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Photochemical formal (4+2)-cycloaddition of imine-substituted bicyclo[1.1.1]pentanes and alkenes

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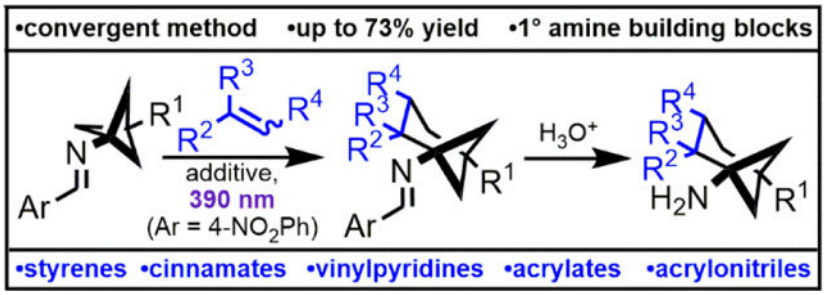
Abstract

Amines containing bridged bicyclic carbon skeletons are desirable building blocks for medicinal chemistry. Herein, we report the conversion of bicyclo[1.1.1]pentan-1-amines to a wide range of poly-substituted bicyclo[3.1.1]heptan-1-amines through a photochemical, formal (4+2)-cycloaddition of an intermediate imine diradical. To our knowledge, this is the first reported method to convert the bicyclo[1.1.1]pentane skeleton to the bicyclo[3.1.1]heptane skeleton. Hydrolysis of the imine products gives complex, sp^3-rich primary amine building blocks.

Graphical Abstract



The fraction of carbon atoms that are sp^3-hybridized in a drug candidate is positively correlated with the molecule's advancement through development and clinical trials.[1] Growing recognition of this trend among medicinal chemists has amplified interest in building blocks containing bridged polycyclic skeletons. These substructures, like aromatic rings, can provide a conformationally restricted framework upon which to append

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Author Contributions

All authors have given approval to the final version of the manuscript.

ASSOCIATED CONTENT

Supporting Information.

Additional experimental details, materials, and methods, including photographs of experimental setup

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substituents, but often retain the pharmacological benefits of being aliphatic.[2] All—carbon ring systems such as the bicyclo[1.1.1]pentane system are of particular interest due to their inert nature and potential phenyl bioisosterism.[3] However, despite recent innovations in the synthesis of 2-substituted bicyclo[1.1.1]pentanes (Qin, Pfizer, Merck, and academic collaborators) and (oxa)bicyclo[2.1.1]hexanes (Enamine), most commercial compounds in this class are mono- or "*para*"-disubstituted.[4–9] Furthermore, commercial Csp^3-rich polycyclic building blocks are often achiral, despite stereochemical complexity's negative correlation with promiscuity and positive correlation with drug candidate success.[10] The invention of new synthetic methods to access poly-substituted bicyclic cores with uniquely disposed exit vectors will allow for a more complete biological evaluation of low molecular weight, sp^3-rich chemical space.[11]

To this end, our group has developed several methods to synthesize 1-aminonorbornanes.[12,13] In 2019, we reported the photochemical intramolecular formal (3+2)-cycloaddition of cyclopropyl imines bearing a pendant alkene to generate (hetero)aryl-fused 1-aminonorbornanes (Figure 1A).[12] Mechanistically, irradiating the imine with 390 nm lamps generates an excited state with *N*-centered radical character, facilitating the homolytic cleavage of a bond in the adjacent cyclopropane ring, which in turn triggers an intramolecular radical cyclization cascade. Our method intercepts reactive intermediates previously described in Sampedro's reports of the photoinduced rearrangement of cyclopropylimines to 1-pyrrolines (Figure 1B).[14–16] Based on ultraviolet-visible spectroscopy, we have proposed the reaction proceeds via the imine $S_1(n, \pi^*)$ excited state.[12] Our work was among the first use of the *N*-centered radical character of an imine excited state to initiate a radical cyclization cascade. This is a testament to the relatively underexplored nature of the photochemistry of imines compared to that of carbonyls and alkenes.[17,18]

Inspired by the pioneering work of Zheng and related photoredox approaches to access *N*-centered radicals for formal (3+2)- and (4+2)- cycloadditions of strained-ring amines, our group has recently extended our imine-based strategy to the intermolecular context (Figure 1C).[19–29] Though cyclopropane ring-opening was consistently observed, we have detected only trace amounts of cyclobutane ring-opening products under these conditions, despite both species containing ostensibly identical chromophores. This difference in reactivity appears consistent with the relative ring-opening kinetics of cyclopropylaminyl radicals and cyclobutylaminyl radicals.[30]

We reasoned that cyclobutane-containing ring systems with abnormally rapid radical ring-opening kinetics might be more amenable to our reaction design. We were encouraged by the known rate constants for the sequential ring openings of **1r**, which suggested intermediates related to **1s** could be both rapidly generated and long-lived enough to engage in intermolecular reactivity (Figure 1D).[31,32] Specifically, we hypothesized bicyclo[1.1.1]pentan-1-amine **1v** may undergo the desired ring cleavage, generating diradical intermediate **1×**, the primary radical moiety of which could add to an alkene. Subsequent cyclization would afford a compound containing a relatively inert cyclobutylamine, namely racemic (or achiral) bicyclo[3.1.1]heptan-1-amine **1z** (Figure 1E). Alternatively, the diradical alkene adduct might undergo a 1,5-hydrogen atom transfer

(HAT) to produce racemic cyclobutene **1aa**. If alkene capture of **1×** did not occur, **1ab** would be expected.

In our initial attempt to realize this reactivity, we drew conditions from our intermolecular formal (3+2)-cycloaddition work.[19] Gratifyingly, irradiating **2a**, styrene (**3**), and 2,2'-dipyridyl disulfide (Aldrithiol™) in ethyl acetate with 390 nm lamps afforded the desired product **4a** (Table 1, Entry 1). However, **4a** was the minor product of the reaction, and skipped diene **5**, which results from unimolecular background reaction, was the major product. Changing the solvent from ethyl acetate to acetonitrile had little effect on the reaction profile (Table 1, Entry 2). Increasing the concentration led to a significant improvement in yield and selectivity, (Table 1, Entries 3 and 4). Running the reaction in neat styrene further favored the desired intermolecular reactivity over the intramolecular pathway (Table 1, Entries 5 and 6). All other light sources investigated gave inferior conversion and yield of **4a** at 3 hours when compared to the 390 nm lamp, though lamps with emission maxima spanning from 370 nm to 456 nm showed useful levels of reactivity (Table 1, Entries 7–11). A thermal control showed no background reactivity (Table 1, Entry 12), supporting our assertion that the formal cycloaddition is indeed a photochemical process. Degassing (3 freeze-pump-thaw cycles) and inclusion of Aldrithiol™ only modestly improved the reaction profile at 3 hours, encouraging features for operational simplicity and future scaling of the reaction (Table 1, Entries 13 and 14). However, at the prolonged reaction times necessary to achieve full conversion when using 7.5 equivalents of alkene (~16 hours), excluding Aldrithiol™ or including air had a small but noticeable deleterious effect (Table 1, Entries 15–17). The cyclobutene of type **1aa** was not identified as a significant contributor to the crude reaction mixtures.

5 decomposes under the reaction conditions upon prolonged irradiation, forming solid deposits in the reaction vessel. Polymeric styrene-derived material (presumably polystyrene) also forms under such conditions. Though these solids reduce the photon flux entering the reaction solution, thereby slowing conversion, they are easily removed by chromatography and can simplify otherwise challenging chromatographic separations of the desired bicyclo[3.1.1]heptane-containing products from **5**. To reduce alkene waste and simplify purification, we adopted the ~16-hour reaction time with 7.5 equivalents of neat alkene as the standard conditions for our scope study. Clearly, solid alkenes are incompatible with these conditions and necessitate the inclusion of an inert solvent. Furthermore, alkene classes differ in their rates of radical trapping, leading to drastically different levels of by-product formation, changing the calculus for optimal concentration and alkene stoichiometry. Since one set of conditions could not fully capture the potential of the reaction, several modifications were examined (vide infra).

With suitable conditions in hand, the reaction scope of alkenes was studied broadly (Table 2). Gratifyingly, electron-rich and electron-poor styrenes showed the desired reactivity, albeit with modest yields. Reaction of **2b** with styrene gave product **4b** in 41% yield on 10 mmol scale (1.56 g product). 1,1-Diarylethylenes underwent the desired ring closure to form sterically hindered bicyclo[3.1.1]heptan-1-amines, but also produced a significant amount of cyclobutene byproducts. For instance, cyclobutene **6** was isolated in 11% yield alongside a 31% yield of **4h**. α-Methyl styrene was well-tolerated, giving **4i** in 32% yield.

Though relatively unreactive, methyl cinnamate and ethyl cinnamate provided **4l** and **4m**, respectively, with high diastereoselectivity. As with other styrenes, cinnamates proceed with regioselectivity that suggests the intermediacy of a benzylic radical. Since a thermodynamic control argument invoking the reversibility of alkene addition would be inconsistent the competitive formation of **4l** and **4m** versus **5**, we attribute the regioselectivity to kinetic control.

Alkene classes besides styrenes also undergo this chemistry. Vinyl-substituted heteroaromatics gave modest to moderate yields of the desired products (Table 2, examples **4o**-**4s** and **4aa**-**4ae**). Unsaturated carboxylic acid derivatives also participated in this reaction. Reaction of **2b** with 2-chloroacrylonitrile gave **4z** in 73% yield. The formation of skipped diene byproducts was completely suppressed by 2-chloroacrylonitrile based on crude NMR analysis, suggesting some alkenes may be sufficiently reactive to compete with the unimolecular background reaction in the solution phase and/or at decreased loadings. Indeed, in acetonitrile solution, the solid alkene 2-acetamidoacrylate showed comparable performance using the standard 7.5 equivalents versus 1.1 equivalents of alkene (Table 2, example **4u**).[33]

The reaction also shows good functional group tolerance with respect to "*para*"- substitution of the bicyclo[1.1.1]pentane component. The easily accessed **2b** was compared to **2a** across a variety of alkenes and generally showed comparable isolated yields (Table 2). A broader comparison was performed when employing 2-vinylpyridine as the alkene (Table 2, examples **4aa**-**4ae**). The free hydroxyl group of **2c** did not interfere in the reaction. The benzene-sulfonyl group of **2d**, though a potential leaving group via homolysis of the C-S bond prior intermolecular reactivity, was tolerated in the reaction to give **4ad**. Alkyne functionality was likewise tolerated to give **4ae**.

We next turned our attention to synthetic manipulations of the formal cycloadducts, focusing on reactions most relevant to medicinal and agrochemical applications. Primary amines **7a**, **7e**, and **7f** were each produced on multi-millimole scale by hydrolysis of their corresponding crude cycloaddition reaction mixtures (Figure 2A). Acid-base extraction operations purged excess alkene and the carbonyl-containing hydrolysis byproducts, affording crude bicyclo[3.1.1]pentan-1-amines, often in good purity. This was particularly attractive as the chromatographic separation of byproducts of type **1aa** and **1ab,** as well as trace 4-nitrobenzaldehyde (resulting from imine hydrolysis by adventitious water), from several of the bicyclo[3.1.1]heptane-containing imines, was challenging. For example, amines **7b**, **7c**, and **7d**, were easily isolated in yields approaching the Q^1HNMR assay yields of the corresponding imines **4e**, **4g**, and **4a**, respectively, which had presented purification challenges.

Inspired by previous work from our laboratory, primary amines prepared in this manner were used to synthesize analogues of the succinate dehydrogenase inhibitor (SDHI) fungicide Boscalid, wherein Boscalid's *ortho*-aryl aniline core was replaced with bicyclo[3.1.1]heptan-1-amines (Figure 2A).[34,35] A library mimicking related pyrazole carboxamide SDHI fungicides was similarly prepared via amine-acid coupling mediated by EDC•HCl.[36] Sulfonylation of the primary amines was also simple and high-yielding. For

instance, **7d** was converted in 97% yield to sulfonamide **10**, which is an analogue of **11**, an anti-mitotic compound reported to decrease viability and inhibit growth in several ovarian cancer cell lines (Figure 2B).[37]

Next, imine **4b** was elaborated to several protected ɣ-amino acid building blocks (Figure 2C). First, **4b** was hydrolyzed to give **7g**, which was advanced over two steps to **12. 7g** was similarly converted to **14**. Complementarily, **2a** was carried through formal cycloaddition and hydrolysis in a telescoped fashion to yield **7h**, with comparable yields observed when employing batch or flow processing during the photochemical step.[38] **7h** was converted to carbamate **15** and saponified in a telescoped fashion to yield **16**, a fellow ɣ-amino acid isomer of **14**.

We next sought to synthesize ring systems with additional complexity using the formal (4+2)-cycloaddition described herein as a key step. To this end, isolated imine **4p** was hydrolyzed to give **7i**, which upon copper-catalyzed intramolecular C-N coupling gave **17**, a sp^3-rich analogue of β-carboline (norharmane, **18**), the heterocyclic core of its namesake family of pharmacologically interesting alkaloids (Figure 2D).[39,40] Lastly, we engaged **2a** in formal cycloaddition with **19** to give the sterically congested polycycle **4af** in 11% yield (Figure 2E). **4af** contains features representing two distinct medicinal chemistry strategies for imparting rigidity on sp^3-rich structures: bridged bicyclic (2) and spiro (1) motifs.[41]

In summary, we have developed a method of converting bicyclo[1.1.1]pentan-1-amines to bicyclo[3.1.1]heptan-1-amines using an imine-based, photochemical formal (4+2)-cycloaddition. The key kinetic discrepancy exploited in this study, namely the enhanced susceptibility of the bicyclo[1.1.1]pentane system to radical ring-opening relative to simple cyclobutanes (and relative to bicyclo[3.1.1]heptanes), suggests a rich body of bicyclo[1.1.1]pentane formal cycloaddition chemistry yet to be developed. Further results will be reported in due course.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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REFERENCES

(1). Lovering F; Bikker J; Humblet C Escape from Flatland: Increasing Saturation as an Approach to Improving Clinical Success. Journal of Medicinal Chemistry 2009, 52, 6752–6756. [PubMed: 19827778]

(2). Locke GM; Bernhard SSR; Senge MO Nonconjugated Hydrocarbons as Rigid-Linear Motifs: Isosteres for Material Sciences and Bioorganic and Medicinal Chemistry. Chemistry – A European Journal 2019, 25, 4590–4647. [PubMed: 30387906]

(3). Levin MD; Kaszynski P; Michl J Bicyclo[1.1.1]pentanes, [n]Staffanes, [1.1.1]Propellanes, and Tricyclo[2.1.0.02,5]pentanes. Chemical Reviews 2000, 100, 169–234. [PubMed: 11749237]

(4). Mykhailiuk PK Saturated bioisosteres of benzene: where to go next? Organic & Biomolecular Chemistry 2019, 17, 2839–2849. [PubMed: 30672560]

(5). Levterov VV; Panasyuk Y; Pivnytska VO; Mykhailiuk PK Water-Soluble Non-Classical Benzene Mimetics. Angewandte Chemie International Edition 2020, 59, 7161–7167. [PubMed: 32060990]

(6). Ma X; Han Y; Bennett DJ Selective Synthesis of 1-Dialkylamino-2-alkylbicyclo-[1.1.1]pentanes. Organic Letters 2020, 22, 9133–9138. [PubMed: 33170018]

(7). Anderson JM; Measom ND; Murphy JA; Poole DL Bridge Functionalisation of Bicyclo[1.1.1]pentane Derivatives. Angewandte Chemie International Edition 2021, 60, 24754–24769.

(8). Yang Y; Tsien J; Hughes JME; Peters BK; Merchant RR; Qin T An intramolecular coupling approach to alkyl bioisosteres for the synthesis of multisubstituted bicycloalkyl boronates. Nature Chemistry 2021, 13, 950–955.

(9). Zhao J-X; Chang Y-X; He C; Burke BJ; Collins MR; Del Bel M; Elleraas J; Gallego GM; Montgomery TP; Mousseau JJ; Nair SK; Perry MA; Spangler JE; Vantourout JC; Baran PS 1,2-Difunctionalized bicyclo[1.1.1]pentanes: Long–sought-after mimetics for ortho/meta-substituted arenes. Proceedings of the National Academy of Sciences 2021, 118, e2108881118.

(10). Lovering F Escape from Flatland 2: complexity and promiscuity. MedChemComm 2013, 4, 515.

(11). Tajabadi FM; Campitelli MR; Quinn RJ Scaffold Flatness: Reversing the Trend. Springer Science Reviews 2013, 1, 141–151.

(12). Staveness D; Collins JL; McAtee RC; Stephenson CRJ Exploiting Imine Photochemistry for Masked N-Centered Radical Reactivity. Angewandte Chemie International Edition 2019, 58, 19000–19006.

(13). Staveness D; Sodano TM; Li K; Burnham EA; Jackson KD; Stephenson CRJ Providing a New Aniline Bioisostere through the Photochemical Production of 1-Aminonorbornanes. Chem 2019, 5, 215–226. [PubMed: 30873503]

(14). Sampedro D; Soldevilla A; Rodríguez MA; Campos PJ; Olivucci M Mechanism of the N-Cyclopropylimine-1-pyrroline Photorearrangement. Journal of the American Chemical Society 2005, 127, 441–448. [PubMed: 15631495]

(15). Soldevilla A; Sampedro D; Campos PJ; Rodríguez MA The N-Cyclopropylimine-1-pyrroline Photorearrangement as a Synthetic Tool: Scope and Limitations. The Journal of Organic Chemistry 2005, 70, 6976–6979. [PubMed: 16095330]

(16). Campos PJ; Soldevilla A; Sampedro D; Rodríguez MA N-Cyclopropylimine-1-pyrroline Rearrangement. A Novel Photochemical Reaction. Organic Letters 2001, 3, 4087–4089. [PubMed: 11735591]

(17). Kandappa SK; Valloli LK; Ahuja S; Parthiban J; Sivaguru J Taming the excited state reactivity of imines - from non-radiative decay to aza Paterno-Buchi reaction. Chem Soc Rev 2021, 50, 1617–1641. [PubMed: 33416818]

(18). Latrache M; Hoffmann N Photochemical radical cyclization reactions with imines, hydrazones, oximes and related compounds. Chemical Society Reviews 2021, 50, 7418–7435. [PubMed: 34047736]

(19). Sowden MJ; Collins JL III; Staveness D; Stephenson CRJ A One Pot Photochemical Method for the Generation of Functionalized Aminocyclopentanes. ChemRxiv 2020, DOI: 10.26434/chemrxiv.13079159.v1

(20). Maity S; Zhu M; Shinabery RS; Zheng N Intermolecular [3+2] Cycloaddition of Cyclopropylamines with Olefins by Visible-Light Photocatalysis. Angewandte Chemie International Edition 2012, 51, 222–226. [PubMed: 22109785]

(21). Nguyen TH; Morris SA; Zheng N Intermolecular [3+2] Annulation of Cyclopropylanilines with Alkynes, Enynes, and DiynesviaVisible Light Photocatalysis. Advanced Synthesis & Catalysis 2014, 356, 2831–2837. [PubMed: 26120292]

(22). Wang J; Zheng N The Cleavage of a C-C Bond in Cyclobutylanilines by Visible-Light Photoredox Catalysis: Development of a [4+2] Annulation Method. Angewandte Chemie International Edition 2015, 54, 11424–11427. [PubMed: 26228259]

(23). Wang J; Mao C; Feng P; Zheng N Visible-Light-Mediated [4+2] Annulation of N-Cyclobutylanilines with Alkynes Catalyzed by Self-Doped Ti3+ @TiO2. Chemistry – A European Journal 2017, 23, 15396–15403. [PubMed: 28608493]

(24). Wang Q; Zheng N A Photocatalyzed Synthesis of Naphthalenes by Using Aniline as a Traceless Directing Group in [4 + 2] Annulation of Amino-benzocyclobutenes with Alkynes. ACS Catalysis 2017, 7, 4197–4201.

(25). White DH; Noble A; Booker-Milburn KI; Aggarwal VK Diastereoselective Photoredox-Catalyzed [3 + 2] Cycloadditions of N-Sulfonyl Cyclopropylamines with Electron-Deficient Olefins. Organic Letters 2021, 23, 3038–3042. [PubMed: 33821661]

(26). Uraguchi D; Kimura Y; Ueoka F; Ooi T Urea as a Redox-Active Directing Group under Asymmetric Photocatalysis of Iridium-Chiral Borate Ion Pairs. Journal of the American Chemical Society 2020, 142, 19462–19467.

(27). Yin Y; Li Y; Gonçalves TP; Zhan Q; Wang G; Zhao X; Qiao B; Huang K-W; Jiang Z All-Carbon Quaternary Stereocenters α to Azaarenes via Radical-Based Asymmetric Olefin Difunctionalization. Journal of the American Chemical Society 2020, 142, 19451–19456.

(28). Muriel B; Gagnebin A; Waser J Synthesis of bicyclo[3.1.0]hexanes by (3 + 2) annulation of cyclopropenes with aminocyclopropanes. Chemical Science 2019, 10, 10716–10722.

(29). De Nanteuil F; De Simone F; Frei R; Benfatti F; Serrano E; Waser J Cyclization and annulation reactions of nitrogen-substituted cyclopropanes and cyclobutanes. Chem. Commun. 2014, 50, 10912–10928.

(30). Musa OM; Horner JH; Shahin H; Newcomb M A Kinetic Scale for Dialkylaminyl Radical Reactions. Journal of the American Chemical Society 1996, 118, 3862–3868.

(31). Branchaud BP; Glenn AG; Stiasny HC Round-trip radical probes: ring cleavage of the bicyclo[1.1.1]pentylcarbinyl radical. The Journal of Organic Chemistry 1991, 56, 6656–6659.

(32). Walton JC 3-Methylenecyclobutyl, cyclopent-3-enyl, and 3-methylenecyclobutylmethyl radicals; absence of homoallylic conjugation. Journal of the Chemical Society, Perkin Transactions 2 1987, 231.

(33).

See supporting information for a more complete comparision of reaction conditions for the synthesis of 4u

(34). Sierotzki H; Scalliet G A Review of Current Knowledge of Resistance Aspects for the Next-Generation Succinate Dehydrogenase Inhibitor Fungicides. Phytopathology® 2013, 103, 880–887. [PubMed: 23593940]

(35). Staveness D; Breunig M; Ortiz V; Sang H; Collins JL; McAtee RC; Chilvers MI; Stephenson CRJ Photochemically derived 1-aminonorbornanes provide structurally unique succinate dehydrogenase inhibitors with in vitro and in planta activity. Cell Reports Physical Science 2021.

(36).

See supporting information

(37). Huang H-L; Chao M-W; Li Y-C; Chang L-H; Chen C-H; Chen M-C; Cheng C-C; Liou J-P; Teng C-M; Pan S-L MPT0G066, a novel anti-mitotic drug, induces JNK-independent mitotic arrest, JNK-mediated apoptosis and potentiates antineoplastic effect of cisplatin in ovarian cancer. Scientific Reports 2016, 6, 31664.

(38).

See supporting information for more complete comparison of batch and flow protocols

(39). Li S; Cheng X; Wang C A review on traditional uses, phytochemistry, pharmacology, pharmacokinetics and toxicology of the genus Peganum. Journal of Ethnopharmacology 2017, 203, 127–162. [PubMed: 28359849]

(40). Zhang X; Anderson JC A Divergent Synthetic Route to the Vallesamidine and Schizozygine Alkaloids: Total Synthesis of (+)-Vallesamidine and (+)-14,15-Dehydrostrempeliopine. Angewandte Chemie International Edition 2019, 58, 18040–18045. [PubMed: 31538685]

(41). Hiesinger K; Dar'In D; Proschak E; Krasavin M Spirocyclic Scaffolds in Medicinal Chemistry. Journal of Medicinal Chemistry 2021, 64, 150–183. [PubMed: 33381970]

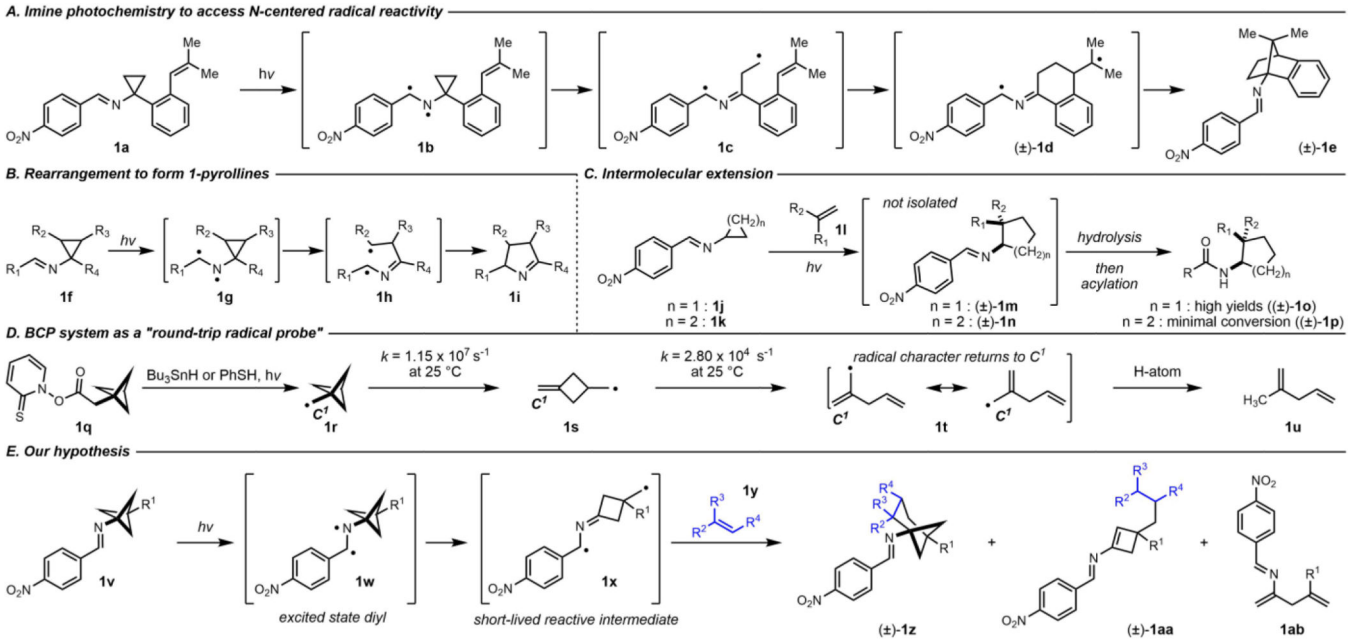


Figure 1.

Precedent for (3+2)-cycloaddition reactivity and bicyclo[1.1.1]pentane ring opening informed our reactivity hypothesis

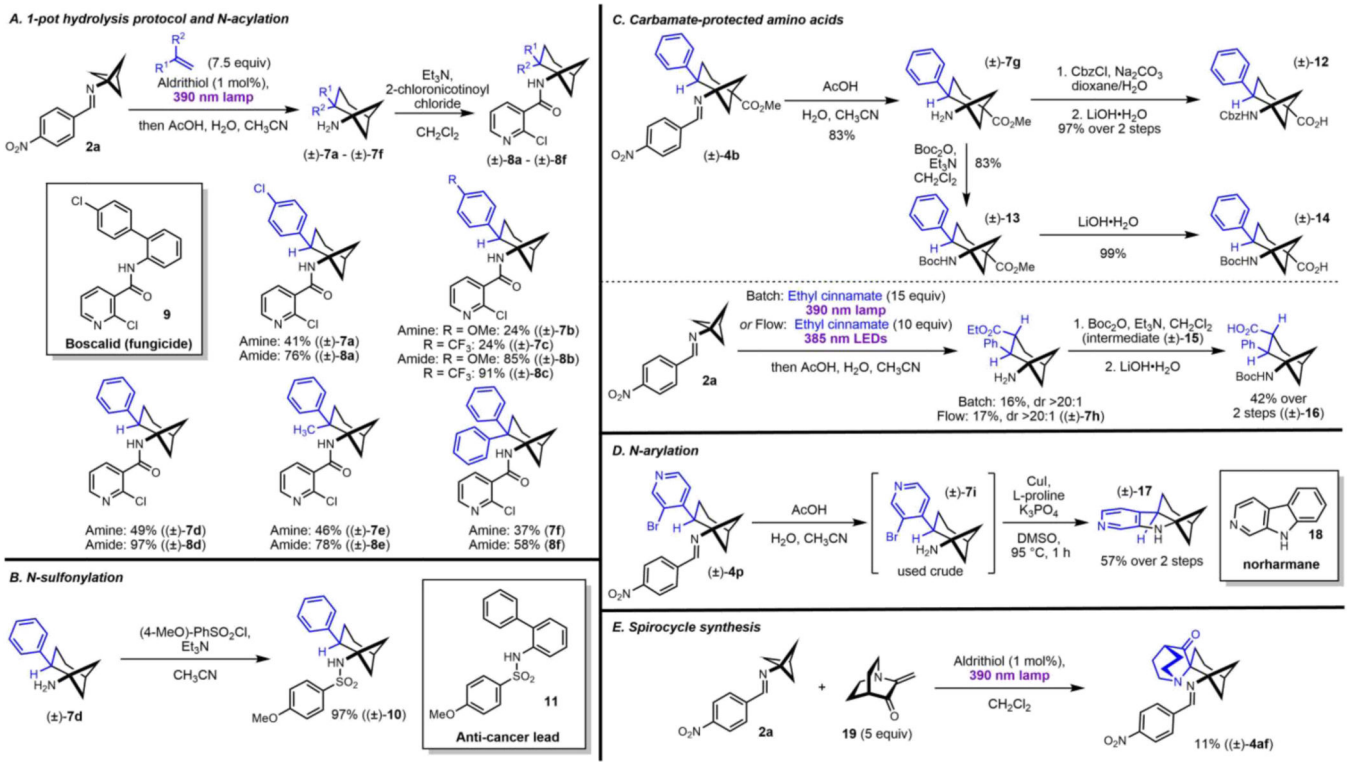
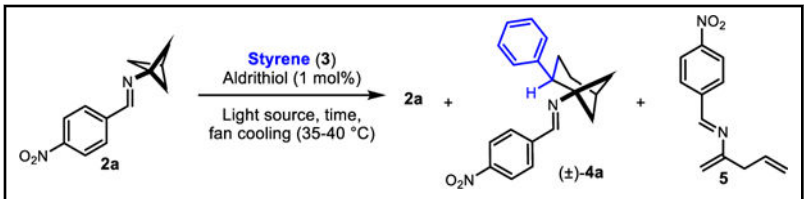


Figure 2.

Application of the formal (4+2)-cycloaddition chemistry to the synthesis of analogues of biologically-relevant molecules. Full experimental details can be found in the supporting information.

Table 1.

Reaction optimization



Entry	time (h)	3 (eq)	Lamp (nm)	Solvent	2a[h] %	4a[h] %	5[h] %
1[a,f]	3	7.5	390	EtOAc	6	15	59
2[a,f]	3	7.5	390	CH_3CN	5	16	57
3[b,f]	3	7.5	390	EtOAc	7	29	40
4[a,f]	3	7.5	390	CH_3CN	6	26	37
5[g]	3	7.5	390	neat	18	38	23
6[f]	3	15	390	neat	6	47	28
7[g]	3	7.5	370	neat	44	26	19
8[g]	3	7.5	427	neat	40	30	17
9[g]	3	7.5	440	neat	58	21	11
10[g]	3	7.5	456	neat	76	12	7
11[g]	3	7.5	525	neat	98	0	0
12[e,g]	3	7.5	--	neat	99	0	0
13[c,g]	3	7.5	390	neat	20	33	20
14[d,g]	3	7.5	390	neat	22	37	22
15[c,g]	16	7.5	390	neat	--	36	8
16[d,g]	16	7.5	390	neat	--	36	9
17[g]	16	7.5	390	neat	--	48	9

[a] 0.65 mL.

[b] 0.172 mL.

[c] no Aldrithiol.

[d] no freeze-pump-thaw.

[e] 60 °C and shielded from light.

[f] 0.2 mmol imine.

[g] 0.4 mmol imine.

[h] yield based on Q^{1}HNMR analysis with 1,3,5-trimethoxybenzene internal standard

Table 2.

Reaction scope study