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

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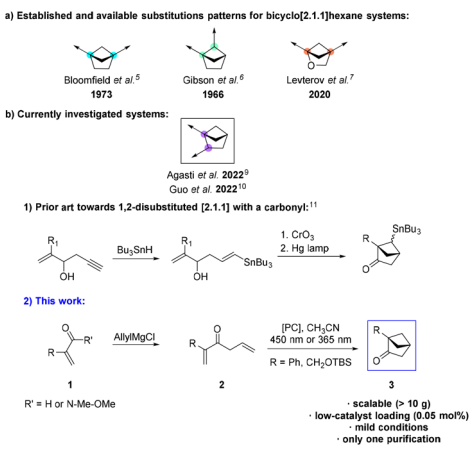
**Among the valuable saturated bicyclic structures incorporated in newly developed bio-active compounds, bicyclo[2.1.1]hexanes are playing an increasingly important role, while being still underexplored from a synthetic accessibility point of view. Here, we disclose an efficient and modular approach 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.**

In the quest to further improve the physicochemical properties of lead compounds, medicinal chemists tend to prefer sp$^3$-rich and strained bicyclic scaffolds as bio-isosteres.[1,2] Their intrinsic properties play a fundamental role in modulating and sometimes improving the solubility, activity, and conformational restriction of candidates,[3] while offering new vector's angle opportunities. The bicyclo[1.1.1]pentane motif remains to date the most renowned example of bicycles used. Following the breakthrough in 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. Bicyclo[2.1.1]hexane systems have been the highlight of numerous works.[5–10] These works 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 work 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-vector 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.2. Only limited prior methods allowed the synthesis of such [2.1.1] hexanes by a crossed [2 + 2]-cycloaddition of 1,5-dienes using a mercury lamp (Scheme 1b.1).[11] 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 making the process even less amenable for large-scale synthesis. Thus, we propose a novel, robust, scalable (>10 g), and mild synthetic route toward systems such as **3** (Scheme 2).

Our efforts started with commercially available phenylacetaldehyde **4a**, which was quantitatively methylenated using a reported procedure[12] 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, and other methods such as




**Scheme 1** a) Established [2.1.1] scaffolds which are 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.

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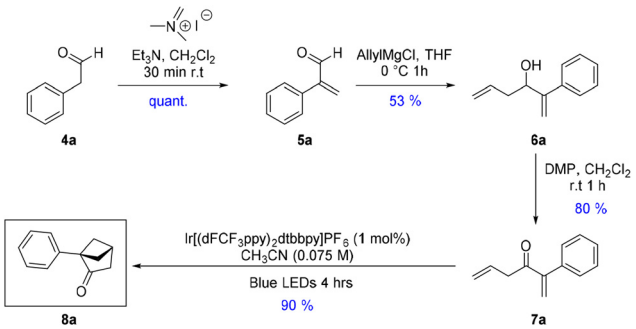



**Scheme 2** Synthetic route towards **8a**.

$MnO_2$, Swern, or PCC led either to degradation or slow conversion towards the desired product.

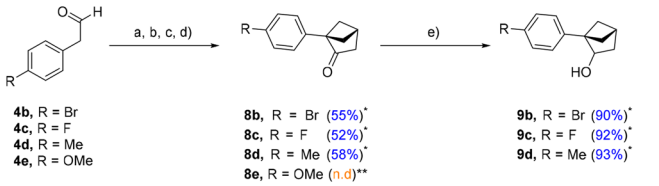
Inspired by the iridium catalyzed [2 + 2] cycloaddition designed by Kwon *et al.*,[13] giving access to bridged benzobicycloheptanone from benzylic dienones, we tested similar conditions for our cycloaddition with dienone **7a**. Gratifyingly, the use of (Ir[dF($CF_3$)ppy]$_2$(dtbpy))$PF_6$ (2 mol%) in dichloromethane under blue LED irradiation at 450 nm enabled the isolation of bicyclic scaffold **8a** (Table 1, entry 1) in 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. A smaller 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 iridium photocatalyst and as expected no reaction occurred (Table 1, entry 5).

With the optimal conditions in hand, the reaction sequence was efficiently scaled up, 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 subjected to the reaction sequence and the ones bearing bromine, fluorine, and methyl performed well towards analogs **8b–d** without any noticeable issues. Ketones **8b–d** were then reduced to their corresponding secondary alcohols **9b–d** in excellent yields (>90%) (Scheme 3). Unfortunately, 4-methoxyphenylacetaldehyde **4e** underwent

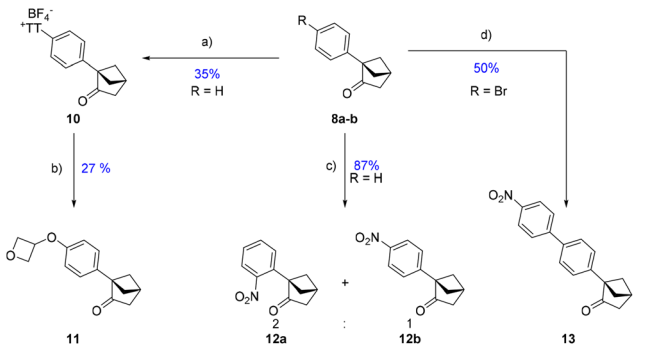
**Table 1** Optimization of conditions to access **8a** from diene **7a** under blue LED irradiation (450 nm)

| Entry | Solvent | Catalyst loading (mol%) | Yield[d] (%) |
|---|---|---|---|
| 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 |

[a] 0.17 mmol scale. [b] 28.6 mmol scale. [c] 2.0 mmol scale. [d] Yields were measured after isolation of product 8 by flash column chromatography.




**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. ** Due to a low yielding first step, the synthesis was not taken further.

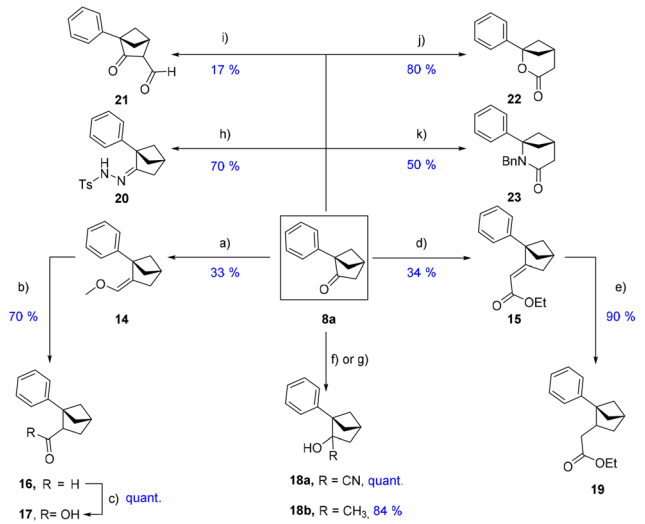



**Scheme 4** Aromatic ring functionalization of **8** derivatives. (a) Thianthrene oxide, TFAA, $HBF_4{\cdot}Et_2O$, $CH_3CN$, r.t., R = H. (b) Oxetan-3-ol, CuTC, $Na_2CO_3$, [Ir[dF($CF_3$)ppy]$_2$(dtbpy)$PF_6$], blue LED, $CH_3CN$, r.t. (c) $H_2SO_4$, $HNO_3$, $Ac_2O$, AcOH, 0 °C, R = H. (d) 4-$NO_2$-Ph-B(OH)$_2$,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

the first methylenation and subsequent Grignard addition but provided a very low yield. Indeed, the methylenation of **4e** (step a) did not reach completion, and the obtained substrate rapidly decomposed (dimerization), as highlighted in the works (described in the ESI) of Davies *et al.*[14] This result guided us towards a "late-stage functionalization" approach (Scheme 4) in order to circumvent the problems inherent to available phenylacetaldehydes, multi-step preparation of intermediates and the electronic nature of substituents (Scheme 4).

Firstly, using the "thianthrenation" approach designed by Ritter's group,[15] we were able to target the *para*-position of the system (**10**). This position was further functionalized with an oxetan-3-ol,[16] allowing the isolation of phenol ether **11**, which demonstrates the mildness of this approach. Alternatively, nitration of the phenyl afforded a 2 : 1 mixture favoring, surprisingly, the *ortho*-substituted moiety **12a**. Lastly, a Suzuki cross-coupling was tolerated and afforded **13** starting from **8b**.

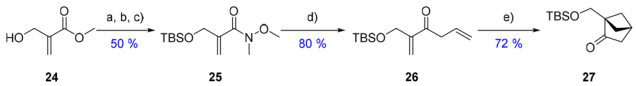
Subsequently, we explored various strategies to exploit the carbonyl motif of our [2.1.1] skeleton **8a** as a useful point of divergence (Scheme 5). The Wittig and Horner–Wadsworth–Emmons-type reactions yielded **14** and **15**, respectively. Unsaturated **15** was further hydrogenated (Pd/C, 1 bar of $H_2$) to obtain acetate **19**, while **14** was treated under acidic conditions




**Scheme 5** Ketone derivatization of **8a**. All yields refer to isolated products after column chromatography. (a) $MeOCH_2P(Ph_3)Cl$, KO*t*Bu, THF. (b) 2 M 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 (2 M). (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-$N_3$, $TiCl_4$, $CH_2Cl_2$.

to give the homologated aldehyde **16.** The latter was quantitatively converted to carboxylic acid **17** using Pinnick's conditions, offering a handle for diversification (amides, esters, decarboxylative couplings, *etc.*). Nucleophiles such as TMS-CN or MeMgBr could react with 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** was effectively formed by the 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.*[17] It is of importance to note that the regioisomers shown in Scheme 5 were the only ones formed during these ring-expansion reactions.

Interestingly, any attempt to form the [3.1.1] lactam product **23** by the Beckmann rearrangement (following oxime formation) only resulted in the 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 ketone group of **8a** seemed less prone to undergo all the "classical" reactions inherent to carbonyl reactivity. This is especially true regarding enolate chemistry, which led to unfruitful results at almost every attempt despite testing a wide 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 the electrophilic partner) but did not provide the *endo* C–C double bond, as could have been expected.[18] Likewise, simple enol-reactivity with initial treatment using a base such as LDA and trapping of the supposedly




**Scheme 6** New synthetic route with only aliphatic groups. (a) $LiOH{\cdot}H_2O$, MeOH : THF, water. (b) TBS-Cl, imidazole, $CH_2Cl_2$. (c) HN(OMe)Me·HCl, EDC, DIPEA, $CH_2Cl_2$. (d) Allyl MgCl, THF. (e) ITX (10 mol%), $CH_3CN$, 365 nm LEDs, o/n. ITX = 2-isopropyl thioxanthone.

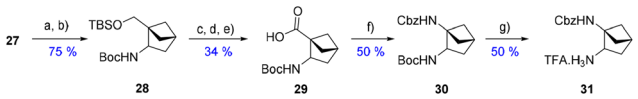
formed enolate with various electrophiles such as MeI or TMS-Cl only led to the recovery of the starting material. This non-enol reactivity was already highlighted in the works of Ho *et al.*[19] Indeed, they demonstrated that the only base/electrophile combination that effectively afforded an enolate product was *N*-propyl-cyclohexylamine/ethyl formate which afforded the α-formyl-ketone. This combination was attempted in our system which 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 **8a**, we were intrigued by the synthetic availability and feasibility of an all-aliphatic scaffold with rightly placed exit vectors. This would enable the construction 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).

By employing a similar route to the one used in Scheme 2, the goal was to evaluate the influence of the absence of the aromatic counterpart on the radical formation events, energy transfer from the photocatalyst and therefore the cycloaddition reaction. Hydroxymethylacrylate **24** was chosen as the starting material (availability and acrylate reactivity). Compound **24** was thus saponified and TBS-protected, followed by Weinreb-amide formation to access **25.** It was then subjected 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 the extended 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 it was therefore higher than its aromatic counterpart **7a**. This change would therefore prevent a proper energy transfer from the iridium catalyst ($E_T$ = 260 kJ $mol^{-1}$) under blue LED 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,[20] it seemed that the thioxanthone family of photo-sensitizers could provide suitable candidates.

Due to its high energy ($E_T$ = 270 kJ $mol^{-1}$),[21] 2-isopropyl thioxanthone (ITX) was picked for our cycloaddition towards **27**. The reaction of **26** with ITX in acetonitrile under 365 nm LED (black light) irradiation 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




**Scheme 7** New-building blocks elaboration starting from **27**. (a) $HONH_2{\cdot}HCl$, NaOAc, MeOH, 60 °C. (b) $NiCl_2{\cdot}(H_2O)_6$, $Boc_2O$, $NaBH_4$, 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, $CH_2Cl_2$.

quantitatively formed using hydroxylamine and sodium acetate. Then, the reduction of this oxime using nickel(II) and sodium borohydride in the presence of Boc anhydride afforded the Boc-protected amine **28** at 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 1,2-substituents by X-ray analysis are underway to compare the bridged scaffold with other unsaturated cyclic linkers found in active compounds (such as 1,2-*trans*-cyclopentane).[22]

## Conflicts of interest

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

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