EurJOC
European Journal of Organic Chemistry

Communications
doi.org/10.1002/ejoc.202100288

Chemistry Europe
European Chemical Societies Publishing



# Para-Functionalization of N-Substituted 4-amino[2.2] paracyclophanes by Regioselective Formylation

Simon Felder,[a] Laurent Micouin,*[a] and Erica Benedetti*[a]

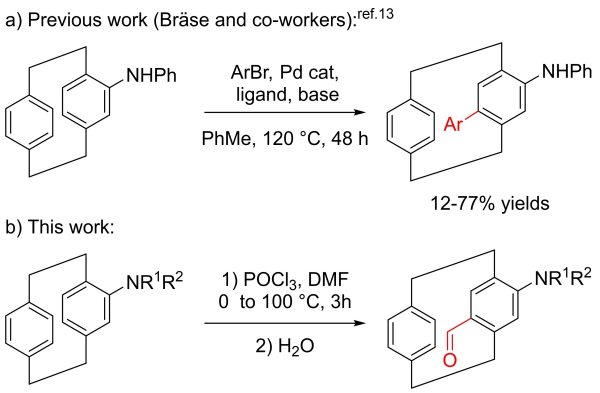
Herein, we report a simple and convenient procedure to prepare *para*-disubstituted [2.2]paracyclophanes in a straightforward manner. Our approach relies on a regioselective formylation of N-substituted 4-amino[2.2]paracyclophanes, which allows an easy access to a series of products incorporating a reactive aldehyde function para to the electron-donating group. These compounds can be engaged in a variety of orthogonal late-stage derivatization processes involving either the carbonyl group or the amine function, and can serve as precursors to rapidly access more complex paracyclophane derivatives. Control of planar chirality is also possible by performing a kinetic resolution of key racemic intermediates through asymmetric transfer hydrogenation. The formylation can be run on a synthetically useful scale, thus confirming the practical applicability of our method.

[2.2]Paracyclophane (pCp)[1] and its derivatives constitute a rather unique class of aromatic compounds characterized by an unusual three-dimensional framework. These substrates incorporate two benzene rings called *decks*, covalently fixed together by two ethylene bridges at their *para* positions. As evidenced by X-ray diffraction crystallography, the aromatic *decks* of pCps are stacked face-to-face and adopt a bent conformation.[2] Due to their geometrical constraints, steric effects and unique π-interactions, [2.2]paracyclophanes display an uncommon reactivity. These molecules can in fact undergo Diels-Alder cycloadditions, hydrogenations, and ionic additions.[3] Functionalized pCps also often show remarkable substituent effects in electrophilic aromatic substitutions: the functional groups on one *deck* can induce the incoming electrophile to preferentially attack the other *deck* at specific positions.[4] Such transannular directive effects are, for example, frequently exploited to selectively access *pseudo-gem* di-substituted paracyclophanes.[5] While various methods can be followed to functionalize both pCp rings, the selective decoration of only one *deck* is more of a synthetic challenge. Indeed, only few examples of regioselective *ortho*- or *para*-functionalization of pCps have been reported to date. Usually, in these cases, carbon-heteroatoms bonds are formed starting form mono-substituted derivatives through bromination,[6] acetoxylation[7] or amination reactions.[8] In our ongoing work on the chemistry of [2.2]paracyclophanes,[9] we became interested in exploring new synthetic routes to access *para*-disubstituted pCps in a straightforward manner through selective carbon-carbon bond formation. Such compounds could potentially be used to develop original chromophores.[10] In addition, since substituted [2.2]paracyclophanes can display planar chirality due to the hindered rotation of their aryl moieties,[11] *para*-disubstituted pCps may be employed as precursors of new chiral ligands and catalysts.[12]

Very recently, a palladium-catalyzed *para*-selective C–H activation/aryl-aryl coupling of 4-phenylamino[2.2] paracyclophane has been reported (Scheme 1a).[13] To the best of our knowledge, this constitute the sole example of a reaction allowing the functionalization of paracyclophanes with the creation of aryl-aryl bonds *para* to an electron-donating amino group.

Herein we present a practical method to perform a regioselective para-formylation of N-substituted 4-amino[2.2] paracyclophanes (Scheme 1b). Our approach is complementary to the Pd-catalyzed aryl-aryl couplings since it provides reactive aldehyde derivatives that can serve as intermediates to create aryl-alkyl or aryl-alkenyl bonds.

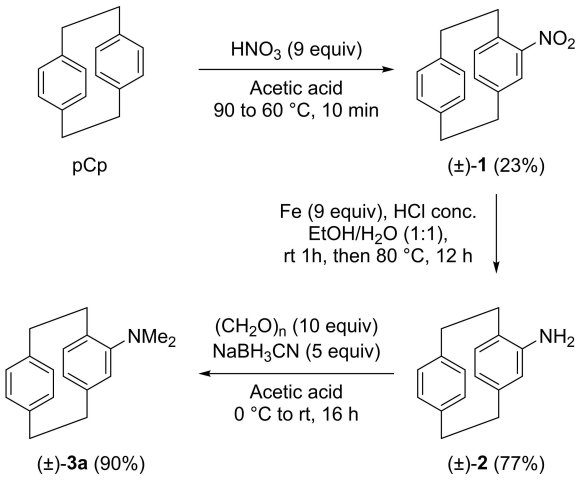
We began our investigations with the synthesis of racemic 4-dimethylamino[2.2]paracyclophane. Compound (±)-**2** was prepared first, starting from commercially available [2.2] paracyclophane, and following a two-step nitration/reduction procedure previously reported in the literature (Scheme 2).[14] Reductive methylation of derivative (±)-**2** then afforded product (±)-**3a** in 90% yield (Scheme 2).




**Scheme 1.** Access to *para*-disubstituted pCps through selective carbon-carbon bond formation.

[a] *S. Felder, Dr. L. Micouin, Dr. E. Benedetti*
*Laboratoire de Chimie et Biochimie Pharmacologiques et Toxicologiques – UMR8601 CNRS*
*Université de Paris*
*45 rue des Saints Pères,*
*75006 Paris, France*
*E-mail: laurent.micouin@u-paris.fr*
*erica.benedetti@u-paris.fr*

*Supporting information for this article is available on the WWW under https://doi.org/10.1002/ejoc.202100288*




**Scheme 2.** Synthesis of racemic compound (±)-**3a**.

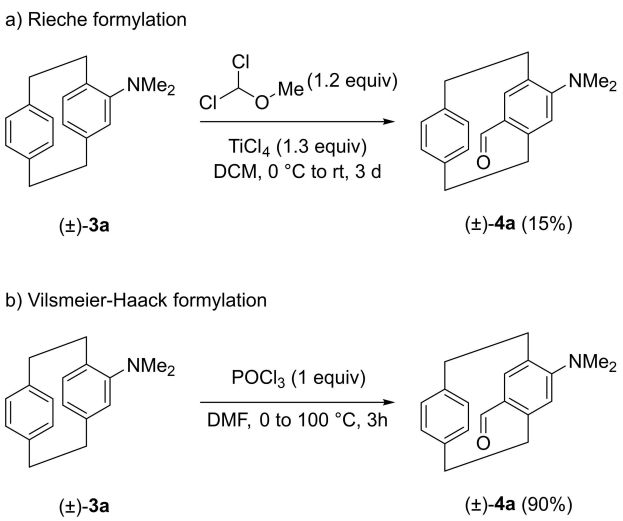
Having pCp (±)-**3a** in hand, we considered the possibility of performing selective formylation reactions. By taking inspiration from a protocol frequently employed to decorate pCps with aldehyde groups,[15] Rieche's conditions were tested in a first assay (Scheme 3a). The introduction of an aldehyde group at the *para* position of 4-methoxy[2.2]paracyclophane has indeed been described to occur in a chemical yield of 90% after only 4 hours of reaction.[16] However, N-substituted analog (±)-**3a** was regioselectively formylated in only 15% chemical yield after 3 days using similar conditions. Amines are known to interact with $TiCl_4$ to form metal-nitrogen bonds.[17] Such reactivity may hamper the activation of dichloromethyl methyl ether and explain the low conversion observed when performing Rieche's formylation. Different conditions were therefore screened to optimize this transformation, and we were pleased to find that the Vilsmeier-Haack protocol could afford aldehyde (±)-**4a** in a short reaction time and 90% yield (Scheme 3b). The reaction could be run on a synthetically useful scale (750 mg) without any appreciable loss of efficiency, thus confirming the practical applicability of our method.

The relative position of the substituents in compound (±)-**4a** (formyl group *para* to the amino group) was deduced from NMR studies, and subsequently confirmed by chemical correlation. Indeed, 4-amino[2.2]paracyclophane (±)-**2** was converted into *para*-iodinated compound (±)-**5** using a previously described synthetic protocol.[18] *N,N*-Dimethylation of amine (±)-**5**, followed by iodine-lithium exchange and formylation with DMF afforded product (±)-**4a** in 35% overall yield (Scheme 4). The proton and carbon NMR spectra of this aldehyde and the one obtained through the direct formylation pathway showed identical signal patterns.

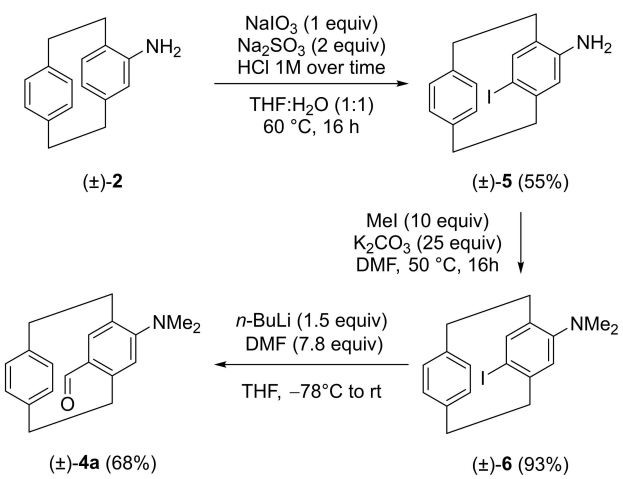
The Vilsmeier-Haack reaction proved to be a robust method to functionalize *N*-substituted 4-amino[2.2]paracyclophanes at their *para* position. In fact, the formylation was successfully employed to selectively decorate compounds (±)-**3b** and (±)-**3c**, easily obtained through a mono- or di-benzylation of 4-amino[2.2]paracyclophane (±)-**2** (Scheme 5).[19]

*N,N*-Diallyl substituted 4-amino[2.2]paracyclophane(±)-**3d** reacted as well to form product (±)-**4d** in 50% yield (Scheme 5). Interestingly, when Fmoc-protected amine (±)-**3e** was subjected to formylation under the same conditions, product (±)-**4d** could be isolated in 42% yield (Scheme 5). This last example clearly shows that the reaction also tolerates substrates incorporating mild electron-withdrawing groups on the nitrogen atom. All transformations are supposed to proceed through the mechanism proposed to explain the Vilsmeier-Haack formylation of more common benzene derivatives.[20]

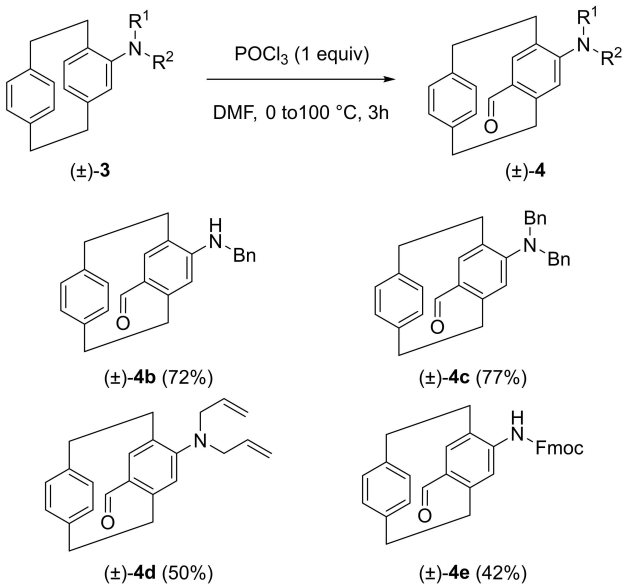
The formylated products (±)-**4a**–**d** incorporate both an electron-donating and an electron-withdrawing group, and exhibit interesting UV-Vis absorption and fluorescence emission properties.[19] In addition, due to the presence of the reactive aldehyde group, these compounds can undergo a variety of derivatization reactions. To exemplify different possibilities, compound (±)-**4a** was reduced to the corresponding benzylic alcohol (±)-**7**, engaged in a reductive amination reaction, and submitted to Grignard addition (Scheme 6). Wittig reactions



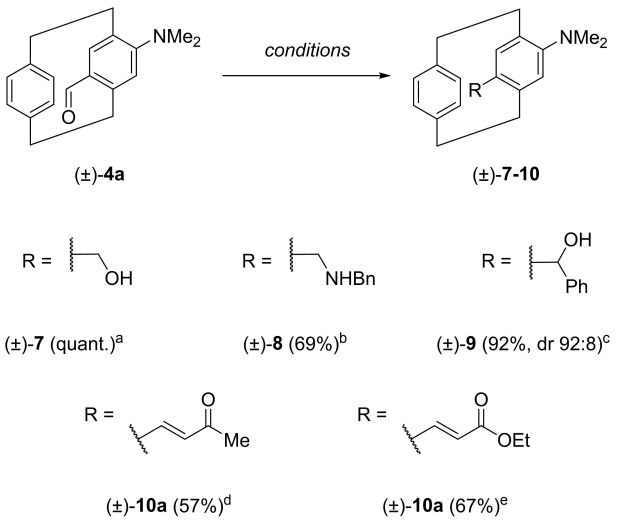

**Scheme 3.** Selective formylation of compound (±)-**3a**.




**Scheme 4.** Chemical correlation studies.




**Scheme 5.** *Para*-formylation of pCps (±)-**3b–e**.

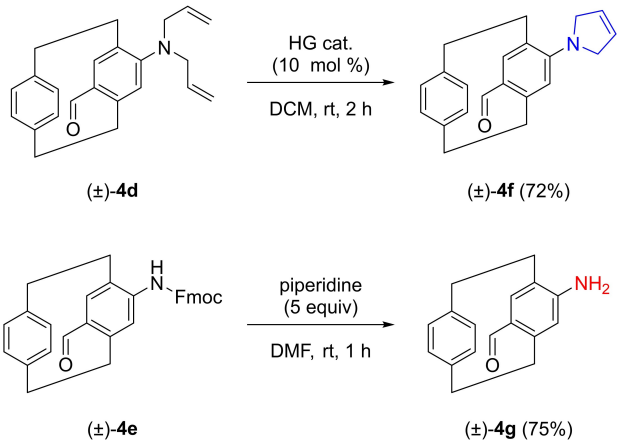



*Conditions:* a) $NaBH_4$ (1.2 equiv), THF/MeOH (1:9), 0 °C, 2 h; b) $BnNH_2$ (1.3 equiv), $NaB(OAc)_3H$ (3.75 equiv), AcOH (1.2 equiv), DCM, rt, 3 h; c) PhMgBr (1.12 equiv), THF, 0 °C to rt, overnight; d) Dimethyl acetylmethylphosphonate (1.2 equiv), $K_2CO_3$ (2 equiv), MeOH, 40 °C, 3 d; e) Triethyl phosphonoacetate (1.56 equiv) DBU, rt, 3 d.

**Scheme 6.** Late-stage derivatization of compound (±)-**4a**.

were also successfully conducted starting from compound (±)-**4a** (Scheme 6).[21]

Derivatization reactions involving reactive substituents at the nitrogen atom can also be performed. For instance, compound (±)-**4d**, showing a *N,N*-diallyl moiety, was successfully submitted to ring-closing metathesis (RCM) in the presence of a 2nd generation Hoveyda-Grubbs catalyst (HG cat, Scheme 7) to generate cyclized product (±)-**4f** in 72% yield (Scheme 7). The Fmoc-protected derivative (±)-**4e**, on its side, was easily

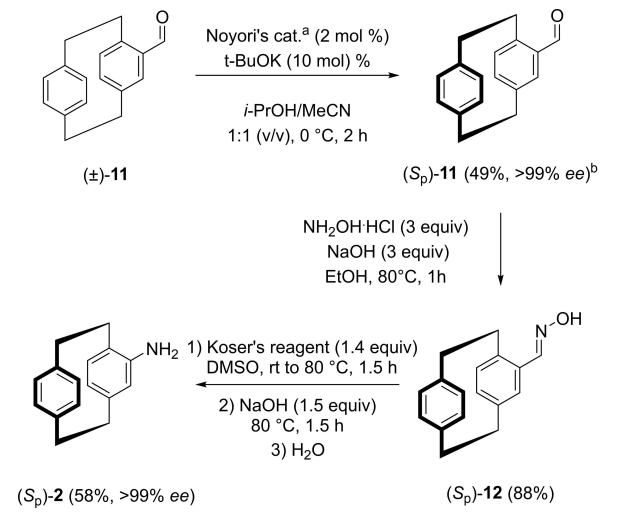



**Scheme 7.** Transformations involving reactive substituents at the nitrogen atom.

converted to the corresponding primary amine (±)-**4g** upon treatment with piperidine in DMF (Scheme 7), thus opening up a plethora of possibilities for further functionalization at the nitrogen atom.

All the transformations described above have been conducted on racemic material. It is however possible to prepare enantiopure 4-amino[2.2]paracyclophane ($S_p$)-**2** taking advantage of a method previously optimized in our laboratory.[9a] In a first step, the kinetic resolution of racemic 4-formyl[2.2]paracyclophane (±)-**11** was performed by asymmetric transfer hydrogenation using RuCl(*p*-cymene)[(*S,S*)-Ts-DPEN] as the catalyst, and *t*-BuOK as the base, in a 1:1 *i*-PrOH/MeCN mixture (Scheme 8).

The resulting enantiopure aldehyde ($S_p$)-**11** was converted into the corresponding oxime ($S_p$)-**12** through a classical condensation reaction. Treatment of compound ($S_p$)-**12** with




a) RuCl(*p*-cymene)[(*S,S*)-Ts-DPEN]; b) Enantioenriched ($R_p$)-4-hydroxymethyl-[2.2]paracyclophane was also isolated as a product

**Scheme 8.** Access to enantiopure 4-amino[2.2]paracyclophane ($S_p$)-**2**.

Koser's reagent[22] and NaOH finally led to the formation of the desired enantiopure amine ($S_p$)-**2**, which was isolated in 58% yield (Scheme 8). Starting from this precursor, it will clearly be easy to prepare a variety of *para*-disubstituted pCps in their enantiopure form simply by using our regioselective formylation protocol as a key synthetic step.

In conclusion, we reported a practical method to regioselectively synthesize *para*-disubstituted [2.2]paracyclophanes in few steps, and good overall yields. Our approach is based on the Vilsmeier-Haack formylation of differently substituted 4-amino[2.2]paracyclophanes, which allows the introduction of a reactive aldehyde function *para* to the electron-donating groups. The formylated products exhibit interesting spectroscopic properties, and can be engaged in a variety of late-stage functionalization processes leading to more complex paracyclophane derivatives. All synthesized compound can be easily obtained in their enantiopure form. We are convinced that our convenient formylation reaction will reveal particularly useful as a key step to access planar chiral paracyclophanes showing interesting photophysical or catalytic properties. The possibility to use this approach for preparing new circularly polarized light emitters is currently under investigation in our laboratory.

## Acknowledgements

*We gratefully thank the Agence Nationale de la Recherche (ANR PhotoChiraPhane), CNRS, Université de Paris and the Ministère de l'Enseignement Supérieur et de la Recherche for financial support. Patrice Gerardo is kindly acknowledged for his help with mass analysis.*

## Conflict of Interest

The authors declare no conflict of interest.

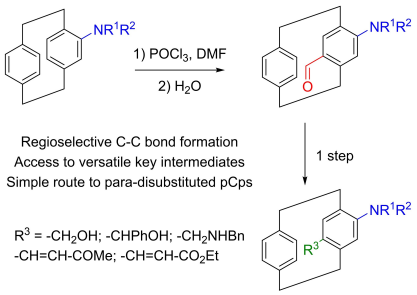
**Keywords:** Formylation · [2.2]Paracyclophanes · Para-disubstitution · Planar chirality · Regioselective reactions

[1] a) C. J. Brown, A. C. Farthing, *Nature* **1949**, *164*, 915–916. For a review on paracyclophanes, see b) Z. Hassan, E. Spuling, D. M. Knoll, J. Lahann, S. Bräse, *Chem. Soc. Rev.* **2018**, *47*, 6947–6963.
[2] H. Hope, J. Bernstein, K. N. Trueblood, *Acta Crystallogr.* **1972**, *B28*, 1733–1743.
[3] a) J. Kleinschroth, H. Hopf, *Angew. Chem. Int. Ed.* **1982**, *21*, 469–480; *Angew. Chem.* **1982**, *94*, 485–496; b) A. A. Aly, H. Hopf, L. Ernst, I. Dix, P. G. Jones, *Eur. J. Org. Chem.* **2006**, 3001–3006; c) A. A. Aly, S. Ehrhardt, H. Hopf, I. Dix, P. G. Jones, *Eur. J. Org. Chem.* **2006**, 335–350; d) A. A. Aly, H. Hopf, L. Ernst, *Eur. J. Org. Chem.* **2000**, 3021–3029; e) L. Minuti, A. Marrocchi, I. Tesei, E. Gacs-Baitz, *Tetrahedron Lett.* **2005**, *46*, 8789–8792.
[4] For a recent review, see: a) Z. Hassan, E. Spuling, D. M. Knoll, S. Bräse, *Angew. Chem. Int. Ed.* **2020**, *59*, 2156–2170. For selected references, see: b) H. J. Reich, K. E. Yelm, *J. Org. Chem.* **1991**, *56*, 5672–5679; c) A. Pelter, B. Mootoo, A. Maxwell, A. Reid, *Tetrahedron Lett.* **2001**, *42*, 8391–8394; d) V. I. Rozenberg, D. Y. Antonov, E. V. Sergeeva, E. V. Vorontsov, Z. A. Starikova, I. V. Fedyanin, C. Schulz, H. Hopf, *Eur. J. Org. Chem.* **2003**, 2056–2061.
[5] a) H. J. Reich, D. J. Cram, *J. Am. Chem. Soc.* **1969**, *91*, 3517–3526; b) H. J. Reich, D. J. Cram, *J. Am. Chem. Soc.* **1969**, *91*, 3505–3516; c) E. A. Truesdale, D. J. Cram, *J. Org. Chem.* **1980**, *45*, 3974–3981; d) S. Mandal, A. Mukhopadhyay, J. N. Moorthy, *Eur. J. Org. Chem.* **2015**, 1403–1408; e) A. Marchand, A. Maxwell, B. Mootoo, A. Pelter, A. Reid, *Tetrahedron* **2000**, *56*, 7331–7338.
[6] B. Wang, J. W. Graskemper, L. Qin, S. G. DiMagno, *Angew. Chem. Int. Ed.* **2010**, *49*, 4079–4083; *Angew. Chem.* **2010**, *122*, 4173.
[7] P. Schaal, H. Baars, G. Raabe, I. Atodiresei, C. Bolm, *Adv. Synth. Catal.* **2013**, *355*, 2506–2512.
[8] M. Cakici, Z. G. Gu, M. Nieger, J. Bürck, L. Heinke, S. Bräse, *Chem. Commun.* **2015**, *51*, 4796–4798.
[9] a) M.-L. Delcourt, S. Turcaud, E. Benedetti, L. Micouin, *Adv. Synth. Catal.* **2016**, *358*, 1213–1218; b) M.-L. Delcourt, S. Felder, E. Benedetti, L. Micouin, *ACS Catal.* **2018**, *8*, 6612–6616; c) E. Benedetti, M.-L. Delcourt, B. Gatin-Fraudet, S. Turcaud, L. Micouin, *RSC Adv.* **2017**, *7*, 50472–50476; d) M.-L. Delcourt, C. Reynaud, S. Turcaud, L. Favereau, J. Crassous, L. Micouin, E. Benedetti, *J. Org. Chem.* **2019**, *84*, 888–899; e) M.-L. Delcourt, S. Felder, S. Turcaud, C. H. Pollok, C. Merten, L. Micouin, E. Benedetti, *J. Org. Chem.* **2019**, *84*, 5369–5382.
[10] For selected examples of pCp-based chromophores, see: a) J. L. Zafra, A. Molina, P. Ontoria, M. Mayorga Burrezo, M. Pena-Alvarez, J. Samoc, F. J. Szeremeta, M. D. Ramirez Lovander, C. J. Droske, T. M. Pappenfus, L. Echegoyen, J. T. Lopez Navarrete, N. Martin, J. Casado J Am, *Chem. Soc.* **2017**, *139*, 3095–3105; b) J. W. Hong, H. Y. Woo, B. Liu, G. C. Bazan *J. Am. Chem. Soc.* **2005**, *127*, 7435–7443; c) H. Y. Woo, J. W. Hong, B. Liu, A. Mikhailovsky, D. Korystov, G. C. Bazan, *J. Am. Chem. Soc.* **2005**, 127, 820–821; d) G. P. Bartholomew, M. Rumi, S. J. K. Pond, J. W. Perry, S. Tretiak, G. C. Bazan *J. Am. Chem. Soc.* **2004**, *126*, 11529–11542; e) J. W. Hong, H. Benmansour, G. C. Bazan, *Chem. Eur. J.* **2003**, *9*, 3186–3192; f) M. Gon, Y. Morisaki, Y. Chujo, *Chem. Eur. J.* **2017**, *23*, 6323–6329.
[11] D. J. Cram, N. L. Allinger, *J. Am. Chem. Soc.* **1955**, *77*, 6289–6294.
[12] a) V. I. Rozenberg, E. V. Sergeeva, H. Hopf in *Modern Cyclophane Chemistry* (Eds.: R. Gleiter, H. Hopf) Wiley-VCH, Weinheim, **2004**, 435–462. For selected reviews, see; b) O. R. P. David, *Tetrahedron* **2012**, *68*, 8977–8993; c) S. E. Gibson, J. D. Knight, *Org. Biomol. Chem.* **2003**, *1*, 1256–1269.
[13] C. Zippel, E. Spuling, Z. Hassan, M. Polamo, M. Nieger, S. Bräse, *Chem. Eur. J.* **2020**, *26*, 13771–13775.
[14] J. F. Schneider, R. Froehlich, J. Paradies, *Synthesis* **2010**, *20*, 3486–3492.
[15] For a recent example of Rieche formylation on unsubstituted pCp, see: J. J. P. Kramer, C. Yildiz, M. Nieger, S. Bräse, *Eur. J. Org. Chem.* **2014**, 1287–1295.
[16] E. V. Sergeeva, V. I. Rozenberg, D. Y. Antonov, E. V. Vorontsov, Z. A. Starikova, I. V. Fedyanin, H. Hopf, *Chem. Eur. J.* **2005**, *11*, 6944–6961.
[17] a) G. Srinivas, M. Periasamy, *Tetrahedron Lett.* **2002**, *43*, 2785–2788; b) D. A. Baldwin R J H Clark, *J. Chem. Soc. A* **1971**, 1725–1727; c) D. C. Bradley, I. M. Thomas, *J. Chem. Soc.* **1960**, 3857–3861.
[18] C. Braun, M. Nieger, W. R. Thiel, S. Bräse, *Chem. Eur. J.* **2017**, *23*, 15474–15483.
[19] For more details, see the Supporting information.
[20] a) A. Vilsmeier, A. Haack, *Ber. Dtsch. Chem. Ges.* **1927**, *60*, 119–122; b) O. Meth-Cohn, S. P. Stanforth, *Comp. Org. Syn.* **1991**, *2*, 777–794; c) U. C. Dyer, D. A. Henderson, M. B. Mitchell, P. D. Tiffin, *Org. Process Res. Dev.* **2002**, *6*, 311–316.
[21] Wittig products (±)-**10a,b**, which incorporate both an amine electron-donating function and an α,β-unsaturated electron-withdrawing group, showed red-shifted absorption and emission bands compared to aldehyde (±)-**4a**. For more details, see the Supporting information.
[22] a) E. A. Merritt, V. M. T. Carneiro, L. F. Silva, B. Olofsson, *J. Org. Chem.* **2010**, *45*, 7416–7419; b) K. P. Jayasundera, D. N. M. Kusmus, L. Deuilhe, L. Etheridge, Z. Farrow, D. J. Lun, G. Kaur, G. J. Rowlands, *Org. Biomol. Chem.* **2016**, *14*, 10848–10860.

Manuscript received: March 8, 2021
Revised manuscript received: March 25, 2021
Accepted manuscript online: March 26, 2021

# COMMUNICATIONS

A regioselective formylation of N-substituted 4-amino[2.2] paracyclophanes is described, which allows an easy access to key synthetic intermediates which are useful for the preparation of a large variety of *para* di-substituted paracyclophanes in a straightforward manner.




*S. Felder, Dr. L. Micouin*, Dr. E. Benedetti**