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Divergent Strain-Release Amino-Functionalization of [1.1.1]-Propellane with Electrophilic Nitrogen-Radicals


Abstract: Herein we report the development of a photocatalytic strategy for divergent preparation of functionalized bicyclo[1.1.1]pentylamines. This approach exploits, for the first time, the ability of nitrogen-radicals to undergo strain-release reaction with [1.1.1]propellane. This reactivity is facilitated by the electrophilic nature of these open-shell intermediates and the presence of strong polar effects in the transition-state for C–N bond formation/ripening. With the aid of a simple reductive quenching photoredox cycle, we have successfully harnessed this novel radical strain-release amination as part of a multicomponent cascade compatible with several external trapping agents. Overall, this radical strategy enables the rapid construction of novel amino-functionalized building blocks with potential application in medicinal chemistry programs as p-substituted aniline bioisosteres.

Introduction

The bicyclo[1.1.1]pentane (BCP)[1] is a rigid, linear, sp²-rich motif frequently used in medicinal chemistry programs as bioisosteric replacement for aromatic rings, alkyynes and t-Bu groups.[2] Bioactive molecules incorporating this substructural unit usually benefit from improved pharmacokinetic properties like lipophilicity and passive permeability.[3]

In particular, bicyclo[1.1.1]pentylamines (BCPAs) are of considerable interest as aniline bioisosteres for the preparation of novel small-molecule therapeutics with resistance towards Wiberg metabolic clearance (Scheme 1A).[4] These building blocks have been developed, generally relying on (Scheme 1B, path a). In contrast, the preparation of C-3-substituted BCPAs is much more difficult and still go through long multi-step synthesis.[5] In an effort to streamline the preparation of these building blocks, Gleason has very recently merged ionic strain-release amination with Cu(I)-catalysis using activated electrophiles to assemble C-3 alkylated and hydroxylated systems (Scheme 1B, path c).[10] This telescopd process requires the accumulation of the magnesiated-BCPA intermediates 4, prior addition of the Cu(I)/electrophile, thus restricting the source of N-partners to benzylc amines.

Radical strain-release amino-functionalization would represent an attractive alternative to target the preparation of these building blocks. So far, the only approach for the direct preparation of BCPAs is based on the amination of C-3 BCP radicals with N-based SOMOphiles as developed by Pfizer.[8] In this case, radical hydro-hydrazination of 1 using DEAD as the SOMOphile thus enabling upon further elaboration, the scalable preparation of building block 5 in three steps (Scheme 1B, path d). More recently Uchiyama has extended this approach to the preparation 3-functionalized BCPAs through a carbo-hydroazidation strategy using alkyl carbazates/aryl hydrazines as radical precursors and DEAD as radical trap (Scheme 1B, path e).[11] Also in this case, the C–N bond is formed after strain-release reaction with acyl/aryl radicals, and therefore only hydrazine-type substituents can be introduced. Albeit this multicomponent strategy has not been extended to any other class of radical traps, it has significantly shortened access to common the BCPAs intermediate 3, which can be further elaborated.

The difficulties in accessing C-3-substituted BCPAs contrast with the ease of preparation of C-3-substituted 1-alkyl-BCPs. Indeed, carbon-, sulfur- and, to a lesser extent, silicon- and tin-radicals have been widely used in ATRA-based (atom-transfer radical addition) strategies to generate, in a single step, 1,3-disubstituted BCPs (Scheme 1C).[5, 6, 7, 13] In this case however, the inherent mechanistic requirement for the chain carrying radical to be regenerated from the precursor in the final atom/group transfer step, does not offer option of divergency. Furthermore, despite the reach radical strain-release chemistry, no example of a nitrogen-radical able to engage 1 in direct strain-release amination has so far been reported.

In view of our previous experience on the use of nitrogen-radicals in olefin amino-functionalization,[14] we recently questioned whether it would be possible to use these species in strain-release settings. Despite there is no example of nitrogen-radical addition to [1.1.1]propellane 1, we reasoned that its successful implementation could have the potential to streamline access to important BCPA building blocks currently elusive from other approaches. Critical to our design was the ability to intercept the C-3 BCP radical resulting from strain-release amination with different SOMOphiles. Divergent radical functionalizations of [1.1.1]propellane 1 have, to the best of our knowledge, not been reported, but their implementation would provide significant expansion in the structure and scope of the process. Herein, we demonstrate that amidyl radicals undergo efficient strain-release reaction with 1 and that this reactivity can be harnessed as part...
of a strategy leading to the multicomponent assembly of 3-functionalized BCPAs (Scheme 1D). This approach displays significant synthetic complementarity to ionic strain-release amination as it enables, for the first time, the direct introduction of amide, carbamate and sulfonamide functionality across the BCP core. The fact that this process does not rely on a radical-chain propagation mechanism has enabled the diversification of the BCPAs with six different SOMophiles that are not compatible with any of the previous amination technologies. Furthermore, as amidyl radicals display a distinct electrophilic character, this cascade reactivity represents an umpolung approach to ionic strain-release amination and, to the best of our knowledge, the first example of a radical process enabling divergent strain-release–amino-functionalization.

RESEARCH ARTICLE

Reaction Design and Analysis

From the outset we recognized that the realization of a divergent strain-release amino-functionalization process with nitrogen-radicals would require developing a three-component cascade compatible with external SOMophiles. We therefore postulated a strategy based on a reductive quenching photoredox cycle compatible with external SOMOphiles. We therefore postulated a strategy based on a reductive quenching photoredox cycle (Scheme 2A). Under these settings, a visible-light excited photocatalyst (PC\(^{-}\)) \[^{[19]}\] would oxidize the carboxylate functionality of the radical precursor A, triggering two fragmentations (extrusion of CO\(_2\) and acetone) and forming the amidyl radical \(\cdot\)HCl. As this species has a distinct electrophilic character, we were hopeful that it would be able to intercept electron rich 1 by cleaving its central and inverted sp\(^{3}\)-sp\(^{2}\) C–C bond. This polarized radical strain-release amination would assemble the key C–N bond and give the C-3 BCPA radical C.\[^{[17]}\] This species would be mechanistically interesting because, while both nucleophiles and nucleophilic radicals can participate in strain-release chemistry, umpolung reactions can only be conducted via radical approaches owing to the known instability of BCP cations.\[^{[18]}\] As strain-release reactions of nitrogen–radicals have not been reported before, we performed computational studies to evaluate the feasibility of the proposed reactivity (Scheme 2B).\[^{[19]}\] Overall, our investigations demonstrated that these reactions share close similarities to the intermolecular additions of amidyl radicals to olefins. They are increasingly exothermic the more electrophilic is the nitrogen radical (determined using their electrophilicity indices, \(\omega(R)\)) and the barrier (\(\Delta G^\ddagger\)) of the reaction (Figure 2B, chart i) and \(\Delta G^\ddagger\) and the electrophilicity of the incoming nitrogen radical (Figure 2B, chart ii). Owing to the electron rich nature of 1 (IP = 9.7 eV),\[^{[20]}\] there is strong

### Scheme 1

**A)** Bioactive molecules containing the BCP motif. **B)** Previous radical and ionic approaches for the synthesis of BCPA building blocks. **C)** Formation of 1,3-disubstituted BCPs using ATRA-based systems. **D)** Proposed radical strategy for the divergent preparation of 3-functionalized BCPs using nitrogen-radicals. Ac = acetyl, Bn = benzyl, Boc = tert-butyloxycarbonyl.
participation of polar effects in the transition state \( (|\text{S}^2|) \) due to the net charge transfer with the electrophilic amidyl radicals. Finally, there is also a linear correlation between bond formation distance \([d(C–N)]\) and the reaction enthalpy, which is in agreement with the Hammond postulate (Scheme 2B, chart (iii)).[27] Overall, these computational findings suggest radical strain-release reactions of amidyl radicals are characterized by early transition states and the enthalpy governs to some extent the transition state geometry.

**Scheme 2.** A) Proposed mechanism for strain-release with nitrogen-radicals. B) Computational studies on the strain-release reaction of nitrogen-radicals. C) Computational studies on the character of C–3 BCPA radicals. D) Comparison of energy profiles for the elementary steps in the radical cascade, compared with the side reactivity leading to staffane. E) Stern-Volmer analyses of 1 with common photocatalysts. Bz = benzoyl, Cbz = benzyloxycarbonyl.

Despite these encouraging features, it is important to note that the success of the strategy does not hinge solely on the feasibility of the strain-release reaction of amidyl radical B (1 + B → C) but also on the following atom/group-transfer reaction (C + X–Y → D). In fact, this step is required to be efficient in order to avoid the known and facile oligomerization of BCP-radicals with other molecules of 1 that leads to common staffane by-products. Indeed, while exploring the reactivity of S-radicals, Scaino demonstrated that despite these species undergo facile strain-release reaction with 1, their reactivity could only be unlocked in systems benefitting
from very efficient ATRA-based chain propagations to stop
staffane formation. As our proposed reactivity relies on
a multicomponent radical cascade where the amidyl radical
generation is dissected by the product formation, there is a
fundamental mechanistic requirement for the final atom/group-
transfer step to be kinetically preferred over BCP-radical
oligomerization. In general, BCP radicals display enhanced
reactivity towards SOMophiles compared to tertiary radicals (e.g.
1-Bu) because of their (i) permanent pyramidal arrangement, (ii)
reduced steric shielding and (iii) increased SOMO s-character.
In our case however, we were concerned that due to the very
short C1–C3 cross-cage distance, the electronegative amide
functionality could retard the C-3 BCPA-radical reactivity with
polarized SOMophiles by inferring a through-space negative
kinetic polar effect that could instead favor the polarity matched
oligomerization. Indeed, our calculations have demonstrated that
C-3 BCPA radicals are significantly less nucleophilic than
1-alkyl-BCP ones and that their electrophilicity closely mirrors
the one of the incoming amidyl radicals (Scheme 2C, chart iv). This
supports the presence of strong cross-cage interaction leading to
a remote through-space modulation of their radical philicity.
Nevertheless, Cl-transfer from N-chlorosuccinimide (NCS)
was calculated to have a slightly lower barrier than staffane formation,
supporting the feasibility of the overall cascade reactivity (Scheme 2D).
Before starting the optimization of the amino-
functionalization strategy, we decided to evaluate the behavior of
1 in the presence of several photocatalysts. As this species is
electron rich and has also demonstrated to undergo energy
transfer (EnT) with triplet benzophenone, we wanted to
evaluate the ease of formation of 1′′/1′, that suffer fast
decomposition. These Stern-Volmer studies demonstrated 1
undergoes appreciable bimolecular quench only with the strongly
oxidant Fukuzumi’s acidinium (Eox > 2.1 V vs SCE) (Scheme 2E).
Importantly, the deprotonated amidyl radical precursors A
undergo luminescence quenching at significant higher rates with
all photocatalyst evaluated, which ensure the overall feasibility of our proposed photoredox manifold.

Reaction Development and Scope

The amino-functionalization strategy was first evaluated using 7
as the amidyl radical precursor, NCS (6a) as the SOMophile,
C3+CO2 as the base and Fukuzumi’s acidinium (PC-1) as the
photocatalyst (*Eox >2.1 V vs SCE) under blue-light irradiation
(λ = 420 nm) in CH2Cl2 solvent (Scheme 3A). The first challenge
to address was the preparation of 1. Baran has demonstrated its
large-scale synthesis as stock solution in Et3O, however, as
amidyl radicals are very electrophilic, they undergo efficient H-
atom transfer (HAT) from this solvent. Indeed, all efforts to
optimize the proposed reactivity using 1 as 1.0 M Et3O solution
resulted in quantitative formation of N-methyl-benzamide 8 (entry 1).
We therefore had to attempt the preparation of 1 in different
solvents to exclude the presence of hydric H-atom donors.
Pleasing, when the reaction was run using 1 as a 0.25 M solution
in perfluoro-n-hexane, 3Cl-BCPA 9 was obtained in 40% yield
albeit in combination with several side products arising from
staffane-formation and inefficient Cl-transfer (entry 2). Crucially,
by co-distilling 1 in benzene (entry 3) and changing the
photocatalyst to the less oxidative Ir[6(F5ppy)3(dtbbpy)](PF6)
(PC-2) (*Emax = 1.69 V vs SCE) (entry 4), we progressively
improved the yield to 78%. Interestingly, when the reaction was
completely run in benzene, 9 was obtained in lower efficiency,
thus pointing to a favorable solvent effect played by CH2Cl2 (entry 5).
Co-distillation of 1 with CH2Cl2 was attempted but found not feasible as this solution underwent decomposition over just 1 h at
room temperature. We therefore evaluated the preparation of 1 in
various benzene:CH2Cl2 mixtures assessing their stability over
time. Eventually we developed a procedure for its reproducible
and large-scale preparation as a 0.5 M solution in a 3:1 benzene:CH2Cl2 mixture. This stock solution can be stored for
over a month at low temperature (−5 °C under nitrogen in the dark)
and displays sufficient stability at room temperature for handling
(>1 day). The use of this propellane source was critical for the
implementation of the strain-release cascade and 9 was obtained in
90% yield (entry 6). Control experiments confirmed the
requirement for both photocatalyst, base and continuous blue-
light irradiation (entries 7–9).

Having identified optimal conditions for strain-release amino-
chlorination, we next explored the possibility to render this
divergent using other SOMophiles (Scheme 3B). While
NBS lead to a complex reaction mixture, Br-CCl3 provided the
amino-bromination product 10 in 20% yield albeit in the presence
of staffane by-products. We rationalized this outcome on the basis of
a more challenging Br-transfer reaction (calculated barrier: ∆G°
= 11.2 kcal mol⁻¹) that can be outcompeted by the oligomerization.

Phtalimide-based reagents 6c–e were efficient for the
introduction of S- and Se-functionalities (11–13). Building block
11 was further modified by simple oxidation providing access to
BCPAs 14 and 15 that contain a C3-sulfone and sulfoxide
respectively. Finally, several HAT catalysts were evaluated to
achieve the formation of amide-containing BCPA 16 that cannot
be accessed by ionic strain-release. While the commonly used
methyl thioglycolate resulted in complex reaction mixtures, 2-Ph-
malononitrile provided 16 in good yield.

The amidyl radical substitution pattern was evaluated next using
NCS 6a as the SOMophile. As shown in Scheme 3C, N-Me-
benzamides containing both electron donating (17) and electron
withdrawing (18) substituents were tolerated without loss in
reaction efficiency. Moreover, the presence of heteroaromatic
(19 and 20) and alkyl (21) substituents did not have a deleterious
impact on the reaction performance.

The N-substituent was also modified and we successfully
obtained 22 and 23 that contain sterically demanding N-
cyclohexyl and N-t-Bu groups. Primary BCPAs (e.g. 24) currently
represent a limitation of the methodology as the reaction with NH-
amidyl radicals gave consistently complex mixtures.

The strategy was then extended to more electrophilic carbamoyl
radicals based on commonly used protecting groups like N-Cbz
(25), N-Boc (26) and N-Ts (27). BCPA 28 contains a N-Boc,N-Bn
substituent and can be orthogonally deprotected and modified.

Pleasingly, we also succeeded in engaging nitrogen-radicals
containing two carbonyl substituents (29–32). Their ability to
success fully take part in the strain-release reactivity is noteworthy
as these species are known to undergo facile intramolecular
addition to aromatics (e.g. benzene). This side reactivity
became particularly problematic when extending the chemistry to
A) Optimization of the strain-release amino-chlorination

B) Other SOMOPhiles used in strain-release amino-functionalization

C) Amidyl radical scope

D) C1–C3 through-space interaction: X-ray analyses

Scheme 3. A) Optimization of the strain-release amino-functionalization using amidyl radical precursor 5 and NCS. B) SOMOPhile compatible to the process. C) Scope and limitation of the process. D) X-ray analysis on 3-functionalized BCPA building blocks. Nphth = phthalimide, mCPBA = meta-chloroperbenzoic acid, Cy = cyclohexyl, Ts = toluenesulfonyl, Tf = trifluoromethanesulfonyl.

the more electrophilic N-Tf,N-Me radical. In these cases, we observed complete formation of the corresponding N-Ph derivative 33 with no trace of the targeted BCPA. Pleasingly, we overcome this hurdle was by preparing 1 as a solution in...
An interesting structural feature of BCP-based building blocks is that despite their rigid and compact nature, the C1–C3 non-suppressed the unwanted crystals suitable for X-ray analysis (Scheme 3D). These substrates display progressively shorter C1–C3 cross-cage distances upon increasing electronegativity of the C3 substituent. In particular, electronegative atoms/groups inductively remove electron density from the bridgehead carbons core near-lone orbitals and, by decreasing orbital repulsion, shorten their distance. As the impact of a nitrogen substituent on a 3-substituted-BCP-core has never been assessed, we prepared BCPAs 35–41 containing a p-Ph-benzamide that enabled growing crystals suitable for X-ray analysis (Scheme 3D). These substrates display progressively shorter C1–C3 cross-cage distances upon increasing electronegativity of the C3 substituent up to a very short 1.828 Å in the case of 36. A good correlation was found between these distances and the field/inductive parameters (F) for the various C3-substituents, which supports the presence of strong through-space C1–C3 interactions.[21, 32]

Conclusions

In conclusion, we have demonstrated that electrophilic nitrogen-radicals are powerful intermediates to achieve multicomponent strain-release amino-functionalization reactions of [1.1.1]propellane 1 using external SOMOPhiles. To the best of our knowledge, the process reported here represents the first example of a divergent radical strain-release–functionalization strategy. The ability to engage a range of different SOMOPhiles has enabled the assembly of novel building blocks with potential application for the preparation of p-substituted aniline bioisosteres. DFT calculations have given an insight into the interplay of both enthalpic, polar and through-space effects operating in the strain-release reaction of nitrogen-radicals and the following functionalization of the resulting C3-BCPA radicals. Furthermore, we have demonstrated that inter-molecular H-atom transfer, a common side reactivity of electrophilic radicals, can be effectively overcome with the preparation of [1.1.1.]propellane 1 in CHCl3–benzene solution. We hope that these insights might lead to the rational design of related strain-release functionalizations using other classes of electrophilic radical species.

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Keywords: strain-release • nitrogen radicals • amino-functionalization • bioisosteres

[17] (a) We have evaluated the kinetic stability of BCP-radical C and found it similar to the one of alkylaryl-substituted ones. (b) For a discussion,


[30] In general, the use CF<sub>3</sub>C₆H₅–CH₂Cl₂ as the solvent provides the desired amino-functionalised BCPAs in lower yield than C₆H₅–CH₂Cl₂. This solvent mixture is beneficial only in the case of very electrophilic nitrogen-radicals that undergo direct reaction with C₆H₅.


[32] The S(O)Ph and SO<sub>2</sub>Ph BCPAs 40 and 41 seem to slightly deviate from the correlation due to the additional presence of “through space” hyperconjugative effects with the BCP-cage. For a computational analysis and discussion of these effects, see: A. R. Campanelli, A. Domenicano, G. Piacente, F. Ramondo, J. Phys. Chem. A, 114, 5162.
Electrophilic nitrogen radicals enable efficient strain-release amino-functionalization of [1.1.1]propellane. This radical reactivity can be used for the divergent assembly of 3-substituted bicyclo[1.1.1]pentylamines, which are powerful aniline bioisosteres.