Preparation of new bicyclo[2.1.1]hexane compact modules: an opening towards to novel sp^3-rich chemical space

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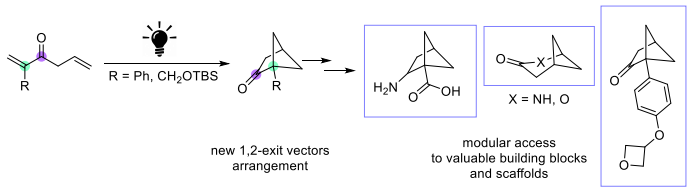
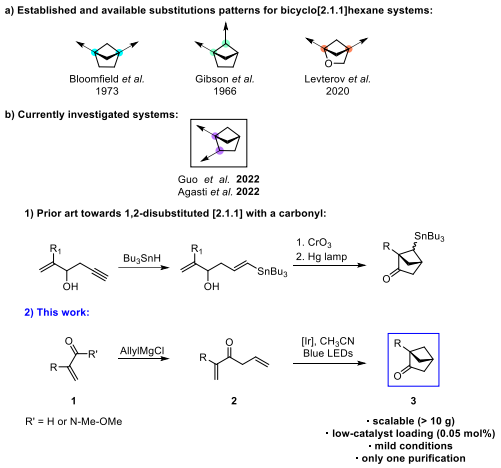
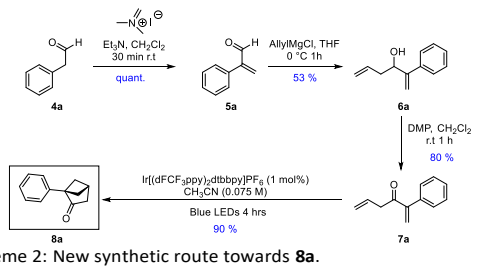


ABSTRACT: Among the valuable saturated bicyclic structures incorporated in newly developed bio-active compounds, bicyclo[2.1.1]hexanes are playing an increasingly important role, while being still underexplored from a synthetic accessibility point of view. Here, we disclose an efficient and modular approach toward new 1,2-disubstituted bicyclo[2.1.1]hexane modules. Our strategy is based on the use of photochemistry to access new building blocks via [2+2] cycloaddition. The system can readily be derivatized with numerous transformations, opening the gate to sp^3-rich new chemical space.



Scheme 1: a) Established [2.1.1] scaffolds broadly applied. b) New atom-arrangement being investigated. b.1) Prior art towards 1,2-disubstituted bicyclo[2.1.1]hexane systems bearing a ketone. b.2) New efficient and mild route proposed towards these systems.

In the quest of further improving the physicochemical properties of lead compounds, medicinal chemists tend to favor sp^3-rich and strained bicyclic scaffolds as bio-isosteres.[1, 2] Their intrinsic properties are playing a fundamental role in modulating and sometimes improving solubility, activity, and conformational restriction of candidates,[3] while offering new vectors's angles opportunities. The bicyclo[1.1.1]pentane motif remains to date the most renowned example of bicycles used. Following the breakthrough establishing its biological value as a para-substituted phenyl isostere in 2012,[4] extensive research has been performed to expand the toolbox of available bicyclic structures. Recently, bicyclo[2.1.1]hexane systems have been the highlight of numerous works.[5-7] These focused on new synthetic routes, implementation of new methodologies, and new exit vectorization. However, access to a diverse range of exit vectors is still limited and additional works is required to fully exploit the rich chemical space surrounding the [2.1.1] platform. For this reason, we were interested in exploring new atom and exit-vectors arrangements for [2.1.1] scaffolds. Hence, we focused on the synthesis of 1,2-disubstituted bicyclo[2.1.1]hexanes (such as **3**) as depicted in Scheme 1b. Only limited prior methods allowed the synthesis of such [2.1.1] via a crossed [2+2]-cycloaddition of 1,5-diene using a mercury lamp (Scheme 1a).[8] Unfortunately, the use of such a lamp is technically challenging (special equipment and glassware needed) and the reaction, therefore, is difficult to scale up. Additionally, the use of toxic stannane reagents is rendering the process even less amenable to large-scale synthesis. Thus, we propose a novel robust, scalable (> 10 g), and mild synthetic route toward systems such as **3**. (Scheme 2).



Scheme 2: New synthetic route towards **8a**.

