OL | Organic Letters

pubs.acs.org/OrgLett Letter

Aminomethylation of Oxabenzonorbornadienes via the Merger of Photoredox and Nickel Catalysis

Abdoul G. Diallo, David Roy, Sylvain Gaillard, Mark Lautens,* and Jean-Luc Renaud*

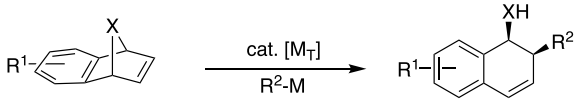
Cite This: https://dx.doi.org/10.1021/acs.orglett.0c00593 Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

ABSTRACT: The first aminomethylation of oxabenzonorbornadienes using dual photoredox/nickel catalysis has been disclosed. This cascade reaction allowed the preparation of the *cis*-aminomethyl dihydronaphthalenols without any prefunctionalization or any use of nucleophilic organometallic species. The control of the regio- and stereoselectivity might be explained by a sequence involving insertion of nickel(0) into the C−O bond followed by the formation of a π-allyl intermediate.

Metal-catalyzed ring-opening reactions of oxabicyclic derivatives have been an intense area of research in the last 20 years.[1] The ring-opened derivatives are important and useful compounds as functionalized intermediates in natural product synthesis and as motifs in medicinal chemistry.[2] Such ring-opening reactions can be carried out with a variety of nucleophiles, including hydride, (non)-stabilized carbanions, alcohols, amines, and carboxylates, in the presence of nickel,[3] palladium,[4] copper,[5] rhodium,[6,7] and cobalt[8] complexes to generate enantioenriched dihydronaphthalenes (Scheme 1).

Scheme 1. Transition-Metal-Catalyzed Nucleophile Addition−Ring Opening of Heterobicyclic Alkenes



X = O, NR
M_T = Ni, Pd, Rh, Cu, Co
M = Li, Mg, Al, Zn, B…
R^2 = H, alkyl, vinyl, aryl, allyl, amines, hydroxyl, alkoxy groups…

To date, there have been few examples of the introduction of nucleophiles bearing a heteroatom at the α-position in such ring-opening processes.[9] However, single-electron oxidation of neutral organic compounds is a known and straightforward way to generate highly reactive radical intermediates. As an example, single-electron oxidation of amines via (photo-induced) electron transfer between excited molecules or oxidants and amines provides access to synthetically useful α-aminoalkyl radicals.[10] Such oxidation to the radical cation also increases the acidity of the α-amino C−H bond and lowers the α-CH BDE.[10b] After subsequent deprotonation, the resulting α-aminoalkyl radical can be engaged in various reactions.[10]

The development of a mild, general, and efficient approach to build complex molecular structures is always an important concern in synthetic organic chemistry.[11] Over the last few decades, the quest for sustainable and environmentally friendly technologies has led to an increasing interest in green chemistry. Among the new approaches, organic photochemistry appears as a valuable application since light can be seen as a clean and traceless reagent. Photoinduced redox processes using visible light offer a variety of catalytic transformations, and new processes appear very frequently in the literature. Moreover, photochemical methods and catalytic reactions can complement each other in terms of scope and chemo- and stereoselectivities.[12−14] The recent literature demonstrates that this preparative toolbox is expanding substantially, but there are still opportunities to develop new reactions and to introduce new substrates in photoredox reactions.

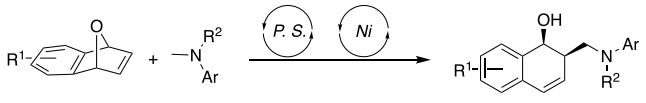
Previous studies by our group demonstrated that the ring opening of oxa- or azabicyclic derivatives was not successful with free radical species. However, recent examples in photoredox chemistry have shown that a radical process can be combined with an organometallic coupling process.[15] The photogenerated amino radical could then be intercepted by an organometallic complex (e.g., a nickel complex), and the new alkylative ring opening of oxabenzonorbornadiene could be anticipated with this in situ-generated aminomethyl organometallic species.[15c,d]

In this contribution, we report the ring opening reaction of oxabicyclic derivatives with methylamine derivatives under visible-light activation and nickel catalysis (Scheme 2).[16] We considered that (i) the dual catalysis strategy would be relevant if it were successful, as this approach avoids the usually

Received: February 19, 2020

https://dx.doi.org/10.1021/acs.orglett.0c00593
Org. Lett. XXXX, XXX, XXX−XXX

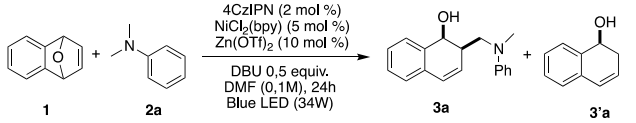
Scheme 2. Outline of Aminomethylation/Ring Opening of Oxabenzonorbornadienes Merging Photoredox and Nickel Catalysis



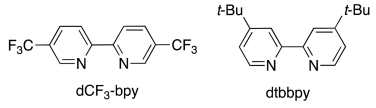
inevitable prefunctionalization of substrates and the formation of the undesirable toxic wastes, and (ii) it would open a straightforward access to aminomethyl dihydronaphthalenols, whose synthesis is still a challenge in organic chemistry.

At the outset, we chose the aminomethylation of oxabenzonorbornadiene **1a** (1 equiv) with dimethylamine **2a** as a model reaction for the optimization of the reaction conditions (Tables 1 and S1–S6). On the basis of previous reports,[10] 4-CzIPN was selected as the photosensitizer (PS) because of its ability to oxidize alkylamines ($E_{1/2}$ = +1.1–1.2 V vs SCE, $E_{1/2}$(PS*/PS$^-$) = +1.35 V vs SCE) and its lower cost compared with iridium-based photocatalysts.[17] In the presence of 2 mol % 4-CzIPN, 5 mol % [Ni(bpy)Cl_2], 10 mol % Zn(OTf)$_2$, and DBU (0.5 equiv) in DMF (0.1 M) at room temperature under blue-light irradiation for 24 h, **2a** reacted with **1a** to furnish the alkylated ring-opening adduct **3a** in 90% conversion and 80% isolated yield (entry 1, Table 1). The reductive ring-opening product **3′a** was also obtained under these conditions in 10% conversion. The side-product formation might be explained by a competitive reaction between a nickel(0) complex and an acid (DBU·H$^+$) to generate a nickel hydride species. Without light, photocatalyst, or nickel catalyst, no reaction occurred (entries 2–4, Table 1). These results ruled out the free radical addition, as suggested by our initial observations. The ligand on the nickel played a crucial role in the catalytic activity. Replacing the bipyridine (bpy) ligand by a phosphine led to a decrease in both the reactivity and the selectivity (entries 5 and 6, Table 1). The reductive ring-opening adduct was favored with phosphine ligands (entries 5 and 6, Table 1). The electron-deficient dipyridine amine dCF$_3$bpy also provided the alkylated ring-opening product in lower yield, while the often-used dtbbpy ligand furnished both ring-opening adducts **3a** and **3′a** with lower conversion (85%) and lower selectivity (entries 7 and 8, Table 1). In addition to nickel complexes, palladium and cobalt precatalysts have also been introduced in dual catalysis.[14] Although Rovis recently reported the aminomethylation of dienes via photoredox/low-valent cobalt catalysis,[18] no ring-opening adduct was formed with a palladium or cobalt complex as the cocatalyst (entries 10 and 11, Table 1). The amount of aniline **2a** drives the formation of **3a** over **3′a** to some extent, and an increase in the amount of **2a** favored the aminomethylated product (entries 1, 13, and 14, Table 1). Any other modification of the reaction conditions (use of a ruthenium complex or 4-CzTPN as the PS, of other solvents, bases, Lewis acids, etc.) had a negative effect on both the conversion and the selectivity for **3a**. A NOE analysis confirmed the structure of **3a**, including the regio- and *cis* stereoselectivity.

Table 1. Optimization of the Reaction Conditions[a]



entry	Deviation from standard conditions	conv. **3a** / **3′a** (%)[b]
1	none	90 (80)[c] / 10
2	in the dark	n.d.
3	no 4-CzIPN	n.d.
4	no nickel catalyst	n.d.
5	using [Ni(PPh$_3$)$_2$Cl$_2$] instead of [Ni(bpy)Cl$_2$]	0/19
6	using [Ni(PCy$_3$)$_2$Cl$_2$] instead of [Ni(bpy)Cl$_2$]	0/24
7	using Ni(dCF$_3$bpy)Cl$_2$] instead of [Ni(bpy)Cl$_2$]	51/21
8	using [Ni(dtbbpy)Cl$_2$ instead of [Ni(bpy)Cl$_2$]	85/10
9	using [Pd(PPh$_3$)$_2$Cl$_2$] instead of [Ni(bpy)Cl$_2$]	n.d.
10	using [Co(dppe)Cl$_2$] instead of [Ni(bpy)Cl$_2$]	n.d.
11	using 1 mol % of 4-CzIPN	86/14
12	using 2.5 mol % of nickel catalyst	83/27
13	using 1.5 equiv. of **2a**	67/33
14	using 2 equiv. of **2a**	70/30



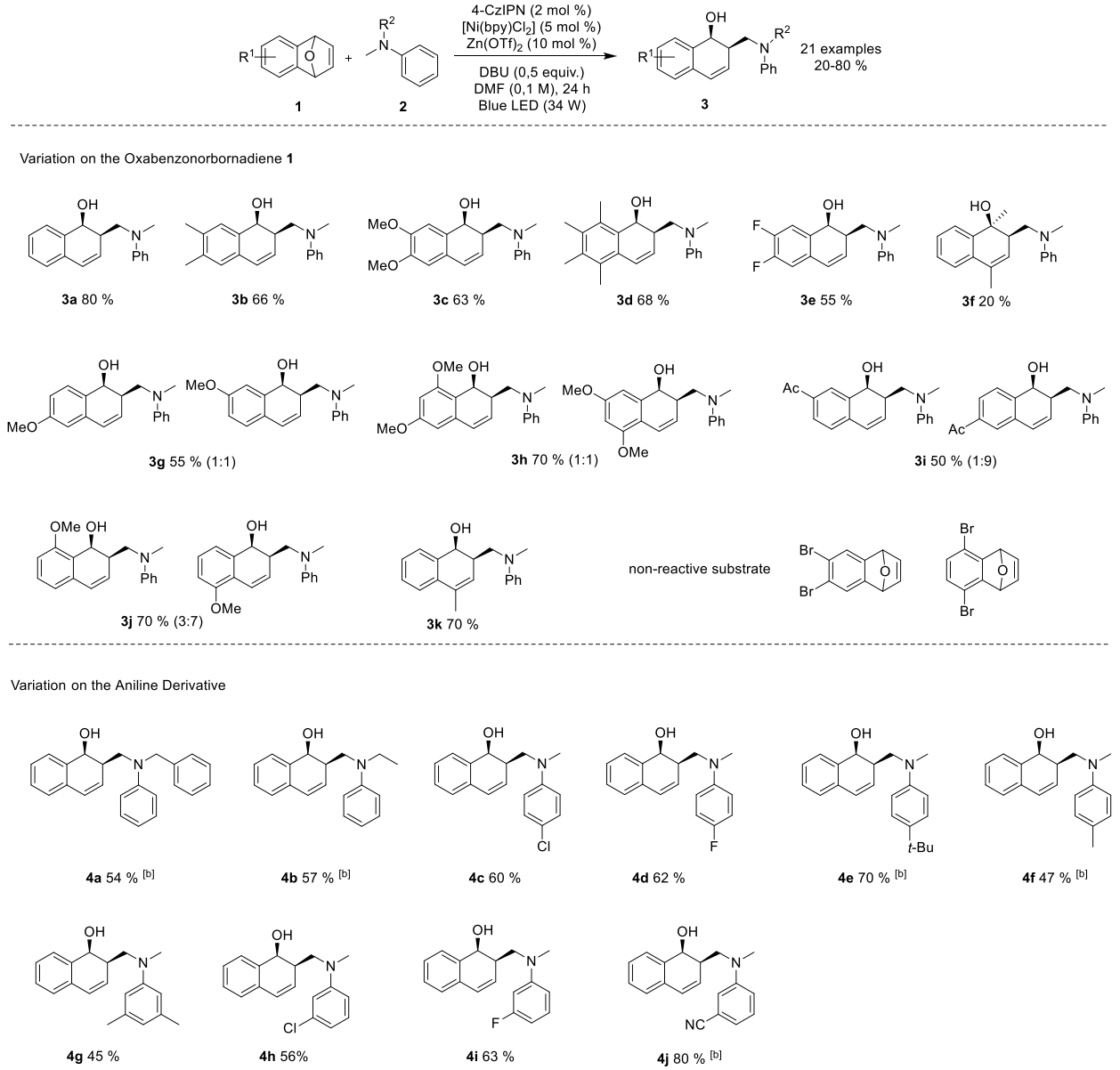
[a]General conditions: **1a** (0.2 mmol), 4-CzIPN (2 mol %), [Ni(bpy)Cl_2] (5 mol %), DBU (0.1 mmol), **2a** (0.6 mmol), DMF (4 mL, 0.1 M), 34 W Kessil blue LED lamp, rt, 24 h. [b]Conversions were determined by ^{1}H NMR analysis of the crude mixtures. [c]The yield in parentheses is based on the isolated product.

With these optimized reaction conditions in hand, we explored the scope of this unprecedented ring-opening reaction. Various substituted oxabenzonorbornadienes **1** were initially evaluated (Scheme 3).

Oxabenzonorbornadienes bearing electron-donating substituents (e.g., Me and MeO) within the aromatic fragment provided the corresponding ring-opening adducts **3b–d** in good yields (63–68%), while electron-withdrawing substituents lowered the chemical yield (**3e**) (Scheme 3). Dibromo-substituted oxabenzonorbornadienes were nonreactive under these dual catalysis conditions (Scheme 3). In all of these examples, apart from the formation of the reductive ring-opening adduct, no dehydration product was observed, and the *cis*-1,2-addition compounds were exclusively formed. The *syn*-1,2-adduct **3f** was also obtained from the disubstituted bridgehead oxabenzonorbornadiene, albeit in a modest 20% yield and 44% conversion (Scheme 3). Unsymmetrically substituted oxabenzonorbornadienes were also introduced. The ring-opening adducts **3g–j** were isolated in moderate to good yields (50–70%) but mainly as 1:1 mixtures of the two possible regioisomers, except for **3i**, for which a 9:1 ratio was observed (Scheme 3). The low control of the regioselectivity might be explained by inefficient steric interactions between the substituents and the nickel complex (see the proposed

https://dx.doi.org/10.1021/acs.orglett.0c00593
Org. Lett. XXXX, XXX, XXX–XXX

Scheme 3. Aminomethylation of Oxabenzonorbornadienes 1[a]



[a]General conditions: **1** (0.4 mmol), 4-CzIPN (2 mol %), [Ni(bpy)Cl_2] (5 mol %), DBU (0.2 mmol), **2** (1.2 mmol), DMF (4 mL, 0.1 M), 34 W Kessil blue LED lamp, rt, 24 h. [b][Ir(dF(CF_3)ppy)$_2$(bpy)]PF_6 was used as the photocatalyst (1 mol %) for 48 h.

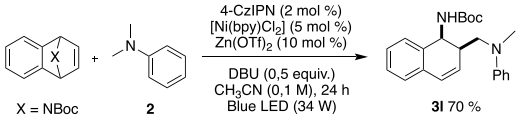
mechanism below). The *syn*-1,2-adduct **3k** was isolated from the monosubstituted bridgehead oxabenzonorbornadiene in 70% yield (Scheme 3).

Substitution on the aniline motif does not hamper the reactivity and the selectivity (Scheme 3). Not only *N*,*N*-dimethylanilines but also *N*-benzyl- and *N*-methylaniline could be used in the photoredox process, and the adducts **4a**−**j** were isolated in 47−80% yield (Scheme 3). Interestingly, the α-aminomethyl radical was selectively generated to furnish **4a** and **4b** in 54% and 57% yield, respectively, without oxidation of the benzylic position or the ethyl substituent. Electron-donating and electron-withdrawing substituents on the aromatic ring were tolerated. Compounds **4a**, **4b**, **4e**, **4f**, and **4j** were isolated when [Ir(dF(CF_3)ppy)$_2$(bpy)]PF_6 was used as the photocatalyst. No reaction was observed with 4-CzIPN. At present, no clear argument can be given to explain these results. The two photocatalysts have almost the same oxidizing potential and are able to promote the SET oxidation process.

Azabenzonorbornadienes could be also used in this tandem process under the same reaction conditions, but in acetonitrile instead of DMF. The corresponding diamino compound **3l** was isolated in 70% yield (Scheme 4).

To gain some insight into the mechanism, radical quenching reactions and spectroscopic investigations were performed. When 2 equiv of TEMPO was added to the reaction medium

Scheme 4. Aminomethylation/Ring Opening of Azabenzonorbornadienes



https://dx.doi.org/10.1021/acs.orglett.0c00593
Org. Lett. XXXX, XXX, XXX−XXX

under the optimized conditions, no desired product **3a** was detected, indicating that a radical is involved in the process. Two pathways can then be suggested to initiate the catalytic ring-opening reaction. First, the aniline might be oxidized into a radical cation; subsequent deprotonation with DBU could then generate the α-aminoalkyl radical (route (a) in Figure 1).

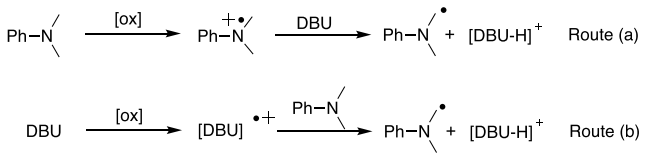


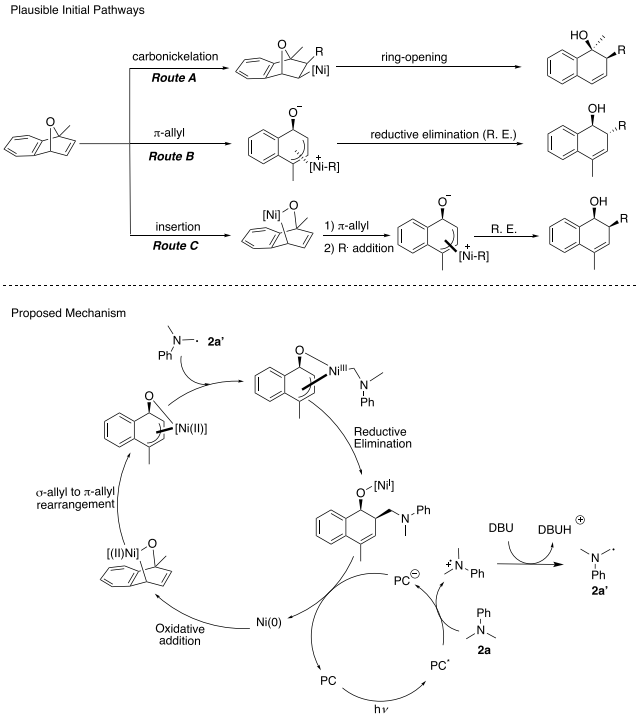
Figure 1. Proposed syntheses of α-aminoalkyl radical.

A second route might be an initial oxidation of DBU. The generated radical cation could be able to abstract hydride from the *N*-methylaniline and produce the α-aminoalkyl radical (route (b) in Figure 1). To discriminate between the two pathways, Stern–Volmer quenching experiments were carried out (Figure S2). Aniline appears to be an efficient quencher of the delayed fluorescence of 4-CzIPN, while DBU is a modest quencher. This observation indicates that the rate of the aniline oxidation by the photocatalyst is higher than that of DBU in the catalytic cycle, and consequently, the aminoalkyl radical might be formed by oxidation of the aniline followed by deprotonation by DBU (route (a) in Figure 1). A second set of Stern–Volmer experiments revealed that neither $[Ni(bpy)Cl_2]$ nor **1a** are quenchers, i.e., there is no reduction of the metal center and no formation of a radical on the oxygen-bridged compound (Figure S2).

Three main pathways can be suggested for the ring opening. The first one involves carbometalation followed by the ring opening. In this scenario, the sterically hindered organometallic species would add on the less encumbered carbon atom (route A in Scheme 5). A second possibility is a π-allyl mechanism. In this sequence, with a monosubstituted oxabicyclic derivative at the bridgehead, C–O bond breaking would occur on the more substituted carbon atom, and the metal and alcoholate would be on opposite sides (route B in Scheme 5). The final reductive elimination would deliver a 1,2-*anti* product bearing a trisubstituted alkene. The last hypothesis is based on initial insertion into the C–O bond followed by reductive elimination leading to the 1,2-*syn* product bearing a trisubstituted alkene (route C in Scheme 5).[16] As in route B, the ionization should occur on the most substituted carbon atom. Experimentally, from the monosubstituted bridgehead oxabenzonorbornadiene, **3k** was obtained regio- and stereoselectively. This result favors the third scenario (Scheme 5) and is in line with the DFT calculations reported by Molander and co-workers.[16]

On the basis of the above-mentioned results, the following mechanism could be postulated. After excitation under blue-light irradiation, the photosensitizer could oxidize aniline **2a** to give the radical cation. The latter would furnish α-aminoalkyl radical **2a′** after deprotonation by DBU (Scheme 5). The reduced PS^- could then reduce the nickel(II) complex to nickel(0), regenerating the photocatalyst and closing the first catalytic cycle ($E_{1/2}(Ni(II)/Ni(0))$ = −1.2 V vs SCE in DMF, $E_{1/2}(PS/PS^-)$ = −1.21 V vs SCE). This nickel(0) synthesis could also explain the undesired ring-opening reduction via a nickel(II)–hydride intermediate.[3a,b] Oxidative addition of the nickel(0) into the C–O bond, facilitated by $Zn(OTf)_2$,[4c] could

Scheme 5. Proposed Mechanism



provide an initial σ-allyl intermediate, and then a π-allyl intermediate (Scheme 5). **2a′** could be intercepted at this stage, leading to a nickel(III) intermediate (Scheme 5). Finally, reductive elimination followed by protonation of the alcoholate would liberate **3a** and a nickel(I) complex, which can be reduced by PS^- and reenter in the second catalytic cycle (Scheme 5).

In conclusion, we have disclosed a regio- and diastereoselective aminomethylation of oxabenzonorbornadienes by merging photoredox and nickel catalysis. Various substituents on the aniline or the oxabenzonorbornadiene are tolerated. Mechanistic studies revealed first that the α-aminomethyl radical is formed by oxidation of the amine followed by deprotonation. Second, the ring opening may evolve through insertion of a nickel(0) complex into the easily ionized C–O bond and subsequent formation of a π-allyl intermediate.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c00593.

Preparation details, optimization of conditions, Stern–Volmer quenching studies, and NMR spectra (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

Jean-Luc Renaud − *Normandie Univ., LCMT, ENSICAEN, UNICAEN, CNRS, 14000 Caen, France;* orcid.org/0000-0001-8757-9622; Email: jean-luc.renaud@ensicaen.fr

Mark Lautens − *Department of Chemistry, Davenport Chemical Laboratories, University of Toronto, Toronto, Ontario M5S 3H6, Canada;* orcid.org/0000-0002-0179-2914; Email: mark.lautens@utoronto.ca

https://dx.doi.org/10.1021/acs.orglett.0c00593
Org. Lett. XXXX, XXX, XXX−XXX

Authors

Abdoul G. Diallo − *Normandie Univ., LCMT, ENSICAEN, UNICAEN, CNRS, 14000 Caen, France*

David Roy − *Normandie Univ., LCMT, ENSICAEN, UNICAEN, CNRS, 14000 Caen, France*

Sylvain Gaillard − *Normandie Univ., LCMT, ENSICAEN, UNICAEN, CNRS, 14000 Caen, France;* orcid.org/0000-0003-3402-2518

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.0c00593

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We gratefully acknowledge financial support from the Ministère de la Recherche et des Nouvelles Technologies, Normandie Université, CNRS, Région Normandie, and the LABEX SynOrg (ANR-11-LABX-0029).

■ REFERENCES

(1) (a) Lautens, M.; Fagnou, K.; Hiebert, S. Transition Metal-Catalyzed Enantioselective Ring-Opening Reactions of Oxabicyclic Alkenes. *Acc. Chem. Res.* **2003**, *36*, 48−58. (b) Lautens, M.; Fagnou, K. Rhodium-Catalyzed Asymmetric Ring Opening Reactions of Oxabicyclic Alkenes: Catalyst and Substrate Studies Leading to a Mechanistic Working Model. *Proc. Natl. Acad. Sci. U. S. A.* **2004**, *101*, 5455−5460. (c) Rayabarapu, D. K.; Cheng, C.-H. New Catalytic Reactions of Oxa- and Azabicyclic Alkenes. *Acc. Chem. Res.* **2007**, *40*, 971−983.

(2) (a) Snyder, S. E.; Aviles-Garay, F. A.; Chakraborti, R.; Nichols, D. E.; Watts, V. J.; Mailman, R. B. Synthesis and Evaluation of 6,7-Dihydroxy-2,3,4,8,9,13b-hexahydro-1H-benzo[6,7]cyclohepta[1,2,3-ef][3]benzazepine, 6,7-Dihydroxy-1,2,3,4,8,12b-hexahydroanthr-[10,4a,4 cd]azepine, and 10-(Aminomethyl)-9,10-dihydro-1,2-dihydroxyanthracene as Conformationally Restricted Analogs of *β*-Phenyldopamine. *J. Med. Chem.* **1995**, *38*, 2395−2409. (b) Lautens, M.; Rovis, T. General Strategy toward the Tetrahydronaphthalene Skeleton. An Expedient Total Synthesis of Sertraline. *J. Org. Chem.* **1997**, *62*, 5246−5247. (c) Kamal, A.; Gayatri, N. L. *Tetrahedron Lett.* **1996**, *37*, 3359. (d) Kim, K.; Guo, Y.; Sulikowski, G. A. Synthetic Studies of the Angucycline Antibiotics. Stereocontrolled Assembly of the SF 2315B Ring System. *J. Org. Chem.* **1995**, *60*, 6866−6871. (e) Kamal, A.; Gayatri, N. L. An efficient method for 4*β*-anilino-4′-demethylepipodophyllotoxins: Synthesis of NPF and W-68. *Tetrahedron Lett.* **1996**, *37*, 3359−3362 and references therein.

(3) (a) Lautens, M.; Chiu, P.; Ma, S.; Rovis, T. Nickel-Catalyzed Hydroalumination of Oxabicyclic Alkenes. Ligand Effects on the Regio-and Enantioselectivity. *J. Am. Chem. Soc.* **1995**, *117*, 532−533. (b) Lautens, M.; Rovis, T. A New Route to the Enantioselective Synthesis of Cycloheptenols. Temperature Effects in the Asymmetric Reductive Ring Opening of [3.2.1] Oxabicycloalkenes. *J. Am. Chem. Soc.* **1997**, *119*, 11090−11091. (c) Mannathan, S.; Cheng, C.-H. Nickel-Catalyzed Regio- and Stereoselective Reductive Coupling of Oxa- and Azabicyclic Alkenes with Enones and Electron-Rich Alkynes. *Adv. Synth. Catal.* **2014**, *356*, 2239−2246. (d) Deng, Y.; Yang, W.; Yao, Y.; Yang, X.; Zuo, X.; Yang, D. Nickel-Catalyzed Syn-Stereocontrolled Ring-Opening of Oxa- and Azabicyclic Alkenes with Dialkylzinc Reagents. *Org. Biomol. Chem.* **2019**, *17*, 703−711.

(4) (a) Lautens, M.; Hiebert, S.; Renaud, J.-L. Enantioselective Ring Opening of Aza and Oxabicyclic Alkenes with Dimethylzinc. *Org. Lett.* **2000**, *2*, 1971−1973. (b) Lautens, M.; Renaud, J. L.; Hiebert, S. Palladium-Catalyzed Enantioselective Alkylative Ring Opening. *J. Am. Chem. Soc.* **2000**, *122*, 1804−1805. (c) Lautens, M.; Hiebert, S.; Renaud, J. L. Mechanistic Studies of the Palladium-Catalyzed Ring Opening of Oxabicyclic Alkenes with Dialkylzinc. *J. Am. Chem. Soc.* **2001**, *123*, 6834−6839. (d) Lautens, M.; Hiebert, S. Palladium-Catalyzed Alkylative Ring Opening. *J. Am. Chem. Soc.* **2004**, *126*, 1437−1447. (e) Li, M.; Yan, X.-X.; Hong, W.; Zhu, X.-Z.; Cao, B.-X.; Sun, J.; Hou, X.-L. Palladium-Catalyzed Enantioselective Ring Opening of Oxabicyclic Alkenes with Organozinc Halides. *Org. Lett.* **2004**, *6*, 2833−835. (f) Cabrera, S.; Arrayaś, R. G.; Alonso, I.; Carretero, J. C. Fesulphos-Palladium(II) Complexes as Well-Defined Catalysts for Enantioselective Ring Opening of Meso Heterobicyclic Alkenes with Organozinc Reagents. *J. Am. Chem. Soc.* **2005**, *127*, 17938−17947. (g) Endo, K.; Tanaka, K.; Ogawa, M.; Shibata, T. Multinuclear Pd/Zn Complex-Catalyzed Asymmetric Alkylative Ring-Opening Reaction of Oxabicyclic Alkenes. *Org. Lett.* **2011**, *13*, 868−871.

(5) For copper-catalyzed reactions featuring *anti* selectivity, see: (a) Bertozzi, F.; Pineschi, M.; Macchia, F.; Arnold, L. A.; Minnaard, A. J.; Feringa, B. L. Copper Phosphoramidite Catalyzed Enantioselective Ring-Opening of Oxabicyclic Alkenes: Remarkable Reversal of Stereocontrol. *Org. Lett.* **2002**, *4*, 2703−2705. (b) Zhang, W.; Wang, L.-X.; Shi, W.-J.; Zhou, Q.-L. Copper-Catalyzed Asymmetric Ring Opening of Oxabicyclic Alkenes with Grignard Reagents. *J. Org. Chem.* **2005**, *70*, 3734−3736. (c) Bos, P. H.; Rudolph, A.; Peŕez, M.; Fañanaś-Mastral, M.; Harutyunyan, S. R.; Feringa, B. L. Copper-Catalyzed Asymmetric Ring Opening of Oxabicyclic Alkenes with Organolithium Reagents. *Chem. Commun.* **2012**, *48*, 1748−1750.

(6) (a) Lautens, M.; Dockendorff, C.; Fagnou, K.; Malicki, A. Rhodium-Catalyzed Asymmetric Ring Opening of Oxabicyclic Alkenes with Organoboronic Acids. *Org. Lett.* **2002**, *4*, 1311−1314. (b) Lautens, M.; Dockendorff, C. Palladium(II) Catalyst Systems for the Addition of Boronic Acids to Bicyclic Alkenes: New Scope and Reactivity. *Org. Lett.* **2003**, *5*, 3695−3698. (c) Menard, F.; Lautens, M. Chemodivergence in Enantioselective Desymmetrization of Diazabicycles: Ring-Opening Versus Reductive Arylation. *Angew. Chem., Int. Ed.* **2008**, *47*, 2085−2088. (d) Zhang, T.-K.; Mo, D.-L.; Dai, L.-X.; Hou, X.-L. Asymmetric Ring-Opening Reaction of Oxabicyclic Alkenes with Aryl Boronic Acids Catalyzed by P-Containing Palladacycles. *Org. Lett.* **2008**, *10*, 3689−3692. (e) Pan, X.; Huang, G.; Long, Y.; Zuo, X.; Xu, X.; Gu, F.; Yang, D. Platinum(II)-Catalyzed Asymmetric Ring-Opening Addition of Arylboronic Acids to Oxabenzonorbornadienes. *J. Org. Chem.* **2014**, *79*, 187−196. (f) Zeng, Z.; Yang, D.; Long, Y.; Pan, X.; Huang, G.; Zuo, X.; Zhou, W. Nickel-Catalyzed Asymmetric Ring Opening of Oxabenzo- norbornadienes with Arylboronic Acids. *J. Org. Chem.* **2014**, *79*, 5249−5257. (g) Yamamoto, T.; Akai, Y.; Suginome, M. Chiral Palladacycle Catalysts Generated on a Single-Handed Helical Polymer Skeleton for Asymmetric Arylative Ring Opening of 1,4-Epoxy-1,4- Dihydronaphthalene. *Angew. Chem., Int. Ed.* **2014**, *53*, 12785−12788.

(7) For examples of rhodium-catalyzed addition of heteronucleophiles, see: (a) Lautens, M.; Fagnou, K.; Rovis, T. Nickel-Catalyzed Hydroalumination of Oxabicyclic Alkenes. Ligand Effects on the Regio-and Enantioselectivity. *J. Am. Chem. Soc.* **2000**, *122*, 5650−5651. (b) Zhu, J.; Tsui, G. C.; Lautens, M. Rhodium-Catalyzed Enantioselective Nucleophilic Fluorination: Ring Opening of Oxabicyclic Alkenes. *Angew. Chem., Int. Ed.* **2012**, *51*, 12353−12356. (c) Zhu, J.; Tsui, G. C.; Lautens, M. Rhodium(I)-Catalyzed Domino Asymmetric Ring Opening/Enantioselective Isomerization of Oxabicyclic Alkenes with Water. *Angew. Chem., Int. Ed.* **2012**, *51*, 12353−12356. (d) Lautens, M.; Fagnou, K. Effects of Halide Ligands and Protic Additives on Enantioselectivity and Reactivity in Rhodium-Catalyzed Asymmetric Ring-Opening Reactions. *J. Am. Chem. Soc.* **2001**, *123*, 7170−7171. (e)

(8) (a) Yang, J.; Sekiguchi, Y.; Yoshikai, N. Cobalt-Catalyzed Enantioselective and Chemodivergent Addition of Cyclopropanols to Oxabicycloc Alkenes. *ACS Catal.* **2019**, *9*, 5638−5644. (b) Li, Y.; Chen, J.; He, Z.; Qin, H.; Zhou, Y.; Khan, R.; Fan, B. Cobalt-Catalyzed Asymmetric Reactions of Heterobicyclic Alkenes with in situ Generated Organozinc Halides. *Org. Chem. Front.* **2018**, *5*, 1108−1112. (c) Huang, Y.; Ma, C.; Lee, Y. X.; Huang, R. Z.; Zhao, Y. Cobalt- Catalyzed Allylation of Heterobicyclic Alkenes: Ligand-

Induced Divergent Reactivities. *Angew. Chem., Int. Ed.* **2015**, *54*, 13696−13700.

(9) For a zirconium-mediated ring-opening reaction, see: Barluenga, J.; Rodríguez, F.; Álvarez-Rodrigo, L.; Zapico, J. M.; Fañanás, F. J. Zirconium-Mediated Coupling Reactions of Amines and Enol or Allyl Ethers: Synthesis of Allyl- and Homoallylamines. *Chem. - Eur. J.* **2004**, *10*, 109−116.

(10) For recent reviews, see: (a) Nakajima, K.; Miyake, Y.; Nishibayashi, Y. Synthetic Utilization of α-Aminoalkyl Radicals and Related Species in Visible Light Photoredox Catalysis. *Acc. Chem. Res.* **2016**, *49*, 1946−1956. (b) Beatty, J. W.; Stephenson, C. R. J. Amine Functionalization via Oxidative Photoredox Catalysos: Methodology Development and Complex Molecule Synthesis. *Acc. Chem. Res.* **2015**, *48*, 1474−1484. (c) Shi, L.; Xia, W. Photoredox Functionalization of C-H Bonds Adjacent to a Nitrogen Atom. *Chem. Soc. Rev.* **2012**, *41*, 7687−7697.

(11) For recent reviews, see: (a) Nicolaou, K. C. The Emergence and Evolution of Organic synthesis and why it is Important to Sustain it as an Advancing Art and Science for its own Sake. *Isr. J. Chem.* **2018**, *58*, 104−113. (b) Blakemore, D. C.; Castro, L.; Churcher, I.; Rees, D. C.; Thomas, A. W.; Wilson, D. M.; Wood, A. Organic Synthesis Provides Opportunities to Transform Drug Discovery. *Nat. Chem.* **2018**, *10*, 383−394.

(12) *Chemical Reviews* special issue "Photochemistry in Organic Synthesis": (a) Oelgemöller, M. Solar Photochemical Synthesis: From the Beginnings of Organic Photochemistry to the Solar Manufacturing of Commodity Chemicals. *Chem. Rev.* **2016**, *116*, 9664−9682. (b) Kärkäs, M. D.; Porco, J. A., Jr; Stephenson, C. R. J. Photochemical Approaches to Complex Chemotypes: Applications in Natural Product Synthesis. *Chem. Rev.* **2016**, *116*, 9683−9747. (c) Poplata, S.; Tröster, A.; Zou, Y.-Q.; Bach, T. Recent Advances in the Synthesis of Cyclobutanes by Olefin [2 + 2] Photocycloaddition Reactions. *Chem. Rev.* **2016**, *116*, 9748−9815. (d) Remy, R.; Bochet, C. G. *Chem. Rev.* **2016**, *116*, 9816. (e) Ravelli, D.; Protti, S.; Fagnoni, M. Carbon-Carbon Bond Forming Reactions, via Photogenerated Intermediates. *Chem. Rev.* **2016**, *116*, 9850−9913. (f) Ramamurthy, V.; Sivaguru, J. *Chem. Rev.* **2016**, *116*, 9914. (g) Ghogare, A. A.; Greer, A. *Chem. Rev.* **2016**, *116*, 9994. (h) Romero, N. A.; Nicewicz, D. A. Organic Photoredox Chemistry. *Chem. Rev.* **2016**, *116*, 10075−10166.

(13) (a) Kärkäs, M. D. Photochemical Generation of Nitrogen-Centered Amidyl, Hydrazonyl, and Imidyl Radicals: Methodology Developments and Catalytic Applications. *ACS Catal.* **2017**, *7*, 4999−5022. (b) Matsui, J. K.; Lang, S. B.; Heitz, D. R.; Molander, G. A. Photoredox-Mediated Routes to Radicals: The Value of Catalytic Radical Generation in Synthetic Methods Development. *ACS Catal.* **2017**, *7*, 2563−2575. (c) Shaw, M. H.; Twilton, J.; MacMillan, D. W. C. Photoredox Catalysis in Organic Chemistry. *J. Org. Chem.* **2016**, *81*, 6898−6926. (d) Huang, H.; Jia, K.; Chen, Y. Radical Decarboxylative Functionalizations Enabled by Dual Photoredox Catalysis. *ACS Catal.* **2016**, *6*, 4983−4988. (e) Hering, T.; Meyer, A. U.; König, B. Photocatalytic Anion Oxidation and Applications in Organic Synthesis. *J. Org. Chem.* **2016**, *81*, 6927−6936. (f) Teegardin, K.; Day, J. I.; Chan, J.; Weaver, J. Advances in Photocatalysis: A Microreview of Visible Light Mediated Ruthenium and Iridium Catalyzed Organic Transformations. *Org. Process Res. Dev.* **2016**, *20*, 1156−1163.

(14) *Accounts of Chemical Research* special issue "Photoredox Catalysis in Organic Chemistry": (a) Chen, J.-R.; Hu, X.-Q.; Lu, L.-Q.; Xiao, W.-J. Exploration of Visible-Light Photocatalysis in Heterocycle Synthesis and Functionalization: Reaction Design and Beyond. *Acc. Chem. Res.* **2016**, *49*, 1911−1923. (b) Goddard, J.-P.; Ollivier, C.; Fensterbank, L. Photoredox Catalysis for the Generation of Carbon Centered Radicals. *Acc. Chem. Res.* **2016**, *49*, 1924−1936. (c) Koike, T.; Akita, M. Fine Design of Photoredox Systems for Catalytic Fluoromethylation of Carbon−Carbon Multiple Bonds. *Acc. Chem. Res.* **2016**, *49*, 1937−1945. (d) Dumur, F.; Gigmes, D.; Fouassier, J.-P.; Lalevée, J. Organic Electronics: An El Dorado in the Quest of New Photocatalysts for Polymerization Reactions. *Acc. Chem. Res.* **2016**, *49*, 1980−1989. (e) Reiser, O. Shining Light on Copper: Unique Opportunities for Visible-Light-Catalyzed Atom Transfer Radical Addition Reactions and Related Processes. *Acc. Chem. Res.* **2016**, *49*, 1990−1996. (f) Margrey, K. A.; Nicewicz, D. A. A General Approach to Catalytic Alkene Anti-Markovnikov Hydrofunctionalization Reactions via Acridinium Photoredox Catalysis. *Acc. Chem. Res.* **2016**, *49*, 1997−2006. (g) Gentry, E. C.; Knowles, R. R. Synthetic Applications of Proton-Coupled Electron Transfer. *Acc. Chem. Res.* **2016**, *49*, 1546−1556. (h) Hernandez-Perez, A. C.; Collins, S. K. Heteroleptic Cu-Based Sensitizers in Photoredox Catalysis. *Acc. Chem. Res.* **2016**, *49*, 1557−1565. (i) Ghosh, I.; Marzo, L.; Das, A.; Shaikh, R.; König, B. Visible Light Mediated Photoredox Catalytic Arylation Reactions. *Acc. Chem. Res.* **2016**, *49*, 1566−1577. (j) Jamison, C. R.; Overman, L. E. Fragment Coupling with Tertiary Radicals Generated by Visible-Light Photocatalysis. *Acc. Chem. Res.* **2016**, *49*, 1578−1586. (k) Fabry, D. C.; Rueping, M. Merging Visible Light Photoredox Catalysis with Metal Catalyzed C-H Activations: On the Role of Oxygen and Superoxide Ions as Oxidants. *Acc. Chem. Res.* **2016**, *49*, 1969−1979.

(15) For recent reviews, see: (a) Skubi, K. L.; Blum, T. R.; Yoon, T. P. Dual Catalysis Strategies in Photochemical Synthesis. *Chem. Rev.* **2016**, *116*, 10035−10074. (b) Gui, Y.-Y.; Sun, L.; Lu, Z.-P.; Yu, D.-G. Photoredox Sheds New Light on Nickel Catalysis: From Carbon-Carbon to Carbon-Heteroatom Bond Formation. *Org. Chem. Front.* **2016**, *3*, 522−526. For recent publications on aminomethylation by merging of photoredox and nickel catalysis, see: (c) Rossolini, T.; Leitch, J. A.; Grainger, R.; Dixon, D. J. Photocatalytic Three-Component Umpolung Synthesis of 1,3-Diamines. *Org. Lett.* **2018**, *20*, 6794−6798. (d) Fan, L.; Jia, J.; Hou, H.; Lefebvre, Q.; Rueping, M. Decarboxylative Aminomethylation of Aryl- and Vinylsulfonates through Combined Nickel- and Photoredox-Catalyzed Cross-Coupling. *Chem. - Eur. J.* **2016**, *22*, 16437−16440.

(16) During the preparation of this letter, Molander reported the alkylation of oxa- and azabenzonorbornadienes using nickel/photoredox dual catalysis. See: Luo, Y.; Gutiérrez-Bonet, Á.; Matsui, J. K.; Rotella, M. E.; Dykstra, R.; Gutierrez, O.; Molander, G. A. Oxa- and Azabenzonorbornadienes as Electrophilic Partners under Photoredox/Nickel Dual Catalysis. *ACS Catal.* **2019**, *9*, 8835−8842.

(17) Luo, J.; Zhang, J. Donor-Acceptor Fluorophores for Visible-Light-Promoted Organic Synthesis: Photoredox/Ni Dual Catalytic $C(sp_3)$-$C(sp_2)$ Cross- Coupling. *ACS Catal.* **2016**, *6*, 873−877.

(18) Thullen, S. M.; Rovis, T. A Mild Hydroaminoalkylation of Conjugated Dienes Using a Unified Cobalt and Photoredox Catalytic System. *J. Am. Chem. Soc.* **2017**, *139*, 15504−15508.

https://dx.doi.org/10.1021/acs.orglett.0c00593
Org. Lett. XXXX, XXX, XXX−XXX