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Phenyliodine Diacetate-Mediated *para*-Functionalizations of Amido- and Amino-Substituted [2.2]Paracyclophanes

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Abstract: The reaction of *N*-[2.2]paracyclophanyl-substituted amides or amines with phenyliodine diacetate (PIDA) and protic nucleophiles affords mixed *para*-substituted [2.2]paracyclophane derivatives in moderate to good yields. As protic nucleophiles carboxylic acids and alcohols as well as pyridine hydrobromide can be used. 4-Hydroxy-[2.2]paracyclophane reacts in an analogous manner.

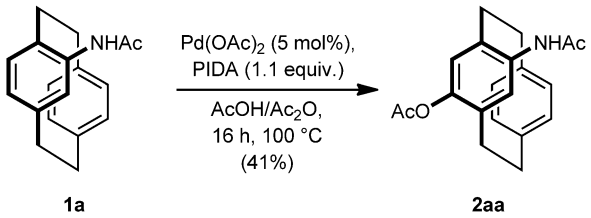
Keywords: cyclophanes; hypervalent iodine compounds; metal-free synthesis; planar chirality; synthetic methods

[2.2]Paracyclophanes are strained bisarenes with two eclipsed benzene rings connected by ethyl bridges. They were discovered in 1949,[1] and since then there has been a continuous interest in determining their properties and finding synthetic applications.[2,3] Utilizing their planar chirality, substituted [2.2]paracyclophanes have been used as auxiliaries, ligands and catalysts in stereoselective synthesis.[4] In addition, applications in polymer and material science have been described.[5]

Although the regioselective functionalization of monosubstituted [2.2]paracyclophanes is a major challenge in [2.2]paracyclophane chemistry, there are various methods for the synthesis of *pseudo-ortho*, *pseudo-geminal*, *pseudo-meta* and *ortho*-substituted derivatives.[6,7] In contrast, only a few reports focus on accessing *para*-substituted [2.2]paracyclophanes, despite the fact that such derivatives proved promising for applications in material science.[8] Most of the *para*-substituted [2.2]paracyclophanes reported so far have either been prepared by a *de-novo* synthesis (providing products with two identical substituents),[9,10] or electrophilic aromatic substitution of [2.2]paracyclophane derivatives with activating methyl or methoxy groups.[11,12] A general approach providing *para*-substituted [2.2]paracyclophanes is still lacking.

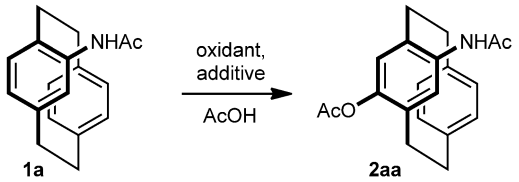
During our investigation of the palladium-catalyzed *ortho*-acetoxylation of donor-substituted [2.2]paracyclophanes,[7f] we noticed an interesting reaction variant. With *N*-acetylamino[2.2]paracyclophane (**1a**) as substrate and phenyliodine diacetate (PIDA) as oxidant, a selective *para*-acetoxylation occurred and **2aa** (instead of the expected *ortho*-substituted product) was isolated in 41% yield (Scheme 1). Although Cram and co-workers described this compound already in 1966,[13] we noted to our surprise that no further reports about **2aa** or structurally related compounds have been published since then.

Recently, hypervalent iodine(III) reagents have attracted much attention.[14] In reactions with anilides, [bis(acyloxy)iodo]arenes [$ArI(O_2CR)_2$] were applied as mild oxidants and arylating agents for *para*-selective C–H oxygenations, fluorinations and arylations under metal-free conditions.[15,16] Based on those reports and in the light of our initial finding (Scheme 1), we decided to investigate the preparation of other *para*-functionalized [2.2]paracyclophanes by



Scheme 1. Initial observation of a *para*-acetoxylation of planar chiral amide **1a**.

Table 1. Optimization of reaction conditions.[a]



Entry	*t* [h]	*T* [°C]	Oxidant (equiv.)	Additive (equiv.)	Yield [%]
1[b]	16	100	PIDA (1.1)	$Pd(OAc)_2$ (0.05)	41
2[b]	16	100	PIDA (1.1)	–	45
3	16	r.t.	PIDA (1.1)	–	60
4	1	r.t.	PIDA (1.1)	–	67
5[c]	1	r.t.	PIDA (1.1)	–	60
6[d]	1	r.t.	PIDA (1.1)	–	60
7[e]	7	r.t.	PIDA (1.1)	AcOH (10)	32
8	2	r.t.	PIDA (1.5)	TFA (1.0)	32
9	2	r.t.	PIDA (1.5)	$BF_3{\cdot}OEt_2$ (1.0)	40
10	0.5	r.t.	PIFA (1.5)	–	<28[f]

[a] *Reaction conditions:* amide **1a** (0.500 mmol), oxidant and additive were stirred under air in AcOH ([**1a**] = 0.1 M).
[b] In $AcOH/Ac_2O$.
[c] [**1a**] = 0.5 M.
[d] [**1a**] = 0.05 M.
[e] In MeCN.
[f] Containing traces of an unknown by-product.

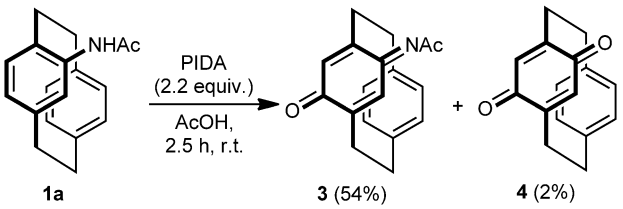
PIDA-promoted reactions of monosubstituted [2.2]paracyclophane derivatives such as amide **1a**.

An early screening of the reaction conditions showed that the presence of $Pd(OAc)_2$ was not needed for the *para*-acetoxylation of **1a** (Table 1, entry 2). Performing the reaction at room temperature and shortening the reaction time from 16 h to 1 h was beneficial allowing us to isolate *para*-acetoxylated acetamide **2aa** in 67% yield (Table 1, entry 4). Changing the reagent concentrations had no major effect (Table 1, entries 4–6). With the goal to avoid product decomposition leading to undefined side reactions, the addition of MeCN as co-solvent with 10 equiv. of AcOH as protic nucleophile was tried. Under those conditions, however, the yield of **2aa** dropped to 32% even after an extended reaction time of 7 h (Table 1, entry 7). In contrast to observations made in *para*-acetoxylations of acetanilides,[15b] no improvement in yield was observed when TFA or $BF_3{\cdot}OEt_2$ was added to a reaction with *N*-[2.2]paracyclophanylamide **1a** (Table 1, entries 8 and 9). Substituting PIDA by the more reactive iodine(III) reagent [bis(trifluoroacetoxy)iodo]benzene (PIFA) led to a lower yield of **2aa** also due to the formation of an unknown by-product, which could not be separated from **2aa** (Table 1, entry 10). In summary, the optimized conditions involved the use of 1.1 equiv. of PIDA to be applied in AcOH as solvent for 1 h at ambient temperature providing *para*-acetoxylated amide **2aa** in 67% yield.

Increasing the amount of PIDA from 1.1 equiv. to 2.2 equiv. led to over-oxidation, and the two planar chiral *para*-benzoquinone derivatives **3** and **4** were obtained in 54% and 2% yield, respectively (Scheme 2).

The *para*-selectivity of the C–O bond formation in the conversion of amide **1a** was revealed by mass spectrometry, NMR spectroscopy, and X-ray crystal structure analysis of product **2aa**. Crystals suitable for X-ray crystal structure analysis were grown from ethyl acetate at room temperature and the structure of *para*-substituted amide **2aa** is shown in Figure 1.[17]

In general, [2.2]paracyclophanes have two very characteristic features: (i) non-planar aromatic rings and (ii) significantly elongated C–C bonds in the ethylene bridges. Here, the carbon atoms bonded to the bridging $-CH_2-CH_2-$ groups (C-1, C-4 and C-9, C-12) in the aromatic rings of **2aa** deviate from the least-squares planes defined by atoms C-2, C-3, C-5, C-6



Scheme 2. Synthesis of planar chiral *para*-benzoquinone derivatives **3** and **4**.

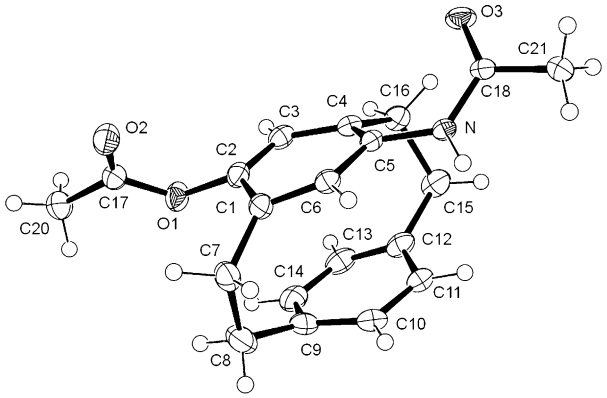


Figure 1. ORTEP diagram of the molecular structure of amide **2aa** as determined by X-ray single crystal structure analysis.

and C-10, C-11, C-13, C-14 by 0.15 Å resulting in sums of C–C–C bond angles within the rings of values close to 717°. The lengths of the bridging C–C bonds in **2aa** are 1.591(2) and 1.588(2), respectively. Compared with the average value of a C–C bond in the solid state [1.530(15) Å[18]] this amounts to an elongation of 0.05–0.06 Å. Mixing of the π orbitals involving the ring atoms bonded to the bridges into their σ* orbital might contribute to this elongation.

Next, the reaction behavior of other [2.2]paracyclophane derivatives was investigated (Table 2). Smooth acetoxylations with 1.1 equiv of PIDA in AcOH as solvent also occurred using [2.2]paracyclophanes **1b** and **1c** as substrates providing the corresponding *para*-acetoxylated products (amide **2ba** and carbamate **2ca**) in 58% and 41% yield, respectively (Table 2, entries 2 and 3). To our surprise, cyclohexadiene-type products (**5da** and **5ea**) were predominantly formed when *N*-(het)aryl-substituted amines **1d** and **1e** were applied under the same conditions. Whereas **1d** bearing a 2-pyridinyl group exclusively led to **5da** in 59% yield, **1e** having a phenyl substituent gave a mixture of *para*-acetoxylated product **2ea** and cyclohexadiene-type product **5ea** in 23% and 53% yield, respectively (Table 2, entries 4 and 5). In both cases, *para*-functionalizations had occurred, but apparently the re-aromatization was hampered. Presumably, the strained [2.2]paracyclophane backbone contributed to the unexpected stability of the observed products. To the best of our knowledge these reactions represent the first examples of *para*-selective functionalizations of *N*-(het)aryl-substituted anilines with hypervalent iodine(III) reagents.

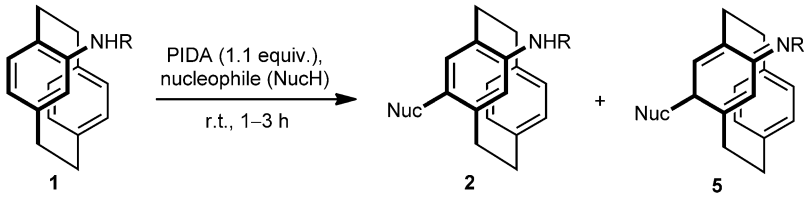
Next, *para*-functionalizations of **1a** with other nucleophiles were studied. Instead of acetic acid, formic acid could be applied, and [2.2]paracyclophane **2ab** was isolated in 59% yield (Table 2, entry 6). Attempts to use trifluoroacetic acid or *p*-toluenesulfonic acid failed, which contrasts with the behaviour of simple anilide derivatives.[15a,c] Being less acidic, methanol and ethanol could only be applied when K_2CO_3 was added as base (Table 2, entries 7–10). Under those conditions, amides **1a** and **1b** showed a straight reaction behaviour leading to *para*-alkoxylated products **2ac**, **2bc**, and **2ad** in yields up to 64% (Table 2, entries 7, 8 and 10). As observed in the acetoxylation of **1d** presented before, the PIDA-mediated reaction of this 2-pyridinyl-substituted aniline derivative with methanol led to a cyclohexadiene-type product (**5dc**), which could be isolated in 65% yield (Table 2, entry 9). None of the expected fully aromatized [2.2]paracyclophane **2dc** was observed.

In the oxidative dearomatization of phenols a mixture of MeCN/H_2O was used for the introduction of a hydroxy substituent.[19] Applying analogous conditions here remained unsuccessful, and in the attempt to *para*-hydroxylate amide **1a** with PIDA and aqueous MeCN only *para*-benzoquinone imine **3** was isolated in 40% yield. Recently, a *para*-selective fluorination of anilides using HF/pyridine was reported.[15d] Considering the interest in parylene F, which is a fluoro-substituted polymer derived from [2.2]paracyclophane showing high stability at elevated temperatures,[20] a *para*-selective fluorination of **1a** was tried. Unfortunately, treatment of **1a** with HF/pyridine and PIDA in MeCN only resulted in decomposition of the starting material and formation of an unidentified compound. In contrast, a combination of HBr/pyridine reacted well affording *para*-brominated amide **2ae** in 46% yield (Table 2, entry 11). This regioselectivity is noteworthy because common brominations of monosubstituted [2.2]paracyclophanes predominately occur in a *pseudo-geminal* position due to a transannular effect.[21] Thus the here reported PIDA-promoted strategy gives access to a product (**2ae**), which might also prove useful for subsequent *para*-functionalizations of [2.2]paracyclophane achievable by transition metal-catalyzed cross-coupling or metal/bromine exchange reactions.

Paracetamol (acetaminophen, **6**) is a widely used drug against pain and fever with only minor side effects.[22] Overdose, however, can cause liver damage and death. Amide **2af** can be considered as structurally extended analogue of paracetamol. As already discussed, the attempted direct *para*-hydroxylation of amide **1a** using the newly developed PIDA-promoted strategy had failed. To our delight, however, **2af** (named "phanacetamol") could be obtained in 87% yield by selective ester hydrolysis of amide **2aa** under acidic conditions (Scheme 3).

As other [2.2]paracyclophane derivatives have already shown interesting bioactivities,[23] we hypothesize that due to the increased lipophilicity and extended three-dimensional structure of phanacetamol (**2af**) as compared to paracetamol (**6**), alternative metabolic pathways are activated leading to a safer and less hep-

Table 2. Substrate scope of the PIDA-promoted *para*-functionalization of [2.2]paracyclophanylamides and -amines.[a]



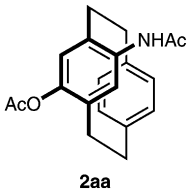
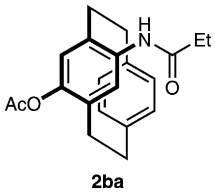
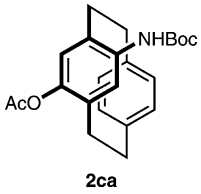
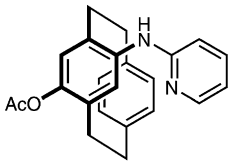
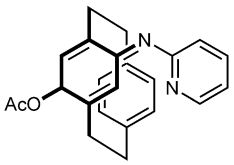
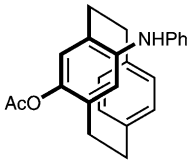
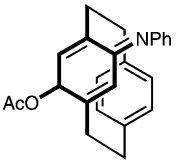
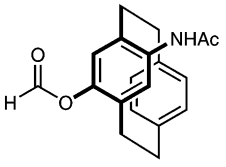
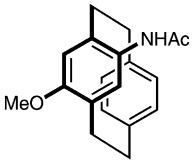
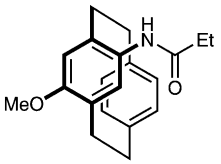
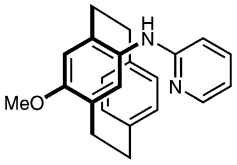
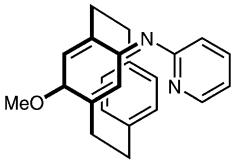
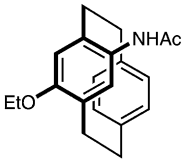
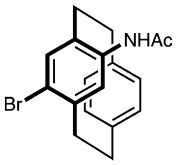
Entry	R	NucH	Products	Yield [%]
1	COMe (**1a**)	AcOH	 **2aa**	67
2	COEt (**1b**)	AcOH	 **2ba**	58
3	Boc (**1c**)	AcOH	 **2ca**	41
4	2-pyridinyl (**1d**)	AcOH	 **2da**  **5da**	0 (**2da**); 59 (**5da**)
5	Ph (**1e**)	AcOH	 **2ea**  **5ea**	23 (**2ea**); 53 (**5ea**)
6	COMe (**1a**)	HCOOH	 **2ab**	59
7[b]	COMe (**1a**)	MeOH	 **2ac**	64

Table 2. (Continued)

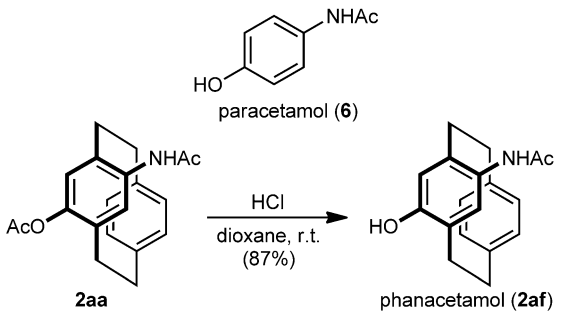
Entry	R	NucH	Products	Yield [%]
8[b]	COEt (**1b**)	MeOH	 **2bc**	52
9	2-pyridinyl (**1d**)	MeOH	 **2dc**  **5dc**	0 (**2dc**); 65 (**5dc**)
10[b]	COMe (**1a**)	EtOH	 **2ad**	56
11[c,d]	COMe (**1a**)	HBr/pyridine	 **2ae**	46

[a] *Reaction conditions:* [2.2]paracyclophane **1** (0.500 mmol) in acid or alcohol (0.1 M).
[b] Addition of K_2CO_3 (1.1 equiv.).
[c] Performed at 0 °C.
[d] Performed in MeCN.

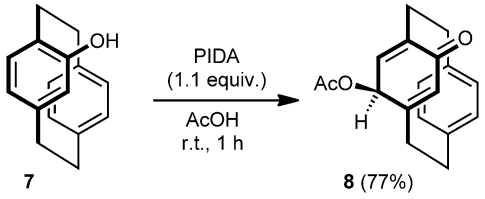
atotoxic drug with potentially useful analgesic properties. Studies along those lines are in progress, and results will be reported in due course.

The oxidative functionalization of phenol derivatives with PIDA results in the formation of cyclohexadienones.[19,24] Having observed *para*-benzoquinone derivatives **3** and **4** in PIDA-mediated *para*-acetoxylations of amide **1a** (Scheme 2), we assumed the latter product to be dominant in analogous reactions starting from 4-hydroxy[2.2]paracyclophane (**7**). However, neither the use of 1.1 equiv. nor applying 2.2 equiv. of PIDA led to the expected product, *para*-benzoquinone **4**. Instead, planar chiral cyclohexadienone **8** was obtained in 77% yield (Scheme 4). Also in this case, no aromatization had occurred revealing an unusual stability of the resulting acetoxylated planar chiral cyclohexadienone derivative **8**.

In line with findings by Rozenberg and co-workers, who had shown that the nucleophilic attack of planar chiral benzoquinone **4** always proceeds from the less shielded top face,[25] the acetoxy substituent of cyclo-



Scheme 3. Paracetamol (**6**) and synthesis of phanacetamol (**2af**).



Scheme 4. PIDA-promoted oxidation of 4-hydroxy-[2.2]paracyclophane (**7**).

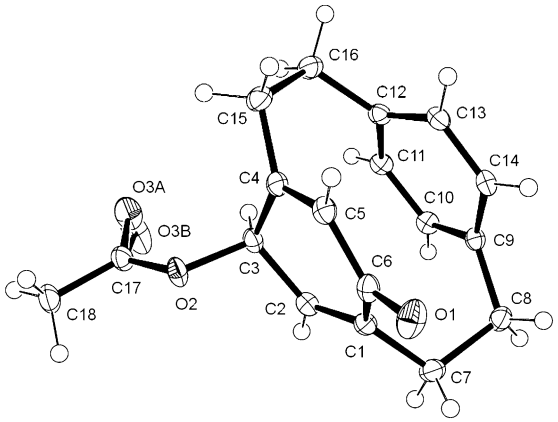


Figure 2. ORTEP diagram of the molecular structure of cyclohexadienone **8** as determined by X-ray single crystal structure analysis.

hexadienone **8** had an *exo*-orientation. The X-ray crystal structure of **8** (Figure 2) confirmed the initial assumption.[26]

In summary, we have developed a protocol for the synthesis of mixed *para*-substituted [2.2]paracyclophanes. Starting from mono-functionalized derivatives the desired products are obtained by treatment with PIDA in good to moderate yields. Various nucleophiles can be applied allowing the introduction of carboxy, alkoxy, and bromo substituents. An application of the method was demonstrated by the synthesis of a planar chiral paracetamol analogue. We consider the products as interesting for material sciences and drug development, and studies along those lines are projected for the future.

Experimental Section

General Procedure for PIDA-Promoted *para*-Acetoxylation/Etherification

To a stirred solution of amide or amine **1** (0.500 mmol) in acetic acid (5 mL) or alcohol (5 mL) was added $PhI(OAc)_2$ (177 mg, 0.55 mmol, 1.1 equiv.). If alcohols were used, K_2CO_3 (76 mg, 0.55 mmol, 1.1 equiv.) was added to the reaction mixture before treatment with $PhI(OAc)_2$. Stirring was then continued for 1–3 h at room temperature. After work-up (for details see the Supporting Information) the product was purified by column chromatography.

Acknowledgements

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