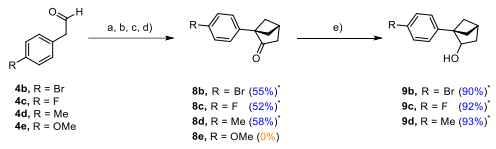
Our efforts started with commercially available phenylacetaldehyde **4a**, which was quantitatively

methylenated using a reported procedure[9] with Eschenmoser's salt to access aldehyde **5a**. The latter was treated with allyl magnesium chloride to yield alcohol **6a**, which was further oxidized using Dess-Martin Periodinane (DMP) to generate diene **7a** in a gratifying yield (80 %). Interestingly, only DMP oxidation gave satisfactory results for this transformation, other methods such as MnO_2, Swern, or PCC led either to degradation or slow conversion towards the desired product.

Table 1: Optimization of conditions to access **8a** from diene **7a**.

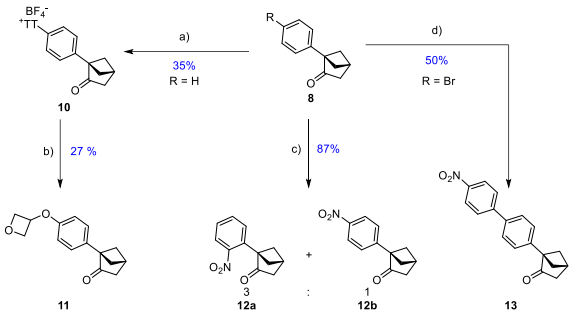
Entry	Solvent	Catalyst loading (mol %)	Yield (%)*
1[a]	CH_2Cl_2	2	55
2[b]	CH_3CN	2	90
3[c]	CH_3CN	0.75	87
4[c]	CH_3CN	0.5	83
5[c]	CH_3CN	0	0

Inspired by the Iridium catalyzed [2+2] cycloaddition designed by Kwon *et al.*, [10] giving access to bridged benzobicycloheptanone from benzylic dienones, we tested similar conditions for our cycloaddition with dienone **7a**. Gratifyingly, the use of $(Ir[dF(CF_3)ppy]_2(dtbpy))PF_6$ (2 mol %) in dichloromethane enabled the isolation of bicyclic scaffold **8a** (Table 1, entry 1) in a 55 % yield. Switching the solvent to acetonitrile further improved the yield to 90 % (Table 1, entry 2). We then looked at decreasing the catalyst loading, to allow for a more cost-efficient synthesis on large-scale. Lesser loading (Table 1, entries 3 & 4) had a modest influence on the isolated yield of **8a**, with for instance an 83 % yield for a loading of 0.5 mol %. As a control experiment, the cycloaddition was attempted without our Iridium photocatalyst and as expected, no reaction occurred (Table 1, entry 5).



Scheme 3: Evaluation of the scope of the phenylacetaldehydes **4b-e** using the designed route and reduction to the corresponding alcohols. Yields refer to isolated products after column chromatography. a) Eschenmoser's salt, Et_3N, CH_2Cl_2. b) AllylMgCl, THF. c) DMP, CH_2Cl_2. d) $Ir[dF(CF_3)ppy]_2(dtbpy))PF_6$ (2 mol %), CH_3CN (0.075 M), Blue LEDs. e) $NaBH_4$, MeOH.

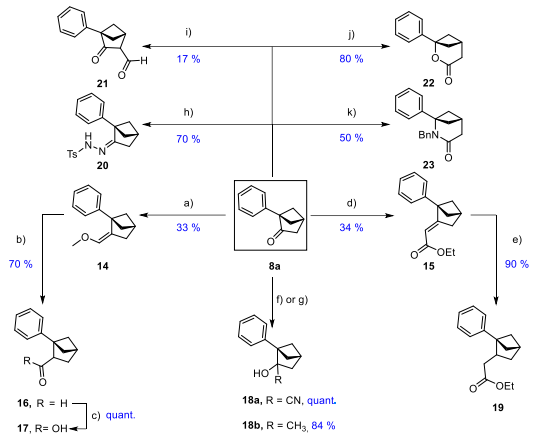
Having optimal conditions in hand, the reaction sequence was efficiently upscaled, yielding 4.50 g of [2.1.1] **8a** starting from 10 g of phenylacetaldehyde **4a**, giving a global yield of 40 % with only one purification by chromatography. These results are proving the scalability and robustness of our sequence. The scope of phenylacetaldehydes was evaluated (Scheme 3). Substrates **4b-e** were submitted to the reaction sequence and the ones bearing Bromine, Fluorine, and Methyl performed well towards analogs **8b-d** without any noticeable issues. Despite our efforts, 4-methoxyphenylacetaldehyde **4e** did not undergo the first methylenation, probably owing to the electron-donating character of this substituent. Ketones **8b-d** were then reduced to their corresponding secondary alcohols **9a-c** in excellent yields (> 90 %) (Scheme 3). Despite the successful completion of the synthetic route with various groups decorating the aromatic moiety from the start, diversity remained dependent on the availability of starting phenylacetaldehydes, multi-steps preparation of intermediates and electronic nature of substituents. To circumvent this problem, we opted for a "late-stage functionalization" (LSF) approach (Scheme 4).



Scheme 4: Aromatic ring functionalization of **8** derivatives. a) Thianthrene-Oxide, TFAA, $HBF_4.Et_2O$, CH_3CN, r.t, R = H. b) Oxetan-3-ol, CuTC, Na_2CO_3, $[Ir[dF(CF_3)ppy]_2(dtbpy)PF_6]$, Blue LEDs, CH_3CN, r.t. c) H_2SO_4, HNO_3, Ac_2O, AcOH, 0 °C, R = H. d) 4-NO_2-Ph-$B(OH)_2$, $Pd(PPh_3)_4$, Cs_2CO_3, Dioxane : H_2O, R = Br.

Firstly, using the "thianthrenation" approach designed by the Ritter group,[11] we were able to target the para-position of the system (**10**). This position was further functionalized with an oxetane-3-ol,[12] allowing the isolation of phenol ether **11,** which demonstrates the mildness of this approach. Alternatively, nitration of the phenyl offered a 3:1 mixture favoring, surprisingly, the ortho-substituted moiety **12a**. Lastly, a Suzuki cross-coupling was tolerated and afforded **13** starting from **8a.**

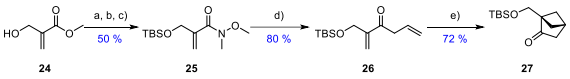
Subsequently, we explored various strategies to exploit the carbonyl motif of our [2.1.1] skeleton as a useful point of divergence (Scheme 5). Wittig and HWE-type reactions yielded **14** and **15**, respectively. Unsaturated **15** was further hydrogenated (Pd/C , 1 bar of H_2) to obtain acetate **19** while **14** was treated in acidic conditions to give the homologated aldehyde **16**. The latter was quantitatively converted to carboxylic acid **17** using Pinnick's conditions, offering a handle for diversification (amide, ester, decarboxylative couplings, …). Nucleophiles such as TMS-CN or MeMgBr could react on the carbonyl and form compounds **18a-b** (in two steps for **18a:** TMSCN addition and cleavage of the TMS group formed)**.** Bicyclo[2.1.1]hexane **8a** could serve as a platform for ring-expanded compounds **22** and **23**. The lactone **22**



Scheme 5: Ketone derivatization of **8a**. All yields refer to isolated products after column chromatography. a) $MeOCH_2P(Ph_3)Cl$, KOtBu, THF. b) 2M HCl, THF. c) $NaClO_2$, Na_2HPO_4, H_2O_2,CH_3CN:H_2O. d) $(OEt)_2P(O)CO_2Et$, NaH, THF. e) H_2, Pd/C, MeOH, r.t o/n. f) TMSCN, ZnI_2, CH_2Cl_2 then HCl (2M). g) MeMgBr, THF. h) Tosyl-NH_2NH_2, MeOH, 60 °C. i) *N*-cyclohexyl-propyl, n-BuLi, Ethyl formate, THF. j) mCPBA, CH_2Cl_2, 45 °C. k) Bn-N_3, $TiCl_4$, CH_2Cl_2.

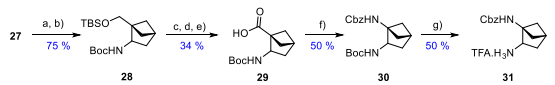
was effectively formed via Baeyer-Villiger rearrangement with mCPBA in refluxed methylene chloride while the lactam counterpart **23** was obtained via a Schmidt reaction using Benzyl azide under the conditions developed by Aubé *et al*.[13] It is of importance to note that the regio-isomers shown in Scheme 5 were the only one formed during these ring-expansion reactions.

Interestingly, any attempt to form the [3.1.1] lactam product **23** via Beckmann rearrangement (following oxime-formation) only afforded decomposition or recovery of the starting material. Additionally, owing to the high degree of conformational restriction and high steric energy (44.8 kcal.mol^{-1}), the carbonyl group of **8a** seemed less prone to undergo all the "classical" reactions inherent to carbonyl reactivity. This is especially true regarding enolate chemistry, which lead to unfruitful results at almost every attempt despite testing a various array of reactions, aiming to functionalize position 3 of the system. To reinforce this statement, after the successful formation of hydrazone **20** (Scheme 5), a Shapiro reaction was attempted (with MeI as electrophilic partner) but did not provide the *endo* C-C double bond, as could have been expected.[14] Likewise, simple enol-reactivity with initial base treatment such as LDA and trapping of the supposedly formed enolate with various electrophiles such as MeI or TMS-Cl only led to the recovery of starting material. This non-enol reactivity was already highlighted in the works of Ho *et al.*[15] Indeed, they demonstrated that the only base/electrophiles combination that effectively afforded an enolate product was *N*-propyl-cyclohexylamine/ethyl formate to afford the α-formyl-ketone. This combination was attempted on our system and yielded the desired formylated product **21**, albeit in a modest yield of 17 %. Further studies are currently ongoing in order to improve this poor enol-reactivity-. Following an extensive diversification study on both the aromatic and center cores of our newly developed system **8**, we were intrigued by the synthetic availability and feasibility of an all-aliphatic scaffold with rightly placed exit vectors. This would enable the fabrication of sp^3-rich building blocks valuable for drug discovery. A new synthetic route had to be developed with an aliphatic group replacing the phenyl rings (Scheme 6).



Scheme 6: New synthetic route with only aliphatic groups. a) $LiOH.H_2O$, MeOH: THF. Water. b) TBS-Cl, imidazole, CH_2Cl_2. c) HN(OMe)Me.HCl, EDC, DIPEA, CH_2Cl_2. d) AllylMgCl, THF. e) ITX (10 mol %), CH_3CN, 385 nm LEDs, o/n. ITX = 2-isopropyl thioxanthone.

By employing a similar route as the one used in Scheme 2, the goal was to evaluate the influence of the loss of the aromatic counterpart on the radical formation events, energy transfer from the photocatalyst and therefore the cycloaddition reaction. Hydroxy-methyl-acrylate **24** was chosen as the starting material of choice (availability and acrylate reactivity). Compound **24** was thus saponified, TBS-protected, followed by Weinreb-amide formation to access **25**. It was then submitted to Allyl Grignard addition to form precursor **26** in 80 % yield. Using the same conditions used previously (Schemes 2 and 3), the cycloaddition towards **27** would not reach completion, despite elongated stirring time and higher catalyst loadings. At this point, it appeared clear to us that the loss of the aromatic ring in the system affected the triplet excited state energy (E_T) of diene **26** and was therefore higher than its aromatic counterpart **7**. This change would therefore prevent a proper energy transfer from the Iridium catalyst (E_T=260 kJ.mol^{-1}) under blue LEDs irradiation. Thus, a new photosensitizer with higher triplet excited state energy had to be selected. Following the review written by the Glorius group about energy transfer and triplet energy,[16] it appeared that the Thioxanthones family of photo-sensitizers could contain suitable candidates. Indeed, considering their higher triplet excited state energy compared to the Iridium catalyst previously used, they could prove to be a better choice.



Scheme 7: New-building blocks elaboration starting from **27.** a) $HONH_2.HCl$, NaOAc, MeOH, 60 °C. b) $NiCl_2.(H_2O)_6$, Boc_2O, $NaBH_4$, MeOH.c) TBAF, THF, 0 °C to r.t. d) DMP, CH_2Cl_2. e) $NaClO_2$, Na_2HPO_4, H_2O_2, CH_3CN : Water (1 : 1) f) BnOH, DPPA, Et_3N, Toluene, reflux o/n. g) TFA, CH_2Cl_2.

Because of its high energy (E_T=270 kJ.mol^{-1}),[17] 2-isopropyl thioxanthone (ITX) was picked for our cycloaddition towards **27.** The reaction of **26** with ITX in acetonitrile at 385 nm LEDs (black light) in a Quartz

tube afforded the desired cyclized product **27** in a very rewarding 72 % yield.

With a useful procedure in hand, we then focused on the diversification that this new substitution pattern offers (Scheme 7). Starting from **27**, the corresponding oxime was quantitatively formed using hydroxylamine and sodium acetate. Then, reduction of this oxime using Nickel (II) and sodium borohydride in the presence of Boc anhydride afforded the Boc-protected amine **28** in position 2 of the system. The silyl-protected alcohol was effectively transformed into the very interesting non-natural amino-acid **29**. A Curtius rearrangement yielded the orthogonally bis-protected-diamine building block **30**. The latter was further mono-deprotected, giving **31** as a TFA salt. These transformations highlight the versatility and modularity that this scaffold offers to construct valuable sp^3-rich building blocks to be incorporated into drug-like compounds.

Conclusions

To conclude, we propose an efficient, scalable, and mild approach toward valuable and innovative bicyclo[2.1.1]hexane systems. The diversifications realized built a platform to efficiently introduce this scaffold into more complex structures. Ongoing studies of the dihedral angles of the 1-2-substituents via X-ray analysis are underway to compare the bridged scaffold to other unsaturated cyclic linkers found in active compounds (such as 1,2-*trans*-cyclopentane).[18]

Conflicts of interest

LH, CS and TF declare a conflict of interest as they are employees and CEO of SpiroChem AG, a Swiss fine chemicals company commercializing the the compounds described in this work.

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