Heck-type coupling of fused bicyclic vinylcyclopropanes: Synthesis of 1,2-dihydropyridines, 2,3-dihydro-1*H*-azepines, 1,4-cyclohexadienes, 2*H*-pyrans, and 1,3-butadienes.

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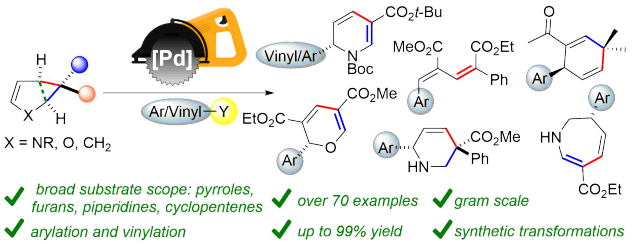
KEYWORDS donor-acceptor cyclopropanes, Heck coupling, 1,2-dihydropyridines, 2H-pyrans, 2,3-dihydro-1H-azepines, 1,4-cyclohexadienes.

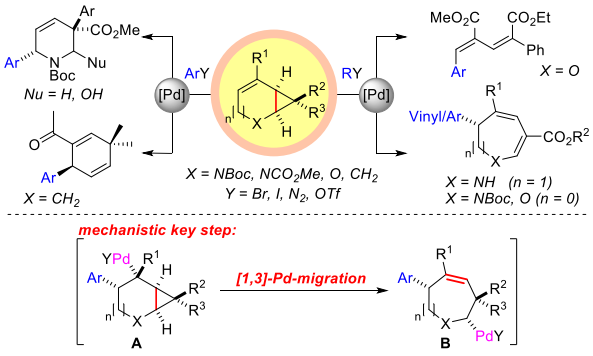
ABSTRACT: Herein, we report a versatile approach for the endocyclic ring-opening of bicyclic vinylcyclopropanes triggered by Heck arylations. Key step for this transformation is a [1,3]-migratory shift of Pd allowing the ring expansion of cyclopropanated pyrroles, piperidines, furans as well as cyclopentadienes to grant access to the corresponding 1,2-dihydropyridines, 2*H*-pyrans, 2,3-dihydro-1*H*-azepines and 1,4-cyclohexadienes, respectively. Additionally, *gem*-disubstituted cyclopropanated furans showed unexpected behavior by giving diastereoselectively asymmetrically substituted dienes. Mechanistic studies and theoretical calculations point towards a facile [1,3]-migratory shift of Pd along the cyclopropane moiety, which can successfully compete with the usual termination step of a Heck reaction via a *syn*-β-hydride elimination.



INTRODUCTION

The utility of vinylcyclopropanes has been proven in numerous synthetic procedures.[1] These compounds may undergo various types of rearrangements[2], nucleophilic and electrophilic ring-opening reactions[3] as well as participate as three-[4] or five-carbon[5] components in cycloadditions. The fragmentation of the three-membered ring is mostly achieved by the use of Lewis acids or transition metal catalysts. While the applicability of the first approach is usually limited to donor-acceptor-substituted substrates, the second strategy is more general and may be also employed to cleave non-activated bonds.[6]

Scheme 1. Heck-type Coupling of Bicyclic Cyclopropanes.



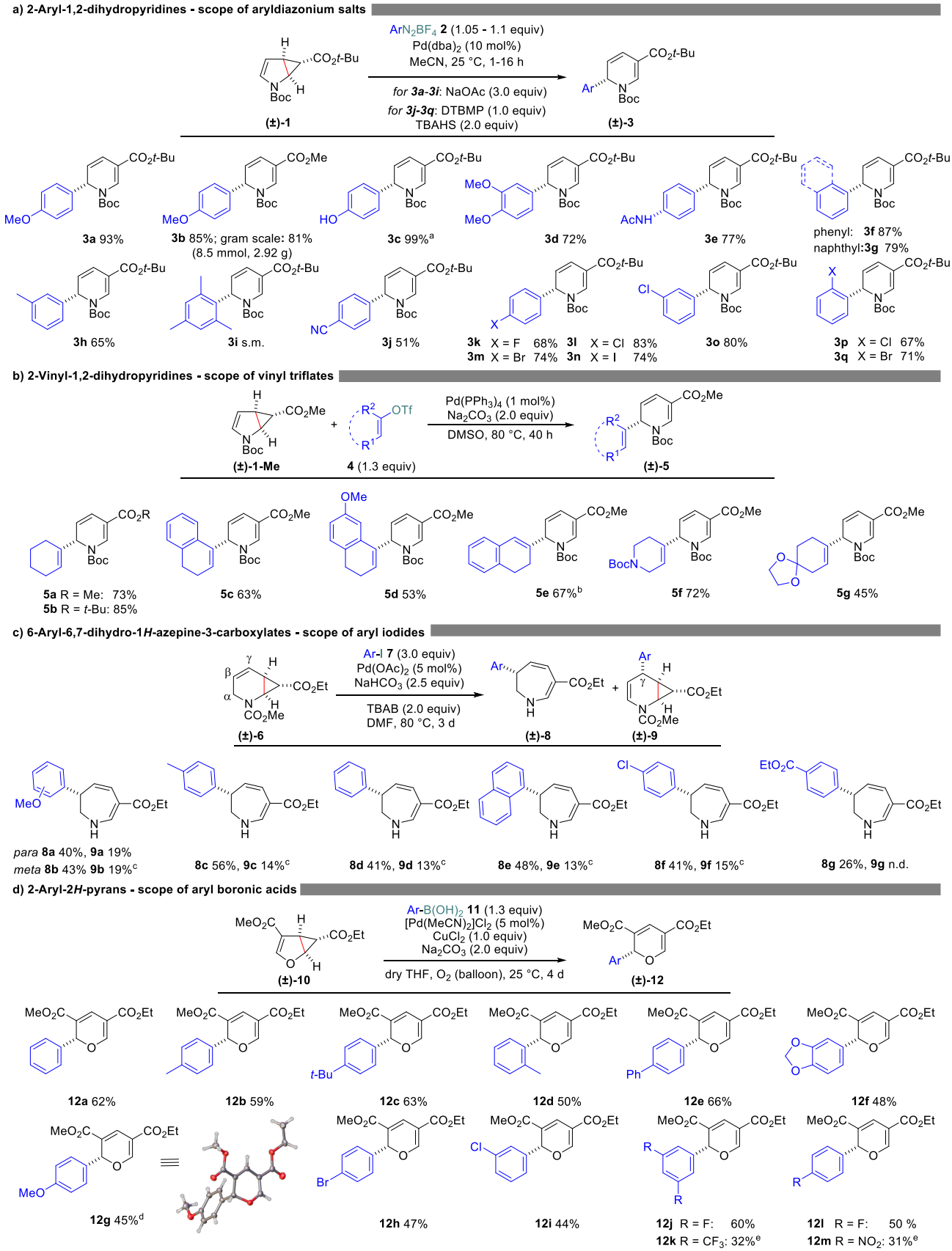
One example for such transformation was presented by our group in 2019 via the palladium catalyzed coupling of cyclopropanated furans and pyrroles with aryl halides,[7] which provides the corresponding 1,2-dihydropyridines and 2*H*-pyrans, respectively. The observed reaction outcome may be rationalized by the initial Heck-adduct **A** that can neither undergo a β-dehydropalladation nor reductive elimination, thus the only possibility for the catalytic cycle to proceed further is by a [1,3]-migration of Pd to provide six-membered species **B** (Scheme 1).[7] These reactions proceed with complete chirality transfer, being rationalized by an attack of the organopalladium species from the convex face of the bicycle.

Based on this mechanistic hypothesis we report here the extension of this strategy to other types of fused cyclopropanes like piperidines or cyclopentadienes. Of our particular interest were *gem*-disubstituted substrates (R^2, $R^3 \neq H$) in the case of which elimination of HPdY from organopalladium intermediate of type **B** is not possible.[7] Moreover, we were able to develop improved protocols, making aryldiazonium salts, vinyltriflates and arylboronic acids suitable coupling partners for the bicyclic cyclopropanes, resulting not only in ring expanded products but also in geometrically pure, highly substituted 1,3-butadienes. Mechanistic and theoretical studies to gain insight into the 1,3-migration of palladium along the cyclopropylmethylene framework, representing the key step of the ring-enlargement, are presented as well.

RESULTS AND DISCUSSION

Our preliminary study had shown that, although feasible, arylhalides are sluggish coupling reagents for pyrroles **1**.[7] Turning to aryldiazonium salts being generally more reactive in Heck-type coupling,[8] led to identification of $Pd(dba)_2$, NaOAc, in MeCN, at 25 °C as the optimal reaction parameters (Scheme 2a; for detailed optimization studies, see Supporting Information). Under these conditions a variety of diazonium salts containing electron-donating groups (**2a**-**2e, 2h**) or an unsubstituted aromatic ring (**2f, 2g**) could be successfully coupled to pyrrolidine **3** giving the corresponding products **5** in good to excellent yields (65-99%). Moreover, the reaction tolerated halogen- and nitrile-substituted substrates (**2j**-**2q**). For the latter better results were, however, obtained using a slightly modified procedure i.e. employing 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) as a base in combination with tetrabutylammonium hydrogen sulfate (TBAHS). Noteworthy, this protocol

Scheme 2. Ring-Expansion of Monocyclopropanated Pyrroles, Piperidine and Furan.



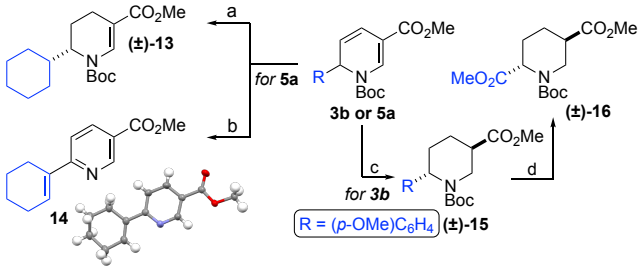
s.m. = starting material; n.d. = not detected. [a]Reaction was performed using 0.5 mmol of salt 2c and 0.75 mmol (1.5 equiv) of cyclopropanated pyrrole 1. Yield based on tetrafluoroborate 2c. [b] reaction time 18 h. [c] NMR yield. [d] Reaction was stirred for 7 d. [e] 3.0 equiv of boronic acid was used.

allowed to upscale the reaction to give 2.92 g (8.5 mmol, 81%) of product **3b**. Initial attempts on performing the analogous vinylation of cyclopropanated pyrroles using vinyl halides gave unsatisfactory results, the application of triflates[9] **4** enabled the preparation of dihydropyridines **5** in good yields on a variety of different substrates including cyclohexenes and dihydronaphthalenes (Scheme 2b). The efficiency of the process could be further enhanced by replacing the methyl ester moiety in substrate **1-Me** with a *tert*-butyl group (*cf.* **5a** and **5b**). Remarkably, the vinylations proceeded well by using only 1 mol% of catalyst.

Furthermore, the application of the title reaction to piperidine derivative **6** allowed the expansion from six to seven membered ring systems to give access to dihydro-1*H*-azepines **8** (Scheme 2c) using aryl iodides as coupling reagents. These products formed, however, among noticeable amounts of γ-arylated bicycles **9** which are the results of an initial carbopalladation with inverse regioselectivity.

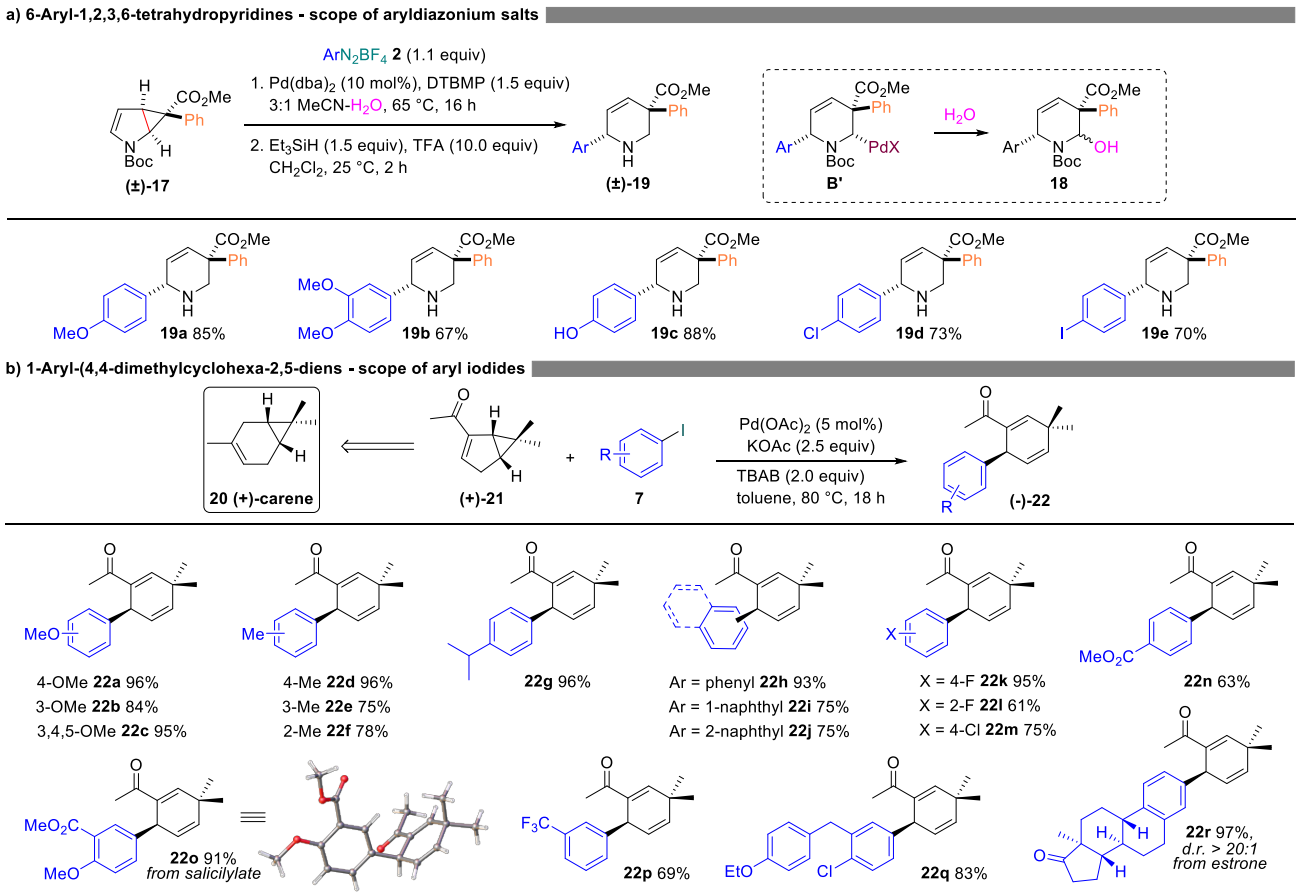
Lastly, we turned our attention to cyclopropanated furan **10**. To improve on the reductive Heck protocol initially developed for this substrate,[7] we evaluated an oxidative variant.[6b,10] The optimized protocol was established using phenylboronic acid as a model substrate and encompassed the use of $[Pd(MeCN)_2Cl_2]$, $CuCl_2$ and Na_2CO_3, in THF (for details, see Supporting Information). These conditions were compatible with a variety of aryl boronic acids, whereby moderately donating substrates containing an alkyl or an aryl moiety exhibited the highest reactivity, while strongly electron deficient aryl boronic acids showed only poor efficiency. As demonstrated with the synthesis of compound **12d**, the process tolerated not only *para* and *meta*, but also *ortho* substitution of the aromatic ring.

Scheme 3. Synthetic Application of Vinyl Dihydropyridines 3b and 5a.



Conditions: a) H_2 (40 bar), Pd/C (7 mol%), MeOH, 25 °C, 18 h, 69%; b) DDQ (2.0 equiv) toluene, 0 to 25 °C, 18 h, 70% c) i) *step 1:* H_2 (balloon), Pd/C, THF, 25 °C, 16 h, 75%; *step 2:* Et_3SiH (3 equiv), TFA (1.8 mL), 50 °C, 3 h, 75%; ii) Boc_2O (1.5 equiv), DMAP (0.1 equiv), CH_2Cl_2, 25 °C, 16 h 81%; d) $RuCl_3$ (0.12 equiv), $NaIO_4$ (17 equiv), EtOAc:H_2O:MeCN (1:2:1), 25 °C, 4 h; iv) CH_2N_2, Et_2O, 75%.

Scheme 4. Ring expansion of *gem*-disubstituted cyclopropanes.

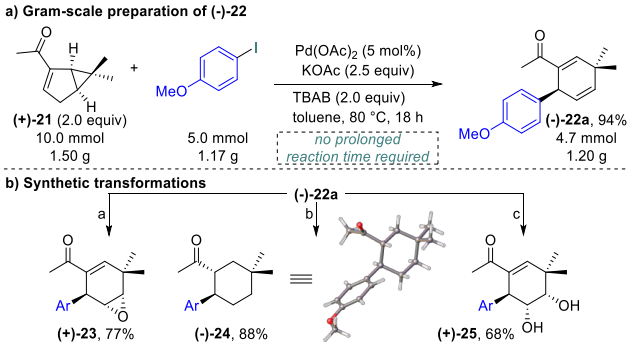


Complementary to our previous report[7] we exemplified the possible transformations of the alkenyl moiety introduced in the developed Heck reaction (Scheme 3). Therefore, we conducted hydrogenation of derivative **5a**, which proceeded with concomitant reduction of the less substituted double bond of the heterocycle to furnish tetrahydropyridine **13** being the product of a formal alkyl coupling. Furthermore, treatment of derivative **5a** with DDQ resulted in selective oxidation of the piperidine ring to furnish **14**. The synthesis of **16** being a hybrid of pipecolic and nipecotic acid being individually attractive building blocks in medicinal chemistry,[11] was, in turn, achieved from compound **3b** *via* oxidation of the aryl ring using $RuCl_3$-$NaIO_4$ system.[12]

Further studies concerned ring expansion of *gem*-disubstituted cyclopropane **17** (Scheme 4a)**.** Since the organopalladium intermediate **B'** is not able to undergo β-dehydropalladation, it was necessary to employ a nucleophile in the reaction capable to displace palladium in this species.[13] Thus, performing the coupling reaction in water, initially tetrahydropyridine derivatives **18** were obtained, which were without isolation subjected to reduction with Et_3SiH/TFA. As a result of these studies, a range of tetrahydropyridines **19** became accessible in good yields.

Switching to carbocycles, bicycle **(+)-21** bearing an enone system, which was prepared from (+)-carene **20**,[14] appeared to be an attractive substrate for our ring-opening protocol (Scheme 4b). To our delight, arylations of this substrate proceeded cleanly and regioselectively to give desired 1,4-cyclohexadienes **(-)-22** in very good to excellent yields. The process featured a broad substrate scope, which encompassed aryl iodides bearing electron-donating and/or electron-withdrawing substituents, sterically demanding moieties and the late stage functionalization of estrone to **22r**. Importantly, scaling up the process to a 5.0 mmol scale did not influence the reaction yield or time affording 1.20 g of (-)-**22a**. (Scheme 5a) All reaction proceeded with excellent chirality transfer dictated by the initial attack of ArPdX from the convex side of the bicyclic system. As an illustration of possible synthetic applications of the obtained products we conducted additionally epoxidation, dihydroxylation and hydrogