An Expedient Radical Approach for the Decarboxylative Synthesis of Stereodefined All-Carbon Tetrasubstituted Olefins

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Abstract: We report a user-friendly approach for the decarboxylative formation of stereodefined and complex tri- and tetra-substituted olefins from vinyl cyclic carbonates and amines as radical precursors. The protocol relies on easy photo-initiated α-amino-radical formation followed by addition onto the double bond of the substrate resulting in a sequence involving carbonate ring-opening, double bond relay, CO_2 extrusion and finally *O*-protonation. The developed protocol is efficient for both mismatched and matched polarity substrate combinations, and the scope of elaborate stereodefined olefins that can be forged including drug-functionalized derivatives is wide, diverse and further extendable to other types of heterocyclic and radical precursors. Mechanistic control reactions show that the decarboxylation step is a key driving force towards product formation, with the initial radical addition under steric control.

Introduction

Stereodefined tri- or tetra-substituted olefins are valuable motifs playing a significant role in natural products[1] and pharmaceuticals.[2] They serve as versatile and structurally diverse fragments in various drugs (Scheme 1a)[3] and are also suitable as precursors for the preparation of complex skeletons that feature contiguous and highly substituted sp^2- and sp^3-hybridized carbon centers.[4] Classical synthetic strategies towards these kind of highly substituted olefins involve for instance Wittig and/or Horner-Wadsworth-Emmons olefination,[5] olefin metathesis[6] and alcohol-based elimination reactions.[7] These approaches have been shown to be generic strategies for the construction of the densely substituted alkenes,[8] however they typically encompass poor regio- and stereoselectivity control.

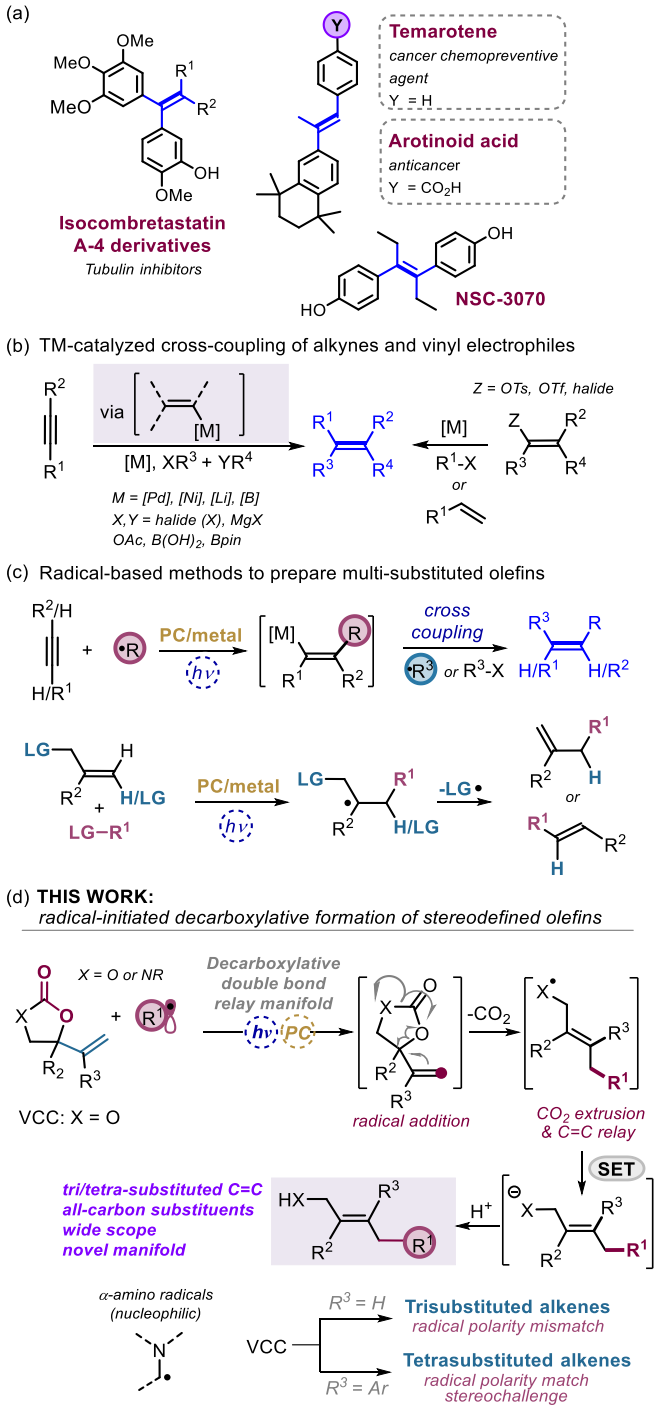
Over the last decades, the cross-coupling of either alkynes or vinyl electrophiles catalyzed by transition metal (TM) catalysts derived from Pd,[9] Ni,[10] Cu[11] among others[8] has emerged as a useful and versatile approximation. Despite that these latter TM-promoted transformations are powerful methods to build up multi-substituted olefins, they may undeniably suffer from overall low stereocontrol and demanding process conditions such as high temperature, the requirement of excess organometallic reagents and the presence of a strong base (Scheme 1b) possibly affecting the level of user-friendliness and functional group tolerance.[8] A common way to generate productive vinyl electrophiles from alkynes is by trapping it via a carbometallated species using an electrophilic halide source,[12] or through enolization of a ketone and trapping the corresponding enolate with sulfonate reagents.[13]

Apart from classical organometallic process towards elaborate olefin synthesis, more recently it was demonstrated that radical-initiated protocols can also offer a practical tool for the late stage functionalization of tedious olefins and alkynes propelled via photocatalytic methodologies (Scheme 1c).[14,15] In this context, the Xie group employed pre-defined alkenyl sulfonates and carboxylic acids as radical precursors to forge stereodefined, tetra-substituted alkenes enabled by dual Ni/photoredox catalysis.[16] Metalla-photocatalytic cascade reactions of alkynes have been more frequently employed in the pursuit of novel, highly substituted alkene frameworks.[17] For instance, Rueping[18] and Chu[19] reported Ni-catalyzed processes towards mostly trisubstituted alkenes that are produced by aryl-sulfonylation and alkyl-arylation of alkynes.

The reactivity paradigm involving radical addition onto olefin substrates has been well-established,[20] and usually follows a sequence of radical addition to the alkene group promoted by a single-electron-transfer (SET) event following deprotonation.[20b] Alternatively, the adoption of radical-mediated desulfonylation of allyl sulfones and similar approaches by β-elimination of a suitable leaving group has marked a novel synthetic strategy for the development of substituted, functional alkenes.[21] However, synthesis of all-carbon tetra-substituted olefins through these latter approaches remains challenging in terms of stereocontrol and alkene complexity.

Herein, we present a conceptually different photocatalytic approach enabling radical chemistry to foster the preparation of both stereodefined tri- and tetra-substituted olefins (Scheme 1d) from vinyl cyclic carbonates (VCCs)[22] using a decarboxylation as a process driver. These highly modular VCCs incorporate a terminal double bond, and we envisioned a manifold that would start with in situ radical addition using tertiary amines as convenient radical precursors. α-Amino radical addition would then provoke decarboxylation in the VCC under visible-light photo-irradiation without the need for a TM catalyst to stabilize the allyl species.[23] The challenge in using VCCs with R^3 = H would be to overcome the polar mismatch between the olefin and radical species[24]. In the case of R^3 being an aryl group there is obviously a better match between the reactants with the C=C bond being a much better acceptor, but here the stereocontrol over the mutual positional of the different carbon-substituents represents a crucial factor. These polarizing effects[24] enable nucleophilic radical

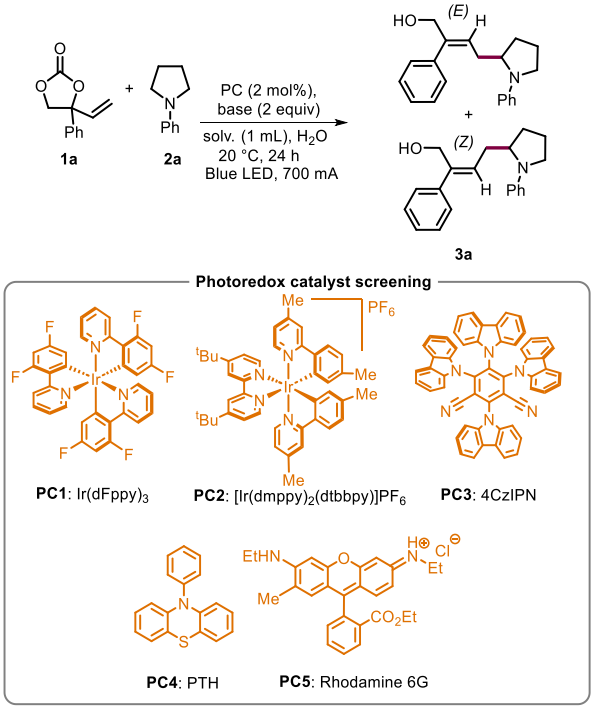
addition of α-amino radical species with high regioselectivity onto the C=C bond of the VCC, and a formal relay of the latter within the final product. The developed photocatalytic process shows wide scope in the target products, and can be extended to other sources of radicals, related heterocycles and can be combined with complex substrates such as drug molecules to build up advanced synthons. Further to this, mechanistic studies support the view that CO_2 extrusion in the VCC is key, and that the stereochemical configurations of the final products are retained under the process conditions.



Scheme 1. (a) Selected examples of bioactive molecules featuring a stereodefined, tetra-substituted all-carbon substituted olefin. (b) Organometallic strategies toward stereodefined olefins. (c) Radical approaches. (d) Focus of this work.

Results and Discussion

Table 1. Screening of reaction conditions and PCs for the conversion of VCC **1a** and *N*-phenyl-pyrrolidine **2a** into targeted trisubstituted olefin **3a**.[a]



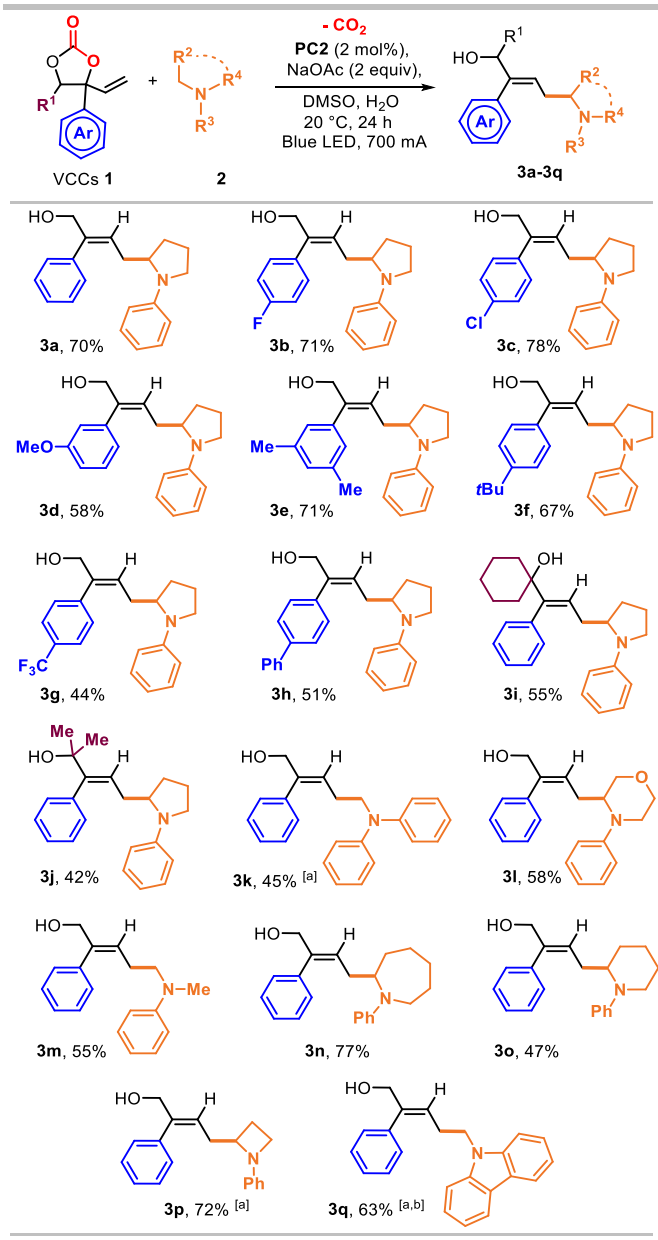
Entry	PC	Solv./base	Conv. **1a** [%][b]	**3a** [%][b]	*E/Z*
1	**PC1**	DMSO, NaOAc	>99	58	>99:1
2	**PC2**	DMSO, NaOAc	>99	71	>99:1
3	**PC3**	DMSO, NaOAc	94	49	65:35
4	**PC4**	DMSO, NaOAc	74	51	78:22
5	**PC5**	DMSO, NaOAc	32	20	30:70
6	**PC2**	DMSO, Ph_3N	82	35	>99:1
7	**PC2**	DMSO, Cs_2CO_3	>99	61	>99:1
8	**PC2**	DMSO, $NaHCO_3$	96	47	>99:1
9[c]	**PC2**	DMSO, NaOAc	95	48	>99:1
10	**PC2**	DMF, NaOAc	>99	27[e]	>99:1
11	**PC2**	CH_3CN, NaOAc	93	42	>99:1
12[d]	**PC2**	DMSO, NaOAc	95	60	>99:1
13	**PC2**	*no light*	0	0	–
14	no **PC**	DMSO, NaOAc	26	18	33:67
15	**PC2**	*under air*	>99	19	>99:1
16	**PC2**	*no base*	0	0	–

[a] General conditions: **1a** (0.10 mmol), **2a** (0.25 mmol), **PC** (2.0 mol%), NaOAc (2 equiv), solvent (1.0 mL), H_2O (50 µL), 700 mA blue LED, 20 ºC for 24 h. [b] Yields were determined by ^1H NMR using 1,3,5-tri-methoxybenzene as internal standard, the *E/Z* values were also determined by this method. [c] In the absence of added H_2O. [d] Using 5 equiv of **2a** (0.50 mmol). [e] Byproduct **13** generated in 26% yield.

Process screening. We started our studies by combining VCC **1a** and *N*-phenyl pyrrolidine **2a** as a substrate combination. Taking advantage of the ease of α-amino radical formation from suitable *N*-based precursors under appropriate photocatalytic conditions,[26] we first screened a small set of photocatalysts (PCs, Table 1; entries 1-5). Among the five **PC**s tested, we found that the use of Ir-derived **PC2** (entry 2) gave the best results and promoted full conversion of **1a** with a 71% NMR yield of **2a** as a single stereoisomer (*E*). Further variations of this protocol (solvents, bases, additives; see the Supporting Information, SI, for full details) showed that (1) the presence of a minimal amount of H_2O boosts the reaction (entry 2 vs. 9; 71 vs. 48% yield of **2a**) and the presence of light (entry 13), the **PC2** (entry 14) and base (entry 16) are indispensable. The reaction under air (entry 15) showed lower efficiency likely as a result of interference with the in situ formed α-amino radicals.

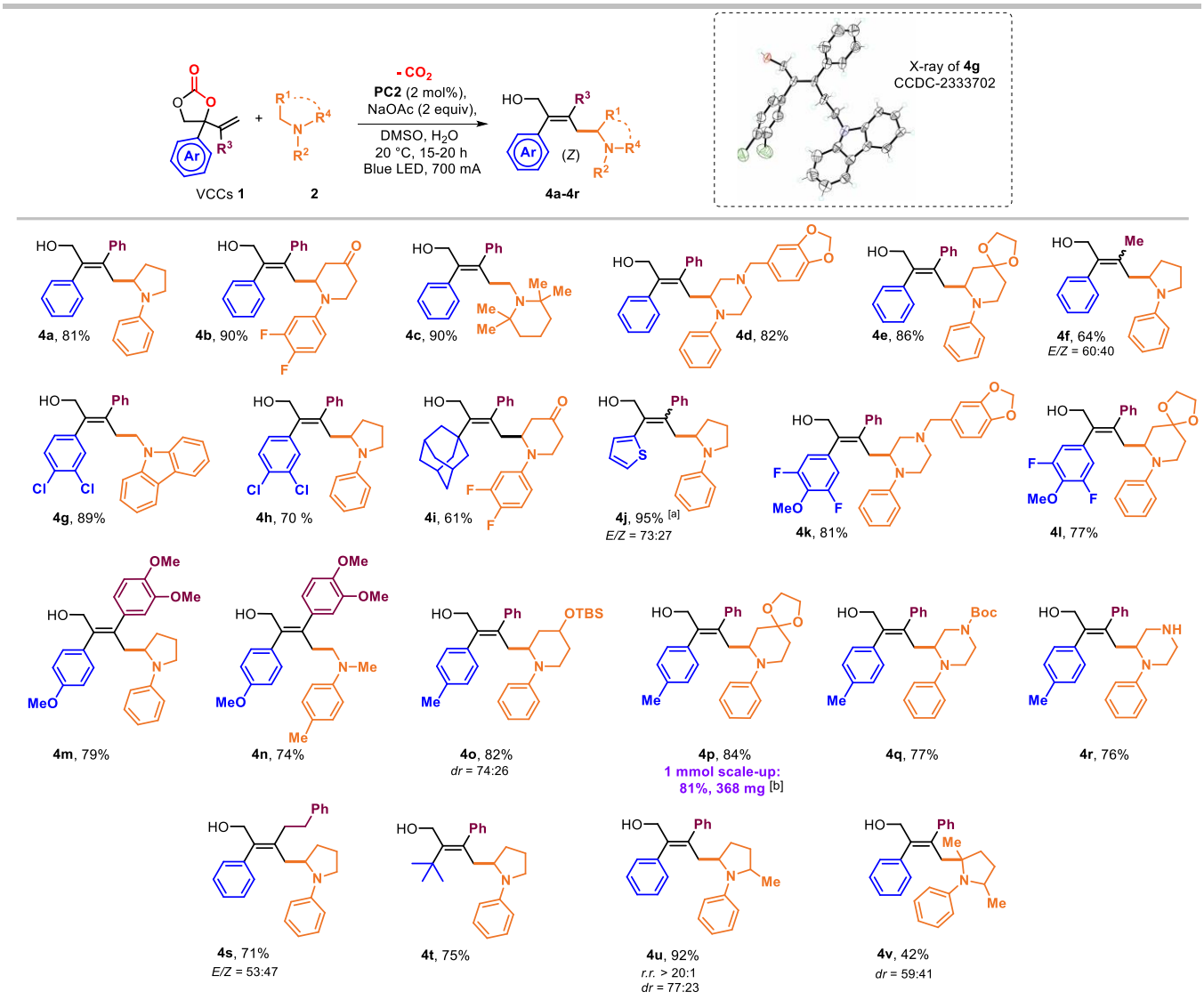
Scope of tri-substituted olefins. We first explored the preparation of trisubstituted olefins starting from VCCs **1** that are devoid of an activating substituent. The terminal C=C bonds are relatively unreactive but undergo the target transformation combining a variety of VCC and amine reagents (Scheme 2). Various aryl groups in the VCC can be employed providing olefin products **3a**-**3h** in yields of up to 78% and, importantly, as a single stereoisomer (*E*). More elaborate VCCs (at R^1) can also be used allowing to further structurally diversify the products (**3i** and **3j**). Apart from the VCC, the structure of the amine precursor can also be easily altered and examples of more functional acyclic and larger cyclic amines with ring sizes ranging from 4 to 7 can productively engage in this protocol leading to their trisubstituted olefin products (**3k**-**3q**) with appreciable yields. It should be noted that the protocol is highly robust, has a high level of user-friendliness and photoreactions are easily set up making it thus attractive towards the formation of challenging stereodefined tetra-substituted olefins (*vide infra*).

Scope of tetra-substituted olefins. Given the success of the formation of products **3a**-**3q**, we then focused on using VCCs with an aryl group introduced at R^3. Obviously, this should more easily stabilize the initial radical addition product, and lead to the target products but simultaneously introduces a stereochemical challenge. The developed protocol could be, however, easily extended to the synthesis of complex olefin scaffolds (Scheme 3, **4a**-**4r**) with overall improved product yields. With R^3 in the VCC **1** being a simple phenyl (**4a**-**4e**) while varying the nature of the amine, good yields of product of up to 90% were attained, and they were isolated as single stereoisomers (note that in these specific compounds, the configurations are assigned as *Z*). Variation of the aryl-group in the VCC was also feasible creating a wider pool of aromatic substituents in the olefin products **4g**-**4r** that were typically formed in yields >75% as stereodefined products (*Z*/*E* >99:1). In a few cases, though, lower *Z*/*E* values were obtained. The synthesis of **4f** (64%, *E*/*Z* = 60:40; R^3 = methyl) and **4s** (71%, *E*/*Z* = 53:47; R^3 = -$(CH_2)_2C_6H_5$) proceeded with lower process control and at this stage we believe that this is a result of a lower degree of steric discrimination between both sides of the C=C bond. In the case of products **4j** (95%, *E*/*Z* = 73:27) and **4o** (82%, *dr* = 74:26), the lower stereo-outcome of the process can be tentatively explained by the presence of a (photoactive) thiophene unit (**4j**). For **4o**, a possible intramolecular HO···Si interaction involving the pendent OTBS group may influence the reactive conformation along its formation pathway. When replacing the aryl group by a *tert*-butyl one in the VCC had no detrimental effect on the selectivity of the process and product **4t** could be isolated in a yield of 75%. We also tested amine precursors with α-substituents (methyl groups; synthesis of **4u** and **4t**) providing **4u** in good yield and excellent regiocontrol (92%, *r.r.* >20:1) while **4t** was produced in moderate yield (42%) likely because of a more sterically hindered radical being in situ formed when exposed to the photocatalyst slowing down its addition to the double bond of the VCC.



Scheme 2. Scope of trisubstituted olefins **3a**-**3q** derived from various VCCs **1** and amine precursors **2** under the conditions of Table 1 entry 2, and all reported yields are of the isolated products with *E/Z* >99:1 unless stated otherwise. [a] 2 equiv of the amine were used. [b] Using $[Ir(dFCF_3ppy)_2(dtbbpy)]PF_6$ instead of $[Ir(dmppy)_2(dtbbpy)]PF_6$.

Apart from the cyclic amine precursors, the synthesis of **4n** (74%) shows that acyclic amines are also efficient reaction partners in this radical based protocol towards tetrasubstituted olefins. Finally, the preparation of **4p** was performed at a 10-fold scale providing similar efficiency (81 vs 84% yield) and showing the process to be robust in this respect. In the case of **4g**, we were



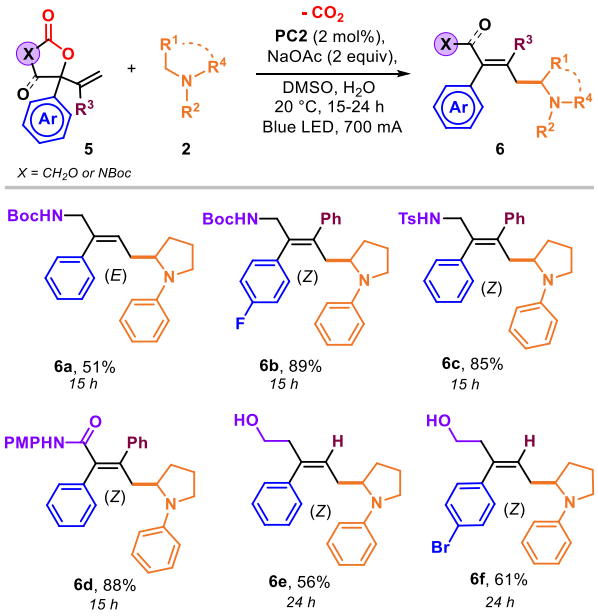
Scheme 3. Scope of tetrasubstituted olefins **4a**-**4r** derived from various VCCs **1** and amine precursors **2** under the conditions of Table 1 entry 2, and all reported yields are of the isolated products with *E/Z* >99:1 unless stated otherwise. The insert shows the X-ray molecular structure of **4g**. [a] The reaction time was 30 minutes. [b] 2 equiv of the amine were used.

able to unambiguously confirm its molecular structure by single crystal structure determination using 3D electron diffraction (see insert at the top of Scheme 3),[27] which in combination with 2D NMR methods (GOESY-^{1}H NMR, see the SI for full details) were used to assign to stereochemical configurations of all products.

Extending the reaction partners. We then set out to amplify the reaction partners in terms of the heterocyclic (Scheme 4) and radical precursors (Scheme 5). We considered both the use of two cyclic carbamates (X = –NBoc) and a larger-ring, six-membered analogue of the VCCs **1** (X = –CH_2O instead of –O) and combined these under the optimized reaction conditions (Table 1, entry 2) with the benchmark amine *N*-phenyl pyrrolidine. The use of NBoc- and NTs- based, five-membered cyclic carbamates is also feasible and shows essentially the same reactivity patterns. The trisubstituted olefin (**6a**; *E*/*Z*>99:1) was isolated in 51% yield, whereas tetrasubstituted **6b** and **6c** were isolated in higher (89% and 85%, respectively) yield as exclusive *Z*-isomers. Other heterocyclic precursors with an additional carbonyl substituent (synthesis of **6d**) can also be effectively employed and allow products such as **6d** (88%) to be isolated featuring an enamide fragment. Apart from five-membered precursors such as cyclic carbonates/carbamates, six-membered vinyl cyclic carbonate analogues of **1a**[26] are also productive substrates leading to the formation of stereodefined trisubstituted olefins **6e** (56%) and **6f** (61%). These results help to establish that the reaction protocol is not necessarily limited to a specific kind of heterocyclic substrate.

We further assessed the use of (slightly) different radical precursors (Scheme 5) taking advantage of the availability and ease of *N*-based radical formation from TMS-based precursors, alkyl trifluoroborate salts and 1,4-dihydropyridines (DHPs). In the case of the TMS-containing *N*-reagents, in the presence of a VCC with a Ph-substituent on the C=C bond, the formation of tetrasubstituted olefins **7a**-**7e** was straightforward in up to 93% yield, and in all case as exclusive *Z*-isomers. When various organotrifluoroborate salts were used as radical precursors, a similar photocatalytic protocol afforded **7f-7h** in 79-96% yield and again the products were isolated as single stereoisomers (*Z*). Similarly, the use of 1,4-dihydropyridines (DHPs) as radical

Drug-modification potential. Given the efficient nature of the use of TMS-derived *N*-based reagents as suitable radical precursors, we then examined four α-amino functionalized drug molecules towards their functionalization using the optimized photocatalytic protocol (Scheme 6, compounds **9a-d**). Gratifyingly, we found that our protocol could also be applied successfully leading to good yields of these drug-modified scaffolds (64-90%) and generally with high stereofidelity.

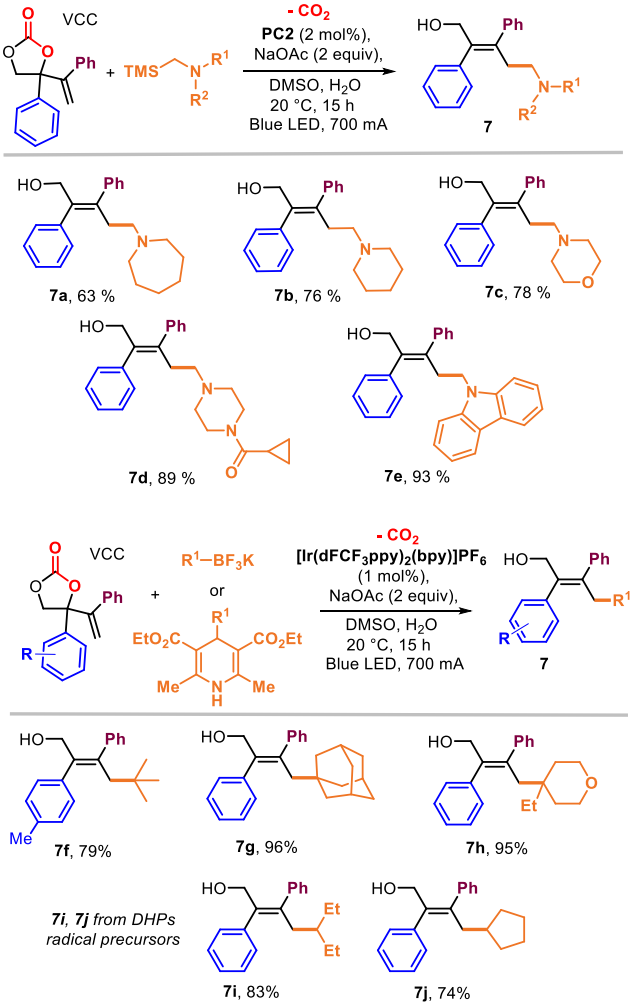


Scheme 4. Use of other heterocycles to expand the scope of the developed photocatalytic process.

precursors gave access to product **7i** (83%) and **7j** (74%) in good yields.

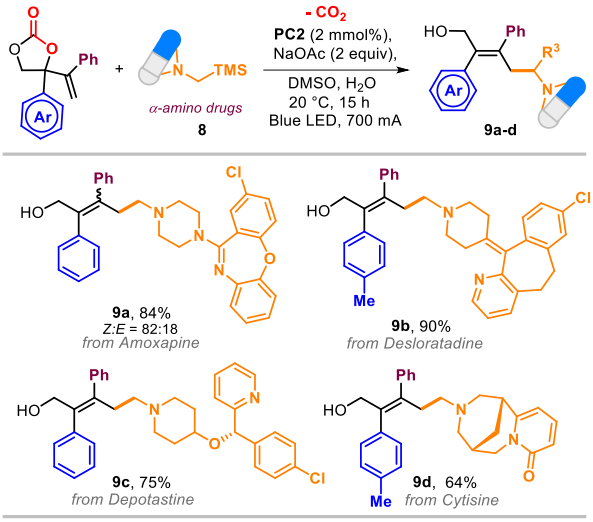
Post-synthetic use of olefinic products. In order to assess the suitability of stereodefined tetrasubstituted olefins as possible synthons, we examined some transformations of **4p** and **9b** that can create entries to further diversified products (Scheme 7). First **4p** was subjected to a formal amination by treating TsNHBoc in the presence of DEAD/PPh_3 (Mitsunobu reaction) delivering allylic amine product **10a** in 73% yield. Next, we examined the oxidation of the same starting material using *m*CPBA, which produced the epoxide **10b** in 85% as a mixture of two diastereoisomers (67:33 *dr*). The alcohol group within **4p** and **9b** were then both used to create conjugates with carboxylic acid-terminated drug molecules (naproxen and indomethacin) under standard Steglich esterification conditions. In both cases (products **10c** and **10d**) the corresponding esters were obtained in high yield (95 and 88% yield, respectively) thus showing further options to create increasing molecular complexity.

Mechanistic control experiments. We finally conducted a number of control experiments (Scheme 8) to support the mechanistic view expressed in Scheme 1d. First (Scheme 8a), we subjected VCC **11a** (with two methyl groups on the terminal carbon of the vinyl fragment) and **11b** (with only one methyl substituent) to the optimized reaction conditions to sterically challenge the envisioned radical addition step. In both cases, we were not able to note any product formation, thus aligning with the view that the reaction starts with radical addition to the double bond of the VCC. Second, to probe the idea that CO_2 extrusion is a crucial step, we performed the optimized procedure on to a vinyl epoxide substrate that cannot undergo decarboxylation but should lead to the same manifold after ring-opening (Scheme 8b).

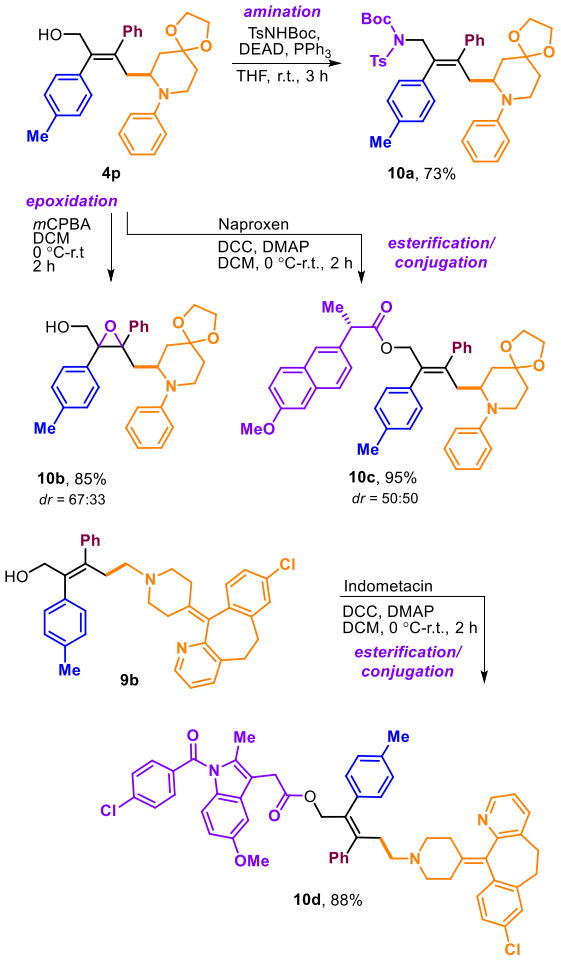


Scheme 5. Use of other radical precursors to expand the scope of the developed photocatalytic process. Here 2 equiv of the TMS-based amine, trifluoroborate salt or DHP radical precursor were used.

In this case we were not able to observe any formation of **3a** suggesting indeed that loss of CO_2 is driving the reaction forward. Further to this, when the optimized protocol is carried out in 1 atm of CO_2, we found a nearly similar yield (Scheme 8c: **4a**, 75 vs 81%) clarifying that the decarboxylation is likely to be irreversible under the reaction conditions. Then competition experiments were designed to demonstrate the polarity mismatch between VCC **1a** and the α-amino radical derived from *N*-phenyl pyrrolidine (Scheme 8d). When equimolar amounts of the latter and the more activated olefin *N*-(*tert*-butyl)acrylamide were used, the product distribution showed mostly compound **12** (82%) as a product with a much lower amount of **3a** (34%).



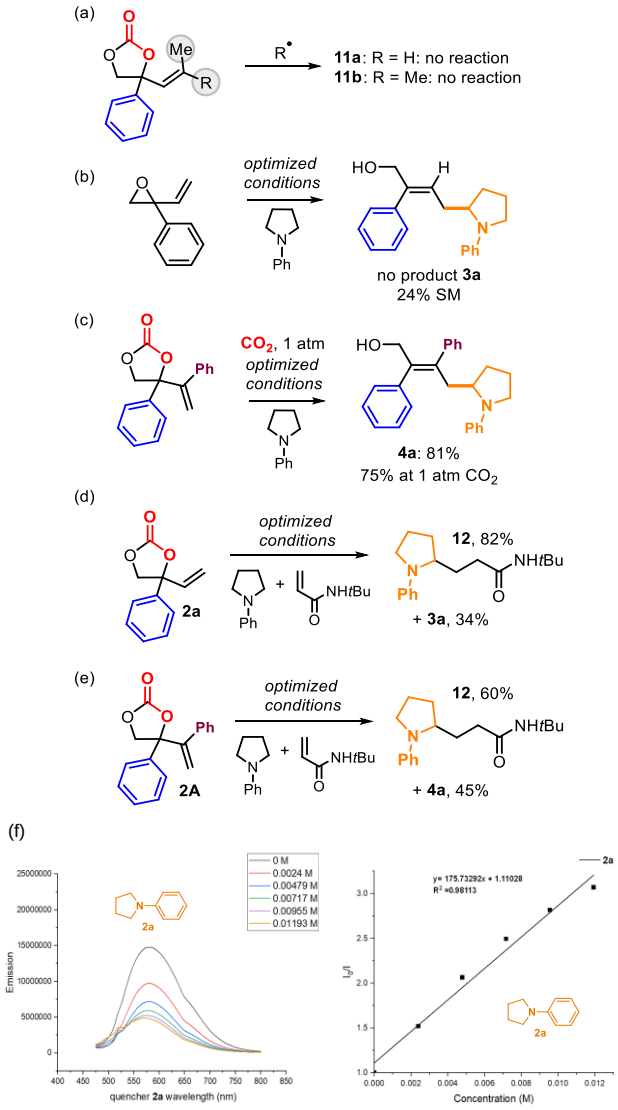
Scheme 6. Functionalization of amine-based drug molecules under the optimized photocatalytic conditions. Here 2 equiv of the TMS-based radical precursor were used.



Scheme 7. Post-synthetic use of compounds **4g** and **9b**.

When switching to a VCC with a phenyl-substituent on the double bond (Scheme 8e), a different product ratio was found and a larger relative amount of the target product **4a** (45%) compared to **12** (60%) was isolated. This can be anticipated taking into account the higher reactivity of these kind of heterocycles towards radical addition and intermediate stabilization.

In order to study the lower stereo-control in the synthesis of tetrasubstituted olefin products **4f** and **4j**, we decided to follow the reactions in time and monitor the *E/Z* ratio (SI for details). We found that for **4f** the initial *E/Z* ratio (60:40) was maintained throughout a total period of 30 h, excluding the possibility of unwanted post-synthetic photo-isomerization.[28] In the case of product **4j** (*E/Z* = 73:27), various conditions were then probed to examine potential post-isolation isomerization of pure *E*-**4j**, *Z*-**4j** and the synthetic mixture in the presence of light and the PC. For all three compositions, the reaction mixture showed after 12 h of irradiation an increase of the *E/Z* ratio in the range of 83:17 up to 86:14 (see full details in the SI). The combined results suggest that undesired photo-isomerization may be a function of the level of conjugation present in the product and whether it contains a photoactive unit (cf., a thiophene in the case of **4j**).



Scheme 8. Mechanistic control experiments. The yields for **12** under d-e are based on the amine reagent, while the ones reported for **3a** and **4a** are based on **2a** and **2A**, respectively. Under (f) the Stern-Volmer quenching experiment with amine **2a** is shown.

Finally, we performed Stern-Volmer quenching studies (SI for details, see for a visual in Scheme 8f) that showed that the excited **PC2** is efficiently quenched by the amine reagent, but not by the VCC substrates (SI). This suggests that radical formation is primarily occurring from the amine reagent, initiating the entire manifold.

Conclusion

We here present an efficient, user-friendly and attractive radical-based method for the synthesis of stereodefined tri- and tetra-substituted olefins with a wide structural diversity. The photocatalytic process enables the coupling between modular VCCs and related reagents, and various radical precursors. Furthermore, more complex substrates can be employed allowing the protocol to be adapted to various synthetic campaigns directed towards fine-chemical or pharmaceutical development. Mechanistic information has been obtained that shows that initial radical addition to the C=C bond of the VCC takes place, following a sequence of double bond migration and a key CO_2 extrusion driving the manifold forward.

Keywords: Amines • Homogeneous Catalysis • Olefins • Photocatalysis • Radical Chemistry

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