Cubane Cross-Coupling and Cubane-Porphyrin Arrays

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Dedicated to Prof. Dr. Dr. h.c. Henning Hopf

Abstract: *The (im)possible Cube – Herein an improved methodology for aryl-cubane cross-coupling is reported. The peculiarities of the cubane core and its behavior during cross-coupling conditions are analyzed, while the versatility of this adapted Baran cross-coupling methodology is demonstrated by the synthesis of various aryl-cubane systems, among them coupling products of cubanes and porphyrins. Furthermore arm extension of alkynyl-cubanes via Sonogashira reactions is demonstrated, showcasing the first proof of the stability of the cubane core in the presence of palladium-catalysts.*

Even 50 years after its first synthesis by Eaton *et al.* in 1964, the chemistry of cubane still presents a synthetic challenge and is underdeveloped, especially in terms of modern cross-coupling methodologies.^[1] Most of the derivatizations arise from various conventional functional group interconversions of the dimethylcubane-1,4-dicarboxylate. Current state of the art is almost solely the use of “classical” carbonyl chemistry,^[2] thus limiting the scope of potential cubane compounds and therefore access to advanced cubane systems. Just recently cubanes began to draw attention again due to their biological properties and their use as a benzene bioisostere.^[3] Our interest in cubane arose from two different origins. Firstly, we recognized the lack of useful reactions to install aryl groups directly onto the cubane core. Secondly, we were interested in utilizing cubanes as a rigid linker unit for applications in materials chemistry. However to achieve this, the right tools had to be developed, tools outside the “carbonyl-world”. Screening the literature revealed only four different approaches, each one with their own significant drawbacks (Scheme 1).

The first example of cubane-aryl systems was mentioned by Moriarty *et al.* in 1989 describing the radical functionalization of cubane carboxylic acid in the presence of $\text{Pb}(\text{OAc})_4$ and benzene.^[4] Even though the yield is high, this method is only suitable for a limited number of aryl groups and suffers from poor regioselectivity. Eaton's group utilized the highly reactive cubane-1,4-diyl diradical for phenylation, in order to prepare cubane rods in “living polymerization”-like fashion.^[5] Here the major disadvantage is the missing functional group tolerance due to harsh conditions. Recently, the Baran group has shown the versatility of their newly developed redox-active ester concept, proving the robustness of their method by preparing mono- and diarylated cubanes shortly after.^[6] Thus far, this

approach represents the benchmark in terms of flexibility, but again only results in low yields, even for simple aryl substrates.

Scheme 1. State-of-the-art of cubane-aryl coupling.

Our own initial approach for applying palladium catalyzed cross-coupling chemistry on cubanes, failed, unfortunately, owing to the instability of the cubane core in presence of palladium.^[7,8] With this knowledge we turned our attention to a single electron transfer mechanism (SET), circumventing the requirement of the oxidative addition of the transition metal to the cubane core. Even though the first approach via an iron-catalyzed Kumada coupling proved unsuccessful,^[9] we were inspired by the versatility of redox-active esters for decarboxylative cubane-aryl cross-coupling (Baran/Weix coupling).^[10] The reported yield of 25 % for the iron-catalyzed coupling^[6] raised our curiosity to identify the key obstacles for the cubane-aryl coupling. A closer look revealed five major contributing factors i) solvent, ii) temperature, iii) concentration, iv) Ni-source, and v) ligand (Scheme 2).

After thorough investigation of the Baran cross-coupling methodology, the influence of the ligand was identified as the key parameter.^[11] Ligand design is a powerful tool to modulate the reactivity of transition metal catalysts and to control the reaction pathway. Ligand redox effects play an important role during the catalytic cycle.^[12] Within the tested library of bipyridines, bisphosphines and tridentate ligands, the very electron-deficient 4,4'-functionalized bipyridines outperformed

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other ligand systems; especially the bisphosphine and rigid phenanthroline ligands. According to our findings the ideal ligand possesses some flexibility along the biaryl axis, has no substituent in the α -position to the nitrogen and carries electron withdrawing substituents in the 4,4'-positions. We hypothesize the influence of the electron-poor 4,4'-position to affect the rate determining step of the catalytic cycle, namely the reductive elimination of the cubane and aryl residue from the nickel center. Bulky ligands (dtbbpy, **L1**) and electron withdrawing substituents (**L2**) favor the reductive elimination due to strain release and electronic stabilization.^[13] This assumption is in accordance with previous findings of cubane's reactivity: i) the cubyl radical is rather stable^[14] and is captured in the presence of Michael acceptors or radical scavengers (e.g., TEMPO);^[15] ii) the reductive elimination proceeds faster for hydrides and the according hydride-coupling product can be obtained in excellent yield.^[16,17]

Scheme 2. Contributing factors influencing cubane cross-couplings.

Realizing the impediments and to test our hypothesis we investigated the scope of our new catalyst/ligand systems (Scheme 3). The coupling of very electron-rich aryl moieties proceeded in good yields of over 50 % (**2d**, **2f**, **2i**). Likewise, unfunctionalized aryl groups could be coupled smoothly (**2a**, **2b**, **2c**). One remaining problem is the coupling of electronic deficient aryl substrates. A weak electron withdrawing substituent in the *p*-position is tolerated, but only with a significant decrease in yield (**2j**, 18 %).

In case of very electron-poor aryl groups and heteroaromatic systems, an electron-rich ligand (**L1**) proved to be beneficial in order to overcome decomposition before the coupling (**2m**, **2n**, **2o**). Generally, the yield is lower for these important classes of compounds, but we were pleased to observe the first directly linked cubane-porphyrin system (**2m**, **2n**, **2o**), a system which has not been reported before.^[18] The preparation of a suitable porphyrin-zinc species was achieved by adapting the iodine-metal exchange developed by the Osuka group.^[19,20]

Notable is the smooth coupling of useful compound **2f**, which can be subject of further functionalization and was used for the preparation of cubane-linked porphyrin-system **10a** (*vide infra*).

In addition, the procedure could be used to prepare difunctionalized aryl-cubane **2h** from **2a** using a sequence of deprotection of the methyl ester, activation of the carboxylic acid, and Ni-catalyzed coupling. A major limitation right now is to overcome the sterical hindrance of ortho-substituents (entry **2e**, 25 %) and to extend the scope for further heteroaromatic coupling partners. With the direct-coupled cubane-aryl systems

in hand we decided to go back to our initial approach of palladium-catalyzed cross-coupling chemistry with cubanes.^[8]

Scheme 3. Nickel-catalyzed cross-coupling and substrate scope.

Since the direct approach proved to be unfruitful, we decided to apply an arm extension of the cubane core with alkynyl-groups, hoping that the palladium/copper-alkynyl-cubane intermediate is more stable than the directly attached counterparts. To our delight the initial reaction showed clean conversion of the cubane alkynyl **3** to the substituted product (Table 1).^[21]

Table 1. Substrate scope for palladium-catalyzed Sonogashira coupling of alkynyl cubane **3**.

Entry	X	R ¹	R ²	R ³	Product	Yield [%]
1	I	CO ₂ Et	H	H	5a	90
2	I	NH ₂	H	H	5b	76
3	I	H	H	Br	5c	90
4	I	H	OH	H	5d	79
5	I	H	H	CHO	5e	88
6	Br	H	H	H	5f	68
7	Br	NO ₂	H	NO ₂	5g	51
8	Br	CN	H	H	5h	64

Reaction conditions: All reactions were performed at 0.1 M cubane concentration using 3 equivalents of aryl halide, Pd(PH₃)₄ (10 mol-%) and CuI (30 mol-%) under argon for 16 h. Where applicable, yields are isolated yields after chromatography on silica gel.

After optimization of the general coupling conditions, we were interested to see, if the Sonogashira reaction was tolerant to electronic changes in the aryl substituent. The presence of electron-withdrawing groups on the aryl iodides in *p*- or *o*-positions (entries 1,3,5) led to product formation in excellent yields (~90 %). With the introduction of electron donating groups (entries 2, 4) a slight decrease in yield was observed (76-80 %).

This behavior is in accordance with the literature, as oxidative addition of the aryl halide to the active palladium species is believed to be the rate-limiting step.^[22] Less reactive aryl bromides required more forcing conditions and only electron-poor aromatic systems (entries 6–8) gave product formation. Particularly product **5g** may be highlighted as belonging to a new family of nitro-cubanes. The ease of attachment of two nitro-groups in the direct proximity to the alkynyl-cubane-core could give a new boost to the search for cheaper cubane-based high energy materials.^[23]

The stability of alkynyl cubanes towards palladium and copper catalysis during Sonogashira-conditions is astonishing as previous findings showed that the presence of Rh(I) leads to a rearrangement of the alkynyl-cubanes to either cyclooctatetraen derivatives or tricyclooctadiene.^[24] In addition, the presence of Pd on charcoal either leads to a ring-opening to cyclooctatetraen,^[25] or to reduction to bicyclo[2.2.2]-octane under hydrogen atmosphere.^[26] However, with this reassuring indication of cubane's stability, we turned our interest to more delicate cubane-porphyrin systems (Scheme 4).

Scheme 4. Cubane-porphyrin systems via Sonogashira coupling.

The transfer of the optimized conditions for Sonogashira coupling for normal aryl substrates was not effective in the initial reaction. Next to insertion of copper into the macrocyclic porphyrin core we observed the formation of the Glaser-coupled cubane-dimer, rather than the Sonogashira product.^[27]

Figure 1. Molecular structure of the porphyrin-alkynyl-cubane **7b** showing top and side views (thermal displacement 50%).

Adjustment of the conditions and utilization of a Cu-free methodology provided us with arm-extended porphyrin-cubane systems **7a** (73 %) and **7b** (63 %) in good yields (Figure 1).^[28] Furthermore, this approach was extended to dibrominated-5,15-porphyrin **6c**, to achieve a linear porphyrin with two cubane handles on each side in **7c** (51 %).^[29] Even more delicate porphyrin-cubane systems were achieved by using the bisalkynyl-cubane, either as mono-protected **8a** or as the bisalkynyl-species **8b** (Table 2).^[21]

Table 2. Sonogashira coupling of bisalkynyl-cubanes with bromoporphyrins.

Entry	M	R ¹	R ²	R ³	Product	Yield [%]
1	2H	Ph	Ph	TMS	9a ^[a]	83
2	Zn(II)	Ph	Ph	TMS	9b ^[a]	83
3	2H	Ph	Ph	H	9c ^[c]	82
4	Zn(II)	Ph	Ph	H	9d ^[c]	86
5	2H	<i>n</i> -hexyl	Ph	TMS	9e ^[b]	12
6	Zn(II)	<i>n</i> -hexyl	Ph	TMS	9f ^[a]	16
7	2H	<i>n</i> -hexyl	Ph	H	9g ^[d]	68
8	Coupling with iodobenzene			H	9h ^[a]	20

Reaction conditions: All reactions were performed with 0.33 mmol of cubane **8a/8b** and 0.29 mmol porphyrin **6d-6g** at 65 °C for 3 h with either [a] Pd(Ph₃)₄ (10 mol-%), CuI (20 mol-%), THF/TEA (10:3) or [b] Pd₂(dba)₃ (15 mol-%), AsPh₃ (30 mol-%), THF/TEA (3:1). Deprotection of the of according TMS-protected coupling product were performed with either [c] TBAF/THF or [d] K₂CO₃/MeOH.

To overcome the low solubility of the triphenylporphyrins **6d-6e**, we changed to more soluble dialkylporphyrins **6f-6g**, but the yield of the isolated pure compound dropped significantly.^[30] Thus far, the limitation for this kind of systems is the preparation of bisporphyrin-alkynyl-cubanes, which could not be isolated.^[31] Interestingly, the instability of the material arises from the porphyrin-fragment rather than the cubane-system, since a double Sonogashira coupling of **8b** with excess of iodobenzene yielded the diarylated-product **9h** without notable decomposition of the cubane core (entry 8).

Finally, we were able to apply the methodology presented for the synthesis of a cubane-linked porphyrin **10a** (Figure 2).

Figure 2. A series of linear linkers: Cubane-linked porphyrin **10a** and molecular structure of precursor **2f** (thermal displacement 50%).

The synthesis was achieved with an overall yield of 20 %, starting from building block **2f** with deprotection of the alkynyl followed by Pd-catalyzed coupling with bromoporphyrin **6e**.^[32] Porphyrin **10a** is the first example of a cubane-linked porphyrin array with a further synthetic handle, which represents a significant step towards using cubane-linked systems as electron transfer compounds with rigid resistor units.^[33] With a dimension of 9.68 Å from one cubane-carbon (C3) to the end of the acetylen-unit (C18) and with all carbons in line ($\angle \text{C}_3\text{C}_{11}\text{C}_{18} = 175^\circ$) this represents an interesting new class of linker system.

In conclusion, a modified cubane-aryl coupling via decarboxylative Baran coupling is reported. After systematic investigations the key obstacle of cubane cross-coupling was identified and circumvented by altering the electron density of the transition metal through an adjusted choice of ligand. Furthermore, for the first time not only the preparation of directly linked cubane-porphyrin system was achieved but also the possibility of Sonogashira functionalization of alkynyl arm-extended cubanes, proving the general compatibility of cubanes and Pd-catalyzed cross-coupling reactions. These cross-coupling reactions allow the preparation of new classes of cubane compounds, important not only for medicinal but also for materials chemistry. Further investigations on the unique behavior of cubane during (radical) cross-coupling conditions and the exact mechanism of decomposition are the topic of ongoing investigations.

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Keywords: Cubanes • Cross-Coupling • Porphyrins • Sonogashira Coupling • Nickel Catalysis

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The compatibility of cubanes and transition metals (Ni, Pd) is explored and a direct arylation of cubanes via a Baran-type nickel-catalyzed radical cross-coupling and arm-extended Sonogashira coupling of alkynyl-cubanes is reported. Furthermore the first series of cubane-porphyrins is prepared.

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Page No. – Page No.

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