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Hot Paper

Towards a General Access to 1-Azaspirocyclic Systems via Photoinduced, Reductive Decarboxylative Radical Cyclizations

Natalia Kiprova^{+, [a]}, Marine Desnoyers^{+, [a]}, Rok Narobe,^[b] Arthur Klufts-Edel,^[a] Juliane Chaud,^[a] Burkhard König,^{*, [b]} Philippe Compain,^{*, [a]} and Nicolas Kern^{*, [a]}

Dedicated to Dr Romain Ruppert on the occasion of his retirement and for his contributions to organometallic chemistry

A convenient and versatile approach to important 1-azaspirocyclic systems relevant to medicinal chemistry and natural products is reported herein. The main strategy relies on a reductive decarboxylative cyclization of redox-active esters which can be rapidly assembled from abundant cyclic azaacids and tailored acceptor sidechains, with a focus on alkyne acceptors enabling the generation of useful exo-alkene moi-

eties. Diastereoconvergent variants were studied and could be achieved either through remote stereocontrol or conformational restriction in bicyclic carbamate substrates. Two sets of metal-free photocatalytic conditions employing inexpensive eosin Y were disclosed and studied experimentally to highlight key mechanistic divergences.

Introduction

Azacyclic molecules and their derivatives play a central role in modern human medicine, arguably standing as the most prominent class of heterocycles in pharmaceuticals.^[1] In recent years, concepts of conformational restriction^[2] and scaffold hopping^[3] have greatly supported the growing interest for the development of valuable bioisosteres of *N*-pharmacophores. With the aim of generating new three-dimensional chemotypes of “high *Fsp*³” character^[4,5] with finely tunable geometrical and physicochemical properties,^[6] important synthetic efforts have been devoted to azaspirocycles (Figure 1, a). In particular, 1-azaspirocyclic systems display additional challenges brought by the α -spirocyclic nitrogen atom (e.g. by largely precluding ionic ring closure by *S_N2* displacement of a leaving group on a tertiary centre). Creative approaches involving various reactivity

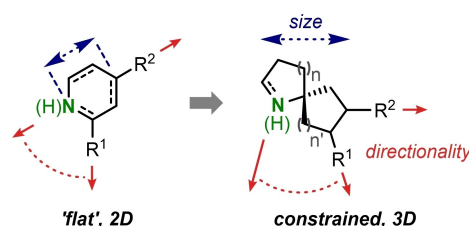
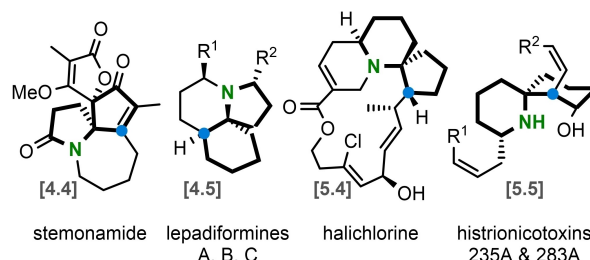
a) Azaspiro[*n.m*]alkane as *N*-ring isosteresb) Azaspiro[*n.m*]alkane natural products

Figure 1. [a] Interest for 1-azaspiro chemotypes in drug design. [b] Selected alkaloid natural product scaffolds comprising substituted 1-azaspiro motifs.

[a] N. Kiprova,⁺ Dr. M. Desnoyers,⁺ Dr. A. Klufts-Edel, Dr. J. Chaud, Prof. P. Compain, Dr. N. Kern
Laboratoire d'Innovation Moléculaire et Applications (LIMA), UMR 7042
Université de Strasbourg/Université de Haute-Alsace/CNRS
ECPM, 25 rue Becquerel, 67087 Strasbourg, France
E-mail: philippe.compain@unistra.fr
nicolas.kern@unistra.fr

[b] Dr. R. Narobe, Prof. Dr. B. König
Institut für Organische Chemie
Universität Regensburg
Universitätsstrasse 31, Germany
E-mail: burkhard.koenig@chemie.uni-regensburg.de

[†] N.Ki. and M.D. should be considered as joint first author.

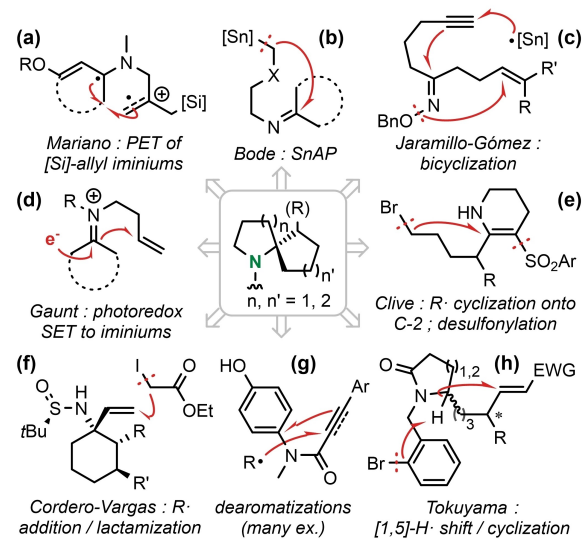
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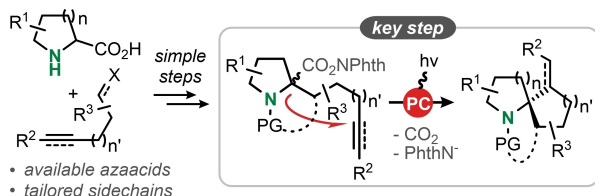
manifolds were therefore developed to access 1-azaspiro derivatives.^[7,8] However, methods enabling construction of both azaspiro[4.4]nonanes and azaspiro[4.5]decanes are scarcer,^[9] as can be stated for [5.4] and [5.5] systems.^[10] Further considering the prevalence of these scaffolds in bioactive alkaloids that often calls for target-specific approaches (Figure 1, b),^[11] novel efficient and practical strategies for the construction of a wide range of substituted azaspiro[*n.m*]alkanes should find general utility.

Among existing approaches to build these ring systems, free radical-based methods have become particularly attractive thanks to the high reactivity of open-shell intermediates and the increasing number of efficient technologies for their generation under mild conditions (Scheme 1, a).^[12] Apart from Clive's seminal work^[12e] and Tokuyama's approach to lepadiformine and histrionicotoxin,^[12h,13] most strategies involve prior construction of the carbocyclic unit followed by ring closure of the azacycle. Therefore, examining a possible general and complementary route to 1-azaspirocycles embedding either five- or six-membered subunits (i.e. pyrrolidine, piperidine, cyclopentane or cyclohexane rings), it was reasoned that steric impediment in the formation of the constrained α -N-spirocentre could be overcome through the decarboxylative generation of endocyclic, tertiary α -amido radicals (Scheme 1, b). Cyclization of the latter onto a remote π -system (alkene or alkyne) via a 5-*exo* or 6-*exo* mode and reduction via HAT or SET would formally enable a reductive decarboxylative version of the Hart cyclization.^[14] Inspired by the elegant work of Overman who developed the use of *N*-hydroxyphthalimide (NHPI) esters^[15] in [Ru]-photocatalyzed reductive radical couplings in complex settings,^[16] we thus aimed to develop a simple and general, yet unreported route to diverse 1-azaspiro scaffolds complementing target-specific approaches with operational simplicity and flexibility.

a) Radical-based syntheses of azaspiro[n.m]alkanes (ref. 12)



b) Photoinduced reductive decarboxylative approach



Scheme 1. [a] Summary of free-radical pathways forming 1-azaspirocycles; homolyzed bonds are depicted with hashed lines. [b] Proposed approach starting from cyclic azaacids with photoinduced reductive decarboxylation as key step.

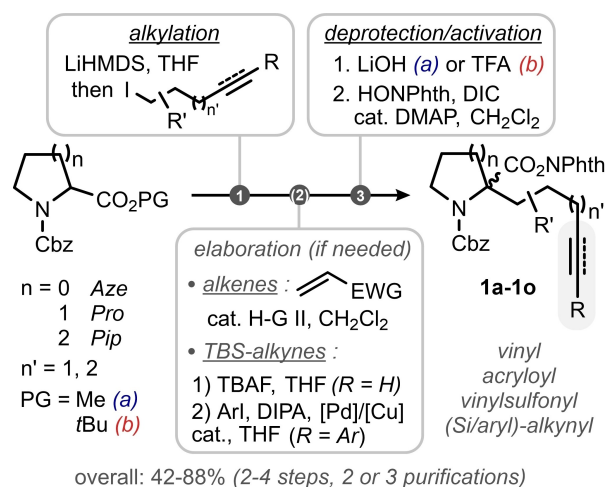
Results and Discussion

Access to cyclization precursors

To ensure a reliable access to a broad range of cyclic α -amido NHPI esters, efficient short routes were optimized starting from readily available Cbz-protected azetidincarboxylic, proline and pipercolic acid derivatives (Scheme 2). Lithiation of methyl- or *tert*-butyl esters (-30°C for proline or -60°C for pipercolic derivatives) followed by addition of various primary iodide alkenyl or alkynyl sidechains at -78°C and warming to the appropriate temperature provided intermediate ω -unsaturated esters commonly in 75–90% yields. When required, the obtained alkenes or (silyl)alkynes were elaborated respectively by cross-metathesis with electron-deficient olefins or desilylated then coupled under classical Sonogashira conditions in high overall yields (see S.I.). Depending on substitution patterns, ester deprotection with aqueous LiOH ($R = \text{Me}$) or trifluoroacetic acid ($R = t\text{-Bu}$) at room temperature yielded the corresponding acids quantitatively in most cases, which were directly coupled to *N*-hydroxyphthalimide using DIC in the presence of catalytic DMAP. The resulting fully substituted redox-active NHPI esters **1a–1o** were found to be stable for weeks under ambient conditions and sunlight, and >2 years in the dark at 4°C . With respect to widespread primary and secondary NHPI esters, they display good stability on silica gel. Analogous tetrachlorophthalimide esters are prone to hydrolysis.

Optimization of the decarboxylative azaspirocyclization

Optimization studies began by attempting azaspirocyclizations of alkyne-tethered NHPI esters, as decarboxylative NHPI-alkyne radical cyclizations are still unexplored and would avoid the formation of diastereomers while forming a synthetically useful *exo*-alkene. Screening of conditions was performed with two model substrates **1a** ($R = \text{H}$) and **1b** ($R = \text{TBS}$) to determine whether stabilization of the highly reactive vinyl radical may be



Scheme 2. General route for the construction of alkenyl and alkynyl *N*-Cbz azaspirocyclization substrates.

required. Table 1 summarizes optimal conditions found for the azaspirocyclization of **1a** and effects of deviations from the latter. On the basis of several precedents for photoinduced NHPI reduction,^[17,18] we eventually found that treating **1a** with inexpensive eosin Y (EY, 5 mol%) in the presence of Bu₃N (2 equiv) and Hantzsch ester (HE, 1.5 equiv) in degassed DMF (0.1 M) under Ar and irradiation with 3 W green LEDs (525 nm) reliably led to the clean formation of methylene-substituted azaspirocyclization **2a** (84% yield, standard conditions [A]). A first important note concerned the apparent reduced stability of EY under these conditions, as lowering the catalyst loading to 2.5 mol% induced incomplete conversion of **1a** and led to variable yields (entry 2), a trend not observed using 5 mol% of EY. The benchmark expensive [Ru(bpy)₃]Cl₂ and Ir(ppy)₃ photocatalysts displayed lower efficiency under identical conditions (entries 3 & 4) and running the reaction at a higher concentration in DMF (entry 5) proved detrimental. However, the robustness of the protocol to aqueous conditions was demonstrated (entry 6) since 68% of **2a** could still be isolated. Of note, among usual solvents employed in photocatalytic reactions

with NHPI esters, only DMF (and more expensive NMP) could allow the isolation of **1a** in >70% yields. Such trend may be (at least partly) due to the enhanced solubility of HE and the catalyst's dibasic form^[19] in these polar solvents. Control experiments showed that omission of HE affected only slightly the conversion of **1a** into **2a** (74%, entry 7) while omission of Bu₃N^[20] was more detrimental (55%, entry 8). As Stern-Volmer plots showed that both species can act as reductive quenchers for EY* (vide infra), the beneficial role of HE was thus difficult to rationalize at this stage, as noted by Overman in the context of conjugate additions of tertiary radicals generated from NHPI esters.^[16a] Different and/or competitive processes may result from inclusion of HE to photocatalytic systems already containing tertiary amines. Furthermore, since several examples of radical initiation by irradiation of a putative charge transfer (CT) complex were reported,^[21] we evaluated this option by omitting both catalyst and amine (entry 9) which resulted in product formation but in low and irreproducible yields, disclosing the need for a catalyst-driven photoinitiation (vide infra) over photosensitization of a CT complex in polar DMF. Intrinsic generation of Hantzsch pyridine from HE also led us to search for more practical additives as (co)reductants. Among known hydrogen atom donors, addition of 1,4-cyclohexadiene (CHD, 5 equiv) in conjunction with Bu₃N also increased the yield of **2a** to 80% (entry 10, standard conditions [B]). Controls showed that using CHD without Bu₃N did not induce any conversion, but adding a sub-stoichiometric amount of the latter was sufficient to trigger the efficient formation of **2a** (entries 11 & 12), hinting that CHD must be involved in the regeneration of the amine quencher from its oxidized form(s) (i.e. radical cation or iminium, vide infra). In the case of TBS surrogate **1b**, (*E*)-configured silyl alkene product **2b** was also formed in all cases in slightly lower yields, with an optimum of 68% (entry 13, standard conditions [A]). Omission of HE in reactions of **1b** was more impactful (32% of **2b** isolated, entry 14), suggesting that steric and electronic properties of the formed (silyl)vinyl radicals may impact the cyclization and/or termination steps involving stable or transiently formed hydrogen atom sources (see Mechanistic aspects & discussion).

Inclusion of 1,4-CHD (standard conditions [B]) also increased the yield of **2b** to 62% (entry 15 vs 13). Interestingly, reactions forming **1b** in the absence of 1,4-CHD invariably led to high (*E*)/(*Z*) ratios while its inclusion usually resulted in slightly lowered selectivity. Also noteworthy, in our early forays thermal conditions reported for decarboxylative alkylation^[22] (cat. Ni(CIO₄)₂, Zn metal and LiCl in MeCN) led to a reversal of (*E*)/(*Z*) selectivity (ca. 1:9, unoptimized 20% yield).

Scope of *N*-Cbz substrates

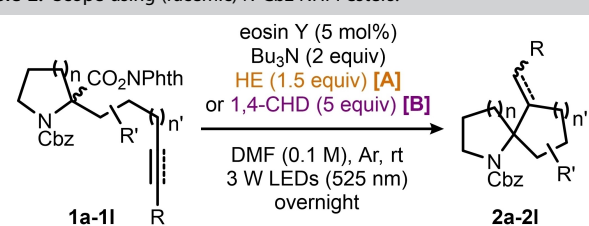
Both sets of standard conditions were evaluated with NHPI ester cyclization precursors **1c–1l** which also included common alkene acceptors (Table 2). First, activation of the alkyne by an appended phenyl group in **1c** led to styryl azaspirocyclization **2c** in enhanced yield (88%). The (*Z*) configuration of the alkene was evidenced easily by NOE analysis, in contrast with (*E*)-TBS-alkene

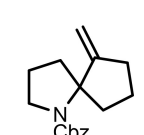
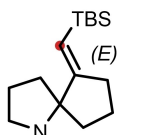
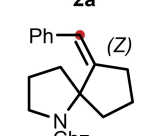
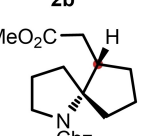
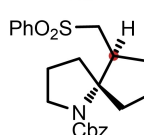
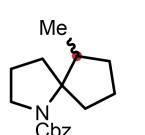
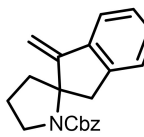
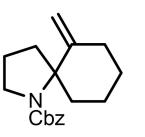
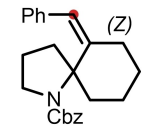
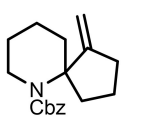
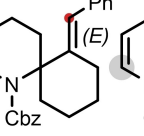
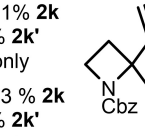
Table 1. Optimization studies with *N*-Cbz NHPI substrates.^[a,b,c]

Entry	Substrate	Deviation(s) from [A]	Yield (%) (<i>E</i>):(<i>Z</i>)
1	1a	None	84
2	1a	2.5 mol% eosin Y	57–65
3	1a	2.5 mol% [Ru(bpy) ₃]Cl ₂ (425 nm)	75
4	1a	2.5 mol% [Ir(ppy) ₃] (405 nm)	73
5	1a	0.2 M in DMF	60
6	1a	0.1 M in 1:1 DMF:H ₂ O	68
7	1a	No HE	74
8	1a	No Bu ₃ N	55
9	1a	No catalyst nor Bu ₃ N	< 15
10	1a	1,4-CHD (5 equiv) instead of HE (Standard conditions [B])	80
11	1a	No Bu ₃ N, 1,4-CHD (5 equiv)	–
12	1a	50 mol% Bu ₃ N, 1,4-CHD (5 equiv)	67
13	1b	None	68 (>95:5)
14	1b	No HE	32 (>95:5)
15	1b	1,4-CHD (5 equiv) instead of HE (Standard conditions [B])	62 (88:12)

[a] Reaction scale: 0.1 mmol of NHPI substrate. [b] Isolated yields. [c] (*E*):(*Z*) ratio determined by crude ¹H NMR analysis.

Table 2. Scope using (racemic) *N*-Cbz NHPI esters.^[a,b,c]



 2a [A] 84% [B] 80%	 2b [A] 68% (E:Z > 95:5) [B] 62% (E:Z 90:10)
 2c [A] 89% (E:Z < 5:95) [B] 58% (E:Z 7:93)	 2d^d [A] 87% (dr 70:30) [B] 82% (dr 52:48)
 2e^d [A] 72% (dr 63:37) [B] 71% (dr 60:40)	 2f [A] 30% (dr 56:44) [B] 57% (dr 58:42)
 2g [A] 42% [B] 54%	 2h [A] 19% [B] nd
 2i [A] 67% (E:Z < 5:95) [B] 68% (E:Z 8:92)	 2j [A] 32% [B] 62%
 2k [A] 41% 2k + 5% 2k' (E) only [B] 33% 2k + 8% 2k' (E) only	 2l [A] 48% [B] 34%

[a] Reaction scale: 0.1 mmol of NHPI substrate. [b] Isolated yields after column chromatography. [c] dr and (E):Z ratio determined by crude ¹H NMR analysis. [d] Diastereomers fully separable by chromatography.

2b. The same stereochemical outcome was observed for all arylalkyne derivatives in the series. This divergence arises through the reduction step involving a *sp* (*R*=Ph) or *sp*²-hybridized (*R*=TBS) vinyl radical,^[23] whose interaction with a hydrogen atom donor opposite to the azacycle would result in high steric impedance between the ring and bulky TBS moiety in the transition state, leading to a less constrained product. In the case of **1c**, free rotation of the phenyl group may provide a

less hindered setting enabling H[•] abstraction from the least hindered face of the (commonly *sp*-hybridized) arylvinyl radical.^[24] Electron-poor alkenes **1d–1e** led to (very) good yields of products **2d–2e**, expectably with low diastereocontrol in the absence of directing substituents. In contrast with vinyl radicals generated from **1a–1c**, the electrophilic radicals formed here through cyclization (ca. –0.7 V vs SCE) are easily reduced by SET rather than HAT (vide infra).^[25] A key note here also concerns the variation of the dr of **2d** depending on the additive used, reminiscent of Tokuyama's observations for a related 6-*exo*-trig process.^[13] This suggests the reversible nature of the cyclization in spite of its acceleration by polar effects, possibly due to the involvement of different species affecting the rate of the termination step. On the other hand, terminal alkene **1f** led to methyl-substituted **2f** in low to moderate yield. The observed lack of stereocontrol using alkene-tethered NHPI esters further motivated studies of alkyne derivatives. Introduction of an aryl tether in **1g** (reversing alkyne polarization with respect to **1c**) was tolerated, leading to **2g** which contains the tricyclic scaffold of impatien A^[11g] in moderate yields. Of note, both reactions of **1f** and **1g** performed better using conditions [B]. A first instance of 6-*exo*-dig cyclization was examined with **1h** which led to **2h** in low yield using conditions [A] only. Expectably, the uncyclized reductive decarboxylation product was detected among unidentified byproducts (range of 20–70% yields estimated by ¹H NMR depending on concentration and additive). As such 6-*exo*-dig radical cyclizations can be nontrivial without acceleration by angle compression (Thorpe-Ingold effect), implementation of a phenylacetylene acceptor in **1i** pleasingly led to styryl azaspiro[4.5]decane **2i** in good yields, in line with Alabugin's insightful studies.^[26,27]

Thus, terminal and phenyl-capped alkynes were also used in the piperolic NHPI ester series (**1j–1k**), leading respectively to methylene azaspiro[5.4] (**2j**) and styryl azaspiro[5.5] (**2k**) systems in moderate yields. Insightful outcomes were noted for the latter transformation, for which small amounts of byproduct **2k'** could be isolated. Unambiguous (*E*)-alkene formation and desaturation of the piperidine core in **2k'** suggest a specific 1,5-HAT facilitated by pseudo-anomeric stabilization by vicinal nitrogen in a six-membered ring, followed by formal dehydrogenative termination (see Mechanistic aspects & discussion). No (*Z*) isomer could neither be detected regarding the reductive cyclization product **2k**. Plausibly, the shortened distance between the bulkier piperidine (vs pyrrolidine) and phenyl moiety may increase the population of a bent (*E*)-*sp*² radical through steric decompression,^[23] thus resulting in opposite face selectivity in the *intermolecular* HAT termination step (as observed earlier with bulkier TBS-alkynes), also enabling *intramolecular* 1,5-HAT as a competitive pathway.

Last, a peculiar methylenated azaspiro[3.4] motif^[6] in **2l** was accessed through generation of a presumed tertiary 2-azetidiny radical from **1l**. Albeit proceeding in moderate yields, this challenging transformation (considering the weaker stabilization ability of nitrogen due to higher *s*-character induced by angular strain) provides a proof of concept for further development. Of note, the corresponding phenylacetylene substrate underwent reductive decarboxylation under conditions [A] or [B] but no

expected styryl spiroazetidone or tractable products were detected, possibly due to decomposition under both conditions.

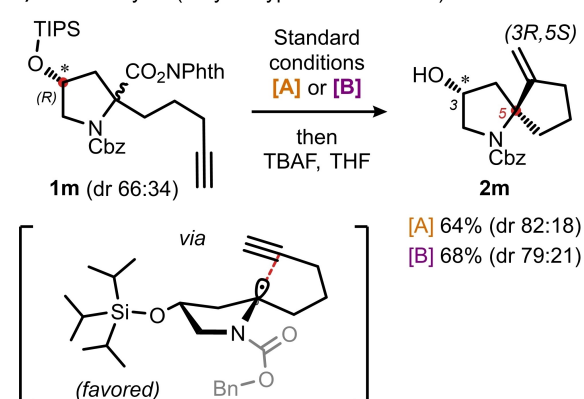
Following these insights with racemic NHPI cyclization precursors, we reasoned that the stereoablative^[28] nature of the radical decarboxylation, while erasing the chiral information in starting materials, may however be leveraged to induce stereoconvergent azaspirocyclizations. With this aim, (diastereomeric mixtures of) *N*-Cbz NHPI derivatives containing a single defined stereocentre were examined. Early attempts using TBS-alkyne substrates led to low stereocontrol (dr 1.1:1) and yields (< 15%). Combination of a terminal alkyne with a bulky *O*-triisopropylsilyl group as steric inductor in substrate **1m** (Scheme 3, a) enabled the formation of hydroxylated azaspiro-

cycle **2m** with improved stereoselectivity (ca. 4:1 in favor of the (3*R*,5*S*) diastereomer) in good yield using both sets of conditions followed by desilylation. A plausible transition state for the formation of the major diastereomer from a pyramidalized *sp*³-hybridized amidoalkyl radical^[29] may reasonably involve an envelope conformer with both the –OTIPS substituent and alkynyl sidechain occupying pseudo-equatorial positions, minimizing repulsive 1,3-pseudodiaxial as well as 1,2-interactions between the sidechain and Cbz group.^[30]

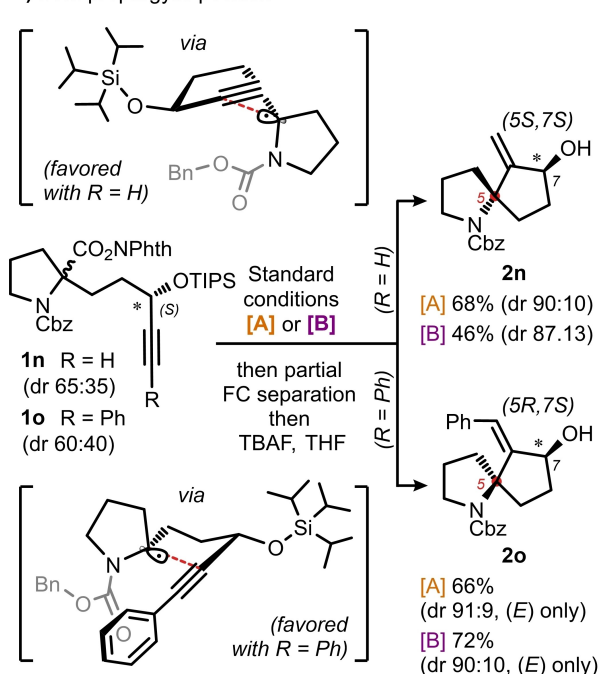
Introduction of the same bulky group at the propargylic position in **1n** (prepared from an enantiopure alkyl iodide) enabled an efficient, diastereoselective azaspirocyclization (ca. 9:1 dr) with conditions [A] as optimum (Scheme 3, b). As above, the bulkiness of the –OTIPS moiety likely precludes its pseudoaxial orientation in an envelope-like transition state, therefore preferential formation of the (5*S*,7*S*) product **2n** would here require radical interconversion and an “envelope flip” with respect to the case of **1m**. Strikingly, the corresponding phenylacetylene substrate **1o** underwent azaspirocyclization with high but opposite diastereoselectivity, forming the (5*R*,7*S*) product **2o**. This might be rationalized by considering the increased steric demand between the arylalkyne and pyrrolidine core, thus leading to radical interconversion^[12h] to accommodate steric bulk while preserving a favorable obtuse angle attack^[27] and pseudo-equatorial positioning of the large silyloxy group. These stereoconvergent azaspirocyclizations were followed by transprotection and *exo*-methylene functionalization (**2m**) or desilylation (**2n–2o**) for suitable purification and characterization (see S.I.).

Induction from remote stereocentres^{a,b}

a) from azacycle (4-hydroxyproline derivative)^c



b) from propargylic position^d

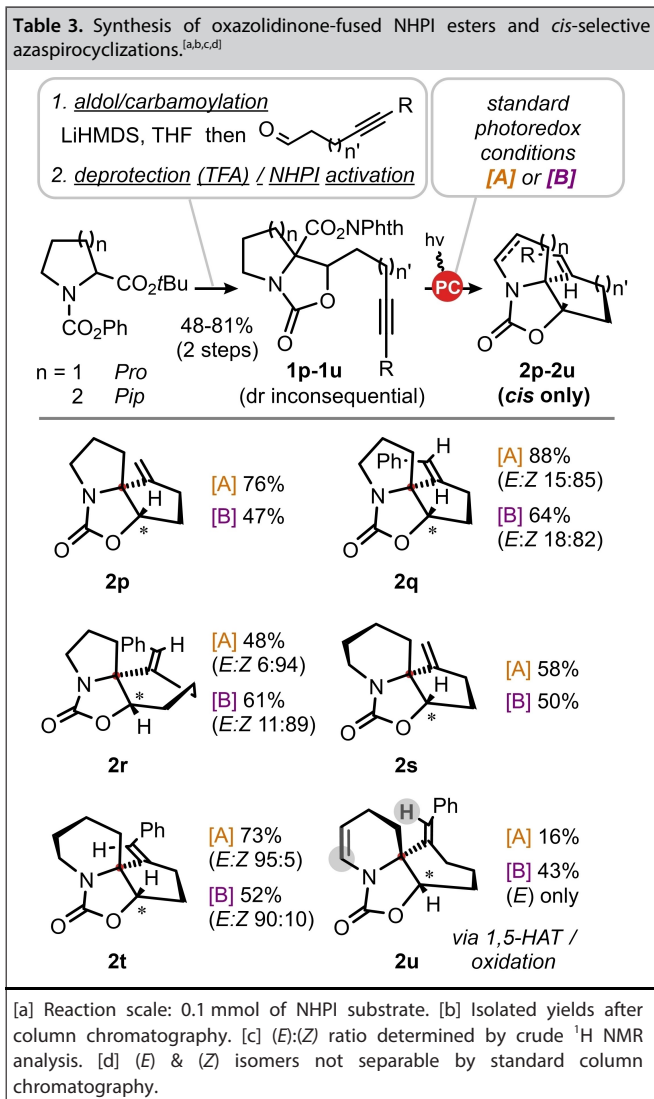


Scheme 3. Stereoconvergent azaspirocyclizations of tertiary *N*-Cbz NHPI esters. [a] Reaction scale: 0.5 mmol of NHPI substrate. [b] dr and (*E*):(*Z*) ratio determined by crude ¹H NMR analysis. [c] Isolated yields after cyclization, desilylation and flash chromatography (FC). [d] Isolated yields after cyclization, partial purification by FC, then desilylation and FC.

Scope of oxazolidinone-fused substrates

Next, it was anticipated that introduction of cyclic constraints could enable selective and stereoconvergent formation of *cis*-configured products. Such trend stands as ‘rule of thumb’ for 5-*exo* radical ring closures (such as the venerable Stork cyclization^[31]) but is far from general regarding 6-*exo* processes.^[32] We opted to study the case of carbamate-fused NHPI substrates, since radical generation vicinally to the acceptor or sidechain should disfavor the formation of *trans* products considering the enforced conformational restriction. Furthermore, the resulting constrained angular tricyclic products would stand as useful masked azaspirocycles hydroxylated at C-6.^[13]

Oxazolidinone-fused NHPI esters were prepared by implementing a tandem aldol/carbamoylation in the synthetic route (Table 3). Here, phenyl carbamates were used to accelerate ring closure subsequently to enolate formation (–60 °C) and rapid aldol (–78 °C), affording racemic carbamate-fused esters as inconsequential mixtures of diastereomers. Since cleavage of these strained oxazolidinones was hardly avoidable in basic medium, *tert*-butyl esters were employed to allow deprotection with TFA. Again, NHPI activation successfully afforded cyclization precursors **1p–1u** in good overall yields over two steps. In contrast to *N*-Cbz derivatives, arylalkyne-NHPI esters in this series tend to decompose upon exposure to sunlight and storage in CDCl₃, but slightly impure samples can be used in



the azaspirocyclization step without major yield losses. Importantly, these substrates still display higher stability than their free acid precursors, further demonstrating the complementarity of such reductive protocol.

Treatment of proline-derived NHPI esters **1p-1q** under both sets of photoredox conditions successfully afforded *cis*-fused angular azaspiro[4.4] scaffolds **2p-2q**, with system [A] as optimum. In line with earlier insights, arylalkyne activation was beneficial to these 5-*exo*-dig processes and mandatory to enable 6-*exo*-dig cyclization forming azaspiro[4.5]decane **2r**, for which system [B] enabled easier purification. Reduction of the styryl radicals formed from **1q** and **1r** proceeded with slightly lowered (*Z*)-selectivity with respect to nonfused *N*-Cbz substrates. Reactions of pipercolic NHPI esters **1s-1t** also testified of the benefits of arylalkyne activation, affording methylene and styryl-containing azaspiro[5.4] frameworks **2s-2t**. The high (*E*) selectivity observed in the formation of **2t** stands in line with the abovementioned reaction of pipercolic *N*-Cbz substrate **1k**. Last, attempted generation of a carbamate-fused [5.5] system led to exclusive formation of desaturated **2u** without detection

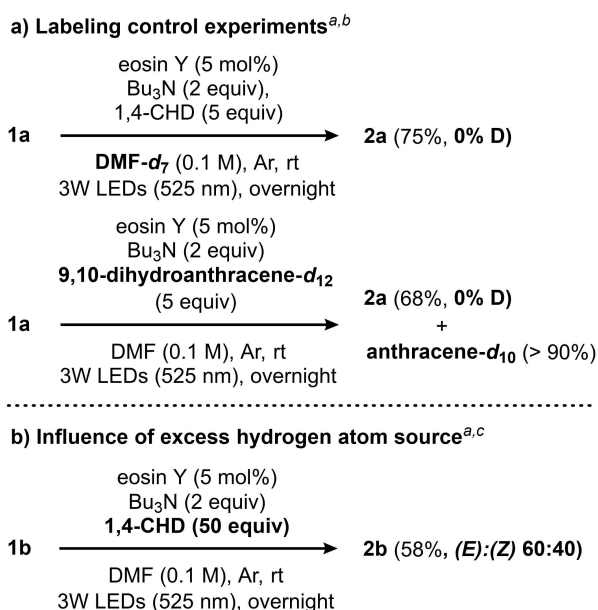
of the usual reductive cyclization product. It is likely that the enforced conformational restriction induced by the bridging carbamate both disfavors (*Z*) alkene formation via *intermolecular* HAT and facilitates the alternative *intramolecular* HAT previously observed while forming an azaspiro[5.5]decane system.

Mechanistic aspects & discussion

Through extensive optimization and scope study, subtle but significant discrepancies regarding selectivity and efficiency were noted using both sets of optimized conditions, raising further questions on the possible roles of HE or CHD as additives. Several examples of photocatalyzed reactions of NHPI esters (including Overman's early work)^[16] were documented using the combination of a tertiary amine and HE for optimal results, despite use of a single dual electron/H atom donor could be expected.^[33,34] In the present work, cyclized products could be obtained using Bu_3N or HE alone, but with much lower efficiency for most substrates. We therefore aimed to decipher distinct features of systems [A] and [B] in an attempt to rationalize reaction outcomes.

Major aspects concerned: 1) using HE, the requirement for tributylamine and DMF to attain optimal yields, while with CHD other solvents (e.g. EtOAc) could be used with only slightly lower efficiency, suggesting a solubility-dependent process involving HE.^[35] 2) the catalytic turnover of tributylamine in the presence of CHD (Table 1, entry 11); and 3) trends of results depending on properties of radicals involved (Table 1, yields of **2a** vs **2b**, **2f** or **2j**, the dr of **2d**, reduction vs cyclization towards **2h**). To top it off, the formal dehydrogenative termination yielding **2u** hints a SET/deprotonation pathway forming the alkene from a translocated, nucleophilic α -amido radical. It seems reasonable here to assume implication of electrophilic tributylaminium radical cation in back-electron transfer^[36] and deprotonation forming the alkene, dominating over reduction via 1) established donation of H^\bullet to the highly reactive vinyl radical^[37] (BDE > 100 kcal/mol) through iminium formation from the aminium (BDE = 42 kcal/mol^[38]), or 2) direct termination via HAT from CHD (BDE = 77 kcal/mol^[39]) or its corresponding radical. The low yield of product **2u** obtained when substituting CHD for HE may suggest a less productive back-electron transfer pathway, possibly resulting from a lower concentration of competent oxidant (i.e. aminium), which may originate from competition of amine and HE in the reductive quenching (vide infra), as well as the faster consumption of the aminium by SET or HAT from HE. Both pathways would generate $\text{HE}^{\bullet+}$ radical (or HE^\bullet radical and protonated amine), a potent HAT agent^[40] which would allow to reduce high-energy vinyl radicals with concomitant aromatization, but is unlikely to undergo back-electron transfer from the putative pseudo-anomeric radical at a productive rate.

Selected control reactions were performed to shed more light on the termination step under conditions [B]. The lack of deuterium incorporation in **2a** after running the model reaction with **1a** in $\text{DMF-}d_7$ (Scheme 4, a) suggests that (classical) HAT between the vinyl radical and solvent is probably not operative.



Scheme 4. Control experiments. [a] Reaction scale: 0.1 mmol of NHPI substrate. [b] Isolated yields after column chromatography, (absence of) D incorporation deduced from ^1H and ^{13}C NMR analysis. [c] Isolated yield after column chromatography, (E):(Z) ratio determined by crude ^1H NMR analysis.

Employing 9,10-dihydroanthracene- d_{12} as an accessible labeled CHD surrogate,^[41,42] a stoichiometric amount of anthracene- d_{10} was formed but product deuteration was neither detected, excluding the involvement of this additive (and its corresponding radical) in direct HAT to the vinyl radical. Unambiguous conclusions cannot be drawn here considering primary kinetic isotope effects, but such observations hint a hydridic process for the catalytic turnover of the amine via iminium reduction, which could easily be envisioned with HE as additive.^[43] However, introduction of CHD in large excess for the conversion of **1b** to **2b** led to significant erosion of the (E):(Z) ratio (Scheme 4, b), a unique case in this whole study. Therefore, vinyl radical termination via HAT from cyclohexadienyl radical or CHD itself as a secondary pathway may not be excluded.^[12d]

Additional experiments were performed to support the mechanistic hypotheses (see S.I. for cyclic voltammetry, fluorescence quenching and quantum yield measurement details). First, as documented and according to redox potentials, SET from tertiary amine (ca. $\cong 0.8\text{ V}$ vs SCE in common solvents) to photoexcited eosin Y ($\text{EY}^*/\text{EY}^{\bullet-} = +0.83\text{ V}$ vs SCE in MeOH) should be exergonic,^[18] or slightly endergonic in case of HE (+0.97 V vs SCE) as an electron donor.^[44] As the established triplet state reactivity of EY^* precludes viable controls by fluorescence quenching experiments, 4-CzIPN was used as surrogate considering its similar short excited state lifetime, potential range and quenching rate in DMF ($\text{PC}^*/\text{PC}^{\bullet-} = +1.43\text{ V}$ vs SCE; $\text{PC}/\text{PC}^{\bullet-} = -1.24\text{ V}$ vs SCE in MeCN).^[45] Its efficiency in the model reaction with **1a** was also verified (72% of **2a** isolated with CHD as additive). Stern-Volmer plots confirmed viable SET processes between 4-CzIPN* and tributylamine as well as with HE as an even better electron donor (see S.I.). Both reductants displayed high quenching efficiency at low

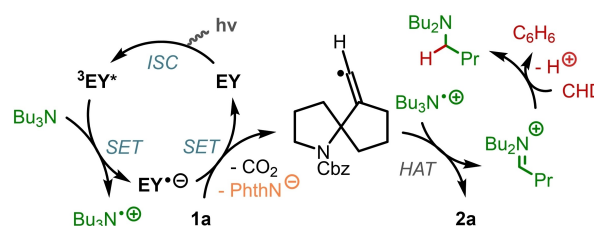
concentrations which may suggest preassociation with the ground state photocatalyst.^[46] Expectably, 1,4-CHD does not act as electron donor, establishing SET from amine to EY^* as the only conceivable redox pathway with conditions [B]. The next elemental step implies the reduction of NHPI ester (-1.23 V vs SCE measured in DMF for **1a**, see S.I.) by SET from $\text{EY}^{\bullet-}$ (-1.08 V in DMF). Although redox potentials cannot be compared directly, this process is thermodynamically accessible and well-established.^[47]

Quantum yields were determined under relevant reaction conditions for both systems (Table 4). In both cases, the optical density of the solution decreased over time due to bleaching of EY. For system [A] using Bu_3N and HE, the high quantum yields indicate the possibility of chain processes^[48] and bleaching was observed within minutes, which could explain the relatively high loading of EY required to secure reproducible yields. It should be mentioned that in an early report, Okada *et al.* noted high quantum yields and proposed a ruthenium-initiated chain mechanism involving the BNA radical as chain carrier in the presence of *t*-BuSH.^[15c] Substituting HE for CHD in system [B], the lower Φ values suggest chain processes are less probable, and bleaching was much slower ($< 10\%$ over 3 h), probing the higher stability of EY in the absence of HE.

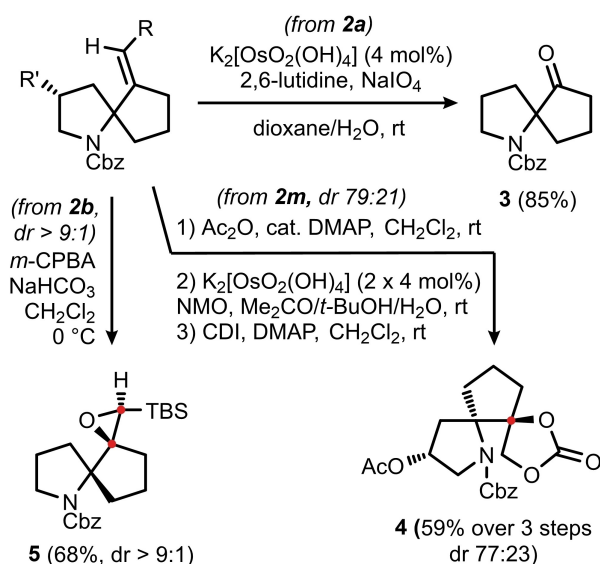
Based on results obtained with system [A] in spite of its lower stability, considering the likely competition of catalyzed processes with photoinitiated chains ("smart initiation"^[49]) and CT photoexcitation, any firm conclusion would be imprudent without performing time-resolved experiments with a better suited photocatalyst, which lie beyond the scope of this work. A reasonable dominant pathway can however be proposed for the better-behaved system [B] (Scheme 5). Photoexcitation of EY and intersystem crossing result in electron transfer to $^3\text{EY}^*$ from the amine, generating the aminium radical cation and $\text{EY}^{\bullet-}$. Catalyst turnover is achieved via SET from $\text{EY}^{\bullet-}$ to NHPI ester **1a**, triggering the decarboxylative cascade with release of

Conditions	[A] (with HE) ^[b]	[B] (with CHD) ^[c]
Φ (1 h)	147% (GC yield = 48%)	10.5% (GC yield = 19%)
Φ (3 h)	42% (GC yield = 55%)	9.5% (GC yield = 48%)

[a] Irradiation with 528 nm LEDs under Ar (15 μM EY, optical path = 4 mm). [b] **1a** (1 equiv), Bu_3N (2 equiv), HE (1.5 equiv), DMF (0.1 M). [c] **1a** (1 equiv), Bu_3N (2 equiv), CHD (5 equiv), DMF (0.1 M).



Scheme 5. Proposed (dominant) mechanism using the $\text{Bu}_3\text{N}/\text{CHD}$ system, involving termination via HAT and (hydridic) amine regeneration from iminium.



Scheme 6. Product elaboration via *exo*-methylene functionalizations.

phthalimide. Rather than reacting with CHD, the aminium likely donates H⁺ to the transient vinyl radical,^[37] yielding **2a** and an iminium. Hydride transfer from CHD regenerates the amine, releasing benzene and a proton.

Some oxidative transformations were performed to briefly showcase the synthetic value of methylenated 1-azaspirocycles (Scheme 6). Lemieux-Johnson oxidation of model compound **2a** under Lin's conditions^[50] afforded azaspiroketone **3**. The hydroxylated derivative **2m** was acetylated and dihydroxylated then treated with CDI, affording carbonate **4**, and (silyl)vinyl azaspiro derivative **2b** underwent smooth epoxidation by treatment with buffered *m*-CPBA. Both latter reactions proceeded with high face selectivity starting from diastereomeric mixtures, with oxidants approaching oppositely to the carbamate moiety.

Conclusions

In summary, we have developed a flexible strategy for the construction of diverse 1-azaspiro[m.n]alkanes motifs through the metal-free photoinduced decarboxylative cyclization of various *N*-hydroxyphthalimide esters, which were readily assembled from simple materials through high-yielding alkylation or one-pot aldolization/carbamoylation routes. The key reaction was especially optimized for alkyne derivatives, generating useful *exo*-methylene functionality for elaboration. Efficient stereoconvergent azaspirocyclizations could be achieved using diastereoisomeric mixtures of precursors through careful choice of bulky remote steric inductors and use of cyclic restriction in bicyclic carbamates, providing proofs of concept for asymmetric synthesis. Aiming for chemical efficiency, two protocols employing either Hantzsch ester or 1,4-cyclohexadiene as additive(s) along inexpensive eosin Y and tributylamine performed better than direct irradiation of known NHPI CT complexes, and were found to be complementary depending on the nature of

substrates employed. Overall, this novel approach should find general utility for the stereocontrolled construction of functionalized important azaspiro[n.m]alkane ring systems with a high degree of predictability.

Supporting Information

The authors have cited additional references (regarding spectroscopic experiments) within the Supporting Information.^[51,52]

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Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: azaspirocycles · radicals · alkynes · decarboxylation · photoredox

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