, DMSO as solvent at 40 °C and a blue LED-setup (λ_{max} = 455 nm) as light source (see SI), with which the substrate scope of the title reaction was evaluated (Table 3).

Besides *N*-*tert*-butyl, also *N*-benzyl and *N*-Boc protected amide derivatives cyclize to the cyclobutane containing compounds in moderate to good yields (Table 3), the *N*-Boc derivates however needed longer reaction times. Depending on the location of the phenyl group on the involved double bonds, the reaction times varied dramatically. If the aromatic substituent is placed on the amine moiety (**5c-*t*Bu, 5c-Bn**) the [2+2] reaction is complete within 3-4 h (entries 5, 6), whereas in the case of **5d-*t*Bu** or **5c-Bn** the [2+2] photocycloaddition takes approximately five times longer to reach full conversion (entries 8, 9). The electron-rich heterocycles thiophene and furan on the carbonyl side also accelerate the [2+2] photocycloaddition with respect to the phenyl substituent (entry 8, 12,13). Additionally, if the aromatic substituent is

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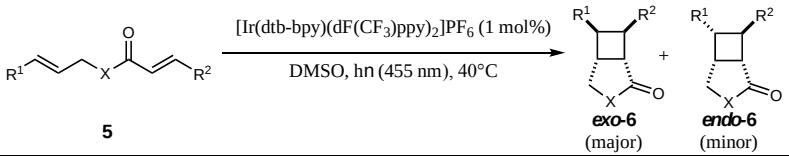
located on the carbonyl side (R^2) a better diastereoselectivity is achieved (entries 8-10, 12-14). The [2+2] cycloaddition of substrates with two aromatic substituents (entry 1-4, 16) resulted in a diastereomeric mixture, from which a minor compound could not be isolated and thus its stereochemistry cannot be assigned with certainty. However, the ^{13}C NMR signals for a methylene carbon and to methylene adjacent carbon in cyclobutane ring of minor isomer are shifted by approximately 5 ppm upfield, which is a common shift for the *endo*- with respect to the *exo* isomer in all azabicyclo[3.2.0]heptanes.[16]

In the case of the ester-linked derivative **5j**, an increase in the reaction temperature to 80 °C was necessary, nevertheless, the cyclobutane **6j** was only obtained in a yield of 29% (entry 16). The low yield, as well as the need for higher temperatures, can be explained by the favorable *s-trans*-conformation of the ester moiety.[24]

Table 3. Substrate scope of the [2+2] photocatalyzed cycloaddition.[a]



entry	R^1	R^2	X	**5/6**	time	yield [%][b]
1	Ph	Ph	*N*-*t*Bu	**5a-/6a-*t*Bu**	3 h	85 (*dr* 81/19)
2	Ph	Ph	*N*-Bn	**5a-/6a-Bn**	4 h	75 (*dr* 72/28)
3	Ph	Ph	*N*-Boc	**5a-/6a-Boc**	24 h	61 (*dr* 78/22)
4	4-MeOPh	Ph	*N*-*t*Bu	**5b-/6b-*t*Bu**	7 h	63 (*dr* 72/28)
5	Ph	H	*N*-*t*Bu	**5c-/6c-*t*Bu**	3 h	78 (*dr* 76/24)
6	Ph	H	*N*-Bn	**5c-/6c-Bn**	4 h	72 (*dr* 85/15)
7	Ph	H	*N*-Boc	**5c-/6c-Boc**	48 h	73 (*dr* 81/19)
8	H	Ph	*N*-*t*Bu	**5d-/6d-*t*Bu**	23 h	60 (*dr* >99/1)
9	H	Ph	*N*-Bn	**5d-/6d-Bn**	19 h	83[c] (*dr* 93/7)
10	H	Ph	*N*-Boc	**5d-/6d-Boc**	14 d	47 (*dr* >99/1)
11	CO_2Me	Ph	*N*-*t*Bu	**5e-/6e-*t*Bu**	48 h	67 (*dr* 76/24)
12	H	2-furanyl	*N*-*t*Bu	**5f-/6f-*t*Bu**	3 h	73 (*dr* >99/1)
13	H	2-thiophenyl	*N*-*t*Bu	**5g-/6g-*t*Bu**	3 h	78 (*dr* >99/1)
14	H	*N*-acetyl-3-indolyl	*N*- *t*Bu	**5h-/6h-*t*Bu**	48 h	35 (*dr* >99/1)
15	H	H	*N*-*t*Bu	**5i-/6i-*t*Bu**	48 h	0
16[d]	Ph	Ph	O	**5j-/6j**	48 h	29 (*dr* 72/28)

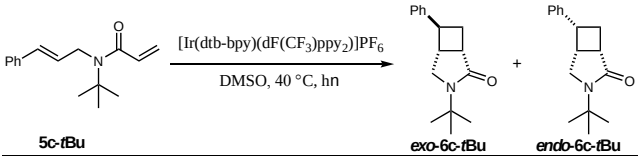
[a] 1 mmol substrate (0.04 M in DMSO), 1 mol% [Ir(dtb-bpy)(dF(CF3)ppy)2]PF6, 40 °C. [b] Diastereomeric ratio was estimated by crude ^1H-NMR. [c] Yield of the major isomer. [d] 80 °C reaction temperature.

Keeping the desired synthesis of cyclic γ-amino acids in mind, we investigated the scale up of the [2+2]-cycloaddition of **5c-*t*Bu** (Table 4).

The best result from a practical point of view was obtained by applying 0.1 mol% of catalyst with a substrate concentration of 0.16 M giving rise to 79% overall yield of the cyclobutane containing substrate (entry 4). A further decrease of catalyst amount led to a prolonged reaction time and concurrently, the yield dropped to 41% and 56%, respectively (entry 6,7).

Thus, employing **5c-*t*Bu** (110 mmol), a conversion of 95% was achieved after 7 d, allowing the production of **6c-*t*Bu** on an 18 g scale (70% yield). The prolonged reaction time was most likely a consequence of the batch reactor that was applied, nevertheless, also under these conditions the catalyst stability was sufficient to achieve the yield that was projected by the optimization studies (Table 4).

Table 4. Catalyst loading of the [2+2] photocycloaddition of compound **5c-*t*Bu**.[a]

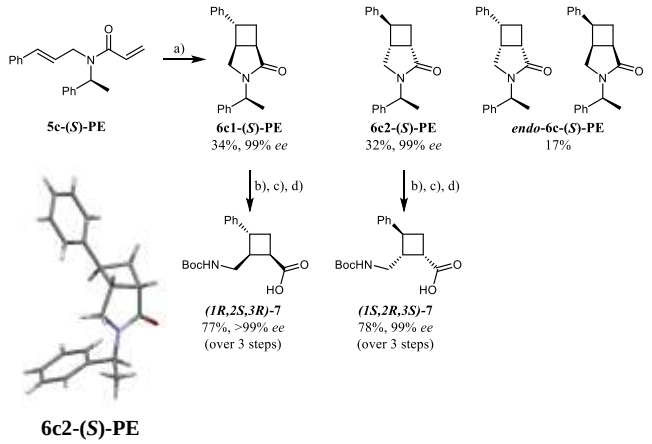


entry	catalyst amount [mol%]	**5c-*t*Bu** Conc. [M]	time [h]	**6c-*t*Bu** yield [%] [a]
1	1	0.04	3	78
2	0.5	0.04	3	73
3	0.5	0.08	3	75
4	0.1	0.04	5	80
5	0.1	0.16	5	79
6	0.01	0.16	48	41
7	0.05	0.16	43	56

[a] Diastereomeric ratio (*exo/endo* 82:18 to 84:16) was estimated by crude ^1H-NMR.

10.1002/adsc.201801413

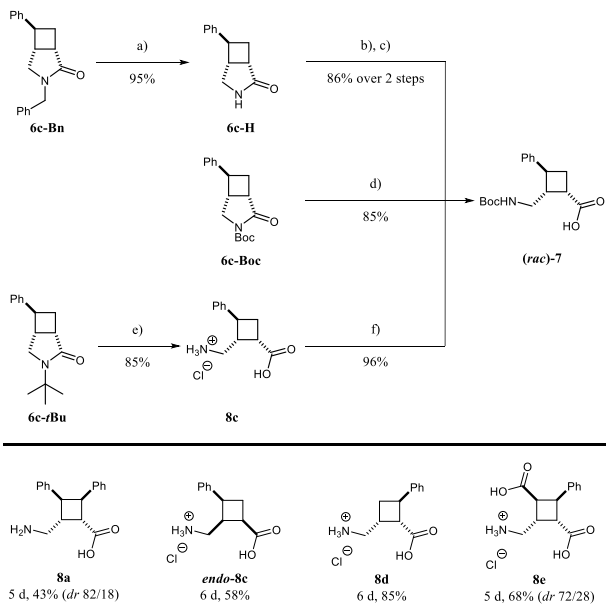
Aiming at the synthesis of the target molecules in enantiopure form, we replaced the *t*Bu group on nitrogen for (*S*)-phenylethyl ((*S*)-PE). Thus, the [2+2] photocycloaddition of the enantiomerically pure amide linked diene **5c-(*S*)-PE** gave rise to a mixture of four diastereomers **6c-(*S*)-PE** (*dr* 43:43:7:7) in an overall yield of 83% (Scheme 2), reflecting well the diastereomeric ratio obtained with achiral **5c-*t*Bu**. Obviously, no asymmetric induction is executed from the chiral auxiliary, nevertheless, the major *exo*-diastereomers **6c1-(*S*)-PE** und **6c2-(*S*)-PE** could be readily separated by column chromatography and isolated in pure form. The absolute stereochemistry could be established by X-Ray analysis of **6c2-(*S*)-PE**. From here, both enantiomers of **7** could be obtained by removing the chiral auxiliary under Birch conditions, followed by *N*-Boc protection and lithium hydroxide-mediated ring opening in high yield.



Scheme 2. Stereoselective strategy for the synthesis of γ-cyclobutane amino acids **7**. Reaction conditions: a) [Ir(dtb-bpy)(dF(CF_3)ppy$_2$)]PF_6 (1 mol%), DMSO, 40 °C, hv, 5 h, 83% (*dr* 43:43:7:7); b) Na, NH_3 (li.), *tert*-BuOH, -33 °C, 1 h; c) Boc_2O, NEt_3, DMAP, MeCN, 0°C to rt, 2 d; d) LiOH, THF/H_2O (1:1), rt, 22 h.

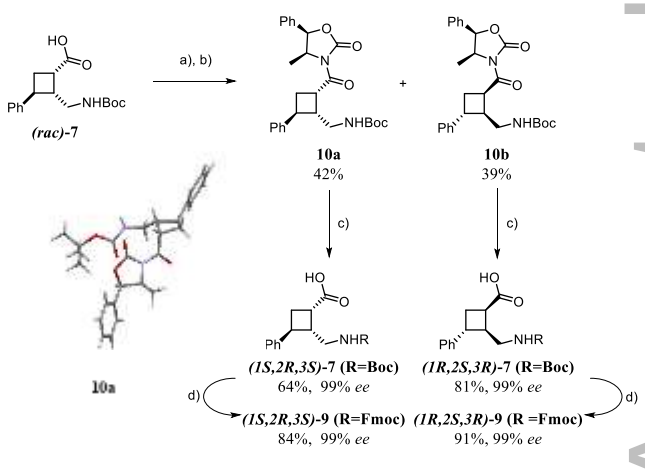
Alternatively, the racemic derivatives **6c-Bn**, **6c-Boc**, or **6c-*t*Bu** could be converted by deprotection / ring opening sequences into (*rac*)**-7** in high yields (Scheme 3).

Analogously to transformation of **6c-*t*Bu** to ***exo*-8c**, bicyclic compounds **6-(a-g)** with *N*-*tert*-butyl group were heated in 25% aqueous HCl to obtain corresponding cyclobutane amino acids (Scheme 3). As a result, amino acids with a single (***endo*-8c**, **8d**) as well as two phenyl groups (**8a**) were prepared in moderate to good yields. Upon the treatment of **6e-*t*Bu** in acidic solution, both ester and amide groups were hydrolysed, and *N*-*tert*-butyl group was cleaved simultaneously to afford **8e**. Other *N*-*tert*-butyl derivatives, such as **6f-**and **6g-*t*Bu** decomposed under the same reaction conditions. Purification of amino acid, derived from **6b-*t*Bu**, was not possible. All amino acids were obtained as chloride salts with the exception of **8a**, which required purification by elution through an ion exchange resin (H^+-form).



Scheme 3. Three different synthetic routes towards racemic *(rac)*-**7**. Reaction conditions: a) Na, NH_3 (li), *tert*-BuOH, –33 °C, 1 h; b) Boc_2O, NEt_3, DMAP, MeCN, 0 °C to rt, 2 d; c) LiOH, THF/H_2O (1:1), rt, 1 d; d) LiOH, THF/H_2O (1:1), rt, 2 d; e) HCl (25% aq), reflux, 5 d; f) Boc_2O, $NaHCO_3$, dioxane/H_2O (1:1), 0 °C to rt, 2 d.

The (*rac*)**-7** was subsequently resolved in its enantiomers following a protocol developed by Aitken and coworkers[25] (Scheme 4). An X-ray structure of **10a** could be obtained, which allowed the correlation of the absolute stereochemistry of the final amino acids of either enantiomer **7**.

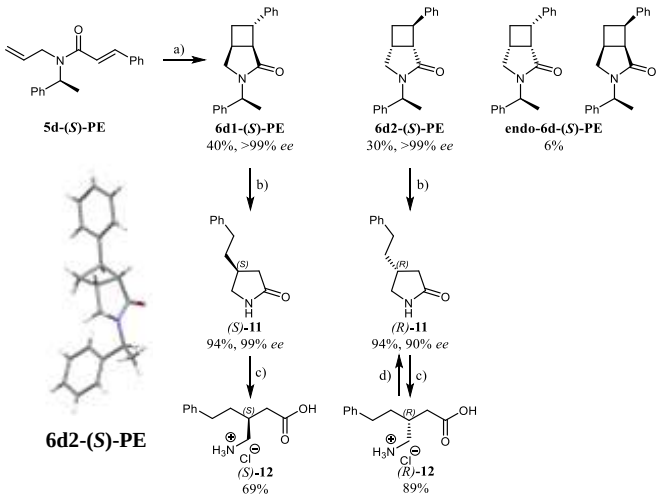


Scheme 4. Chiral resolution of the racemic cyclobutane amino acids **7**. Reaction conditions: a) PivCl, NEt_3, THF, 0 °C, 1 h; b) lithium (4*S*,5*R*)-4-methyl-2-oxo-5-phenyloxazolidin-3-ide, THF, -78 °C, 1 h; c) H_2O_2, LiOH, THF/H_2O, 0 °C, 5 h, (4*S*,5*R*)-4-methyl-2-oxo-5-phenyloxazolidine was almost quantitatively recovered; d) i) DCM, TFA, rt, 24 h, ii) dioxane/H_2O (1:1), FmocOSu, $NaHCO_3$, 0 °C to rt, 24 h.

To be compatible with solid phase peptide synthesis using the Fmoc strategy, the exchange of Boc to Fmoc

could be readily performed, giving rise to either enantiomer of **7** in high yield and enantiopurity of 99% *ee*. Protecting group was performed yielding 84% of enantiomer **(1*S*,2*R*,3*S*)-9** (R=Fmoc) and 91% of enantiomer **(1*R*,2*S*,3*R*)-9** (R=Fmoc) each with an unrelieved enantiomeric excess of 99% (Scheme 4).

A sequence analogous to the one shown in Scheme 2 was also attempted with **5d-(*S*)-PE**, in which the phenyl group is connected to the enone rather than to the allyl fragment. The *exo*-diastereomers **6d1-(*S*)-PE** and **6d2-(*S*)-PE** were formed with high preference over the corresponding *endo*-diastereomers, but again, the chiral auxiliary did not exert an influence on the newly formed stereocenters (Scheme 5).



Scheme 5. Synthetic route towards (*S*)- and (*R*)-3-(aminomethyl)-5-phenylpentanoic acid **12**. Reaction conditions: a) [Ir(dtb-bpy)(dF(CF_3)ppy$_2$)]PF_6 (1 mol%), DMSO, 40 °C, hν, 24 h, 76%; b) Na, NH_3 (li), *tert*-BuOH, –33 °C, 1 h; c) HCl (25% aq), reflux, 24 h, d) EDC•HCl, NEt_3, DCM, rt, 24 h.

Unexpectedly, under Birch reduction conditions to remove the *N*-protecting group in **6d-(*S*)-PE** also the regioselective ring opening of the cyclobutane core was observed giving rise to phenyl ethyl pyrrolidinone **11**. While **6d1-(*S*)-PE** could be isolated in pure form by column chromatography, **6d2-(*S*)-PE** contained minor impurities of the corresponding *endo*-diastereomers, which explains the slight decrease to 90% *ee* that is observed for (*R*)-**11.**

Refluxing either enantiomer of pyrrolidinones **11** in a 25% aqueous solution of HCl gives rise to (*S*)-**12** (99% *ee*) and (*R*)-**12** (90% *ee*) being independently confirmed by X-ray structure analysis, the racemate being described as an anticonvulsant with good biological activity[26]. No erosion of stereochemistry is observed in this ring-opening reaction, which was confirmed by converting back (*R*)-**12** to (*R*)-**11** upon treatment with EDC. So far, only the group of Wu et al. had developed an asymmetric synthesis for the (*R*)-enantiomer (*R*)-**12**.[26], [27], [28]

In conclusion, we have developed a visible light-mediated, intramolecular [2+2] photocycloaddition of amide-linked dienes catalyzed by [Ir(dtb-bpy)-(dF(CF_3)ppy)$_2$]PF_6 as triplet sensitizer. The protecting group at the amide nitrogen atom plays a key role for a successful cyclization, which was elucidated by DFT calculations. The resulting azabicycloheptanones could be converted in an enantiomerically manner into γ-cyclobutane amino acids. Furthermore, this methodology was applied for the enantioselective synthesis of both enantiomers of anticonvulsant 3-(aminomethyl)-5-phenylpentanoic acid.

Experimental Section

Typical Procedure for the [2+2] Photocycloaddition: Synthesis of (±)-3-(*tert*-butyl)-6-phenyl-3-azabicyclo-[3.2.0]heptan-2-one (*exo*-6c-*t*Bu and *endo*-6c-*t*Bu): The amide linked diene **5c-*t*Bu** (241 mg, 990 µmol, 1 equiv.) was dissolved in DMSO (25 mL, 0.04 M) together with [Ir(dtb-bpy)(dF(CF_3)ppy)$_2$]PF_6 (11.2 mg, 0.010 mmol). The reaction mixture was stirred at 40 °C for 3 h with a blue LED-setup. After completion, the reaction mixture was diluted with H_2O (10 mL) and DEE (30 mL). Then the phases were separated, and the aqueous phase was extracted three times with DEE (each 30 mL). The combined organic phases were washed twice with H_2O (each 10 mL) and once with brine (20 mL). Finally, the combined aqueous phases were back-extracted with DEE (30 mL). The combined organic phases were dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. By silica gel column chromatography (hexanes/EtOAc 3:1) both diastereomers of compound **6c-*t*Bu** were separated and were obtained in an overall yield of 78% (*dr* 83:17; ***exo*-6c-*t*Bu**: yellow oil, 157.5 mg, 647 µmol; ***endo*-6c-*t*Bu**: yellow solid, 32.4 mg, 133 µmol). ***exo*-6c-*t*Bu**: R_f = 0.33 (hexanes/EtOAc 2:1); ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.36 – 7.29 (m, 2H), 7.24 – 7.18 (m, 3H), 3.66 (dd, *J* = 10.2, 6.3 Hz, 1H), 3.48 – 3.35 (m, 2H), 3.03 – 2.86 (m, 2H), 2.66 – 2.41 (m, 2H), 1.47 (s, 9H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ = 177.4, 144.1, 128.5, 126.4, 126.3, 54.0, 51.6, 44.4, 39.5, 38.2, 31.8, 27.7; IR (neat) ν [cm^{-1}] = 3060, 3020, 2970, 2870, 1669, 1401, 1364, 1289, 1222, 749, 700; HRMS: (APCI-MS) calc. for $[C_{16}H_{22}NO]^+$ $[M+H]^+$ 244.1696, found 244.1700; ***endo*-6c-*t*Bu**: R_f = 0.2 (hexanes/EtOAc 2:1); mp = 51-52 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.33 (t, *J* = 7.5 Hz, 2H), 7.28 – 7.14 (m, 3H), 3.91 (dd, *J* = 16.5, 9.6 Hz, 1H), 3.31 (dd, *J* = 10.5, 8.2 Hz, 1H), 3.17 – 3.00 (m, 2H), 2.92 (d, *J* = 10.9 Hz, 1H), 2.87 – 2.75 (m, 1H), 2.53 (ddd, *J* = 11.2, 6.6, 4.2 Hz, 1H), 1.22 (s, 9H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ = 177.4, 139.7, 128.3, 128.1, 126.5, 53.8, 46.8, 40.1, 39.9, 32.7, 28.3, 27.7, 27.6, 27.5; HRMS: (APCI-MS) calc. for $[C_{16}H_{22}NO]^+$ $[M+H]^+$ 244.1696, found 244.1707, calc for $[C_{32}H_{43}N_2O_2]^+$ $[2•(M+H)]^+$ 488.3352, found 488.3355.

Acknowledgements

This work was supported by the Friedrich-Ebert-Stiftung and the DFG (Graduiertenkolleg 1626 Photocatalysis and RE948-9). The authors thank the Department of Crystallography, Universität Regensburg, for carrying out the X-Ray crystal structure analyses, Marsel Shafikov for phosphorescence measurements and Regina Hoheisel for cyclic voltammetric measurements.

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[21] Considering that the energy transfer occurs from the Ir-catalyst in its triplet excited state to the substrate, the first onward reaction step of the formal cycloaddition process was calculated in the triplet manifold (Table 2, Figure 1). In addition, the triplet state is significantly lower in energy by 17.1 kcal/mol (R=^{t}Bu) and 18.6 kcal/mol (R =H) for the NAC conformer.

[22] The recombination of singlet biradicals in close proximity are usually barrier-free processes.

10.1002/adsc.201801413

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[27] The optical rotation of (*R*)-**12** was reported as α_D^{25} +48.2 (c 4.02, MeOH, 95% *ee*, Ref. [23]) whereas in this work the optical rotation was determined to be α_D^{20} – 14.7 (c 1.0, MeOH, 90% *ee*). We have converted back (*R)*-**12** to (*R*)-**11**, which allowed the correlation of enantiopurity by chiral HPLC (see SI for details).

[28] CCDC 1874440, **6c2-(*S*)-PE**, CCDC 1874440 **6c2-(*S*)-PE**, 1874442 **10a**, 1874443 (*R*)-**12**, and 1874444 (*S*)-**12**. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

10.1002/adsc.201801413

UPDATE

Visible Light-Mediated Synthesis of Enantiopure γ-Cyclobutane Amino and 3-(Aminomethyl)-5-phenylpentanoic Acids

Adv. Synth. Catal. **Year**, *Volume*, Page – Page

Sabine Kerres, Eva Plut, Simon Malcherek, Julia Rehbein,* and Oliver Reiser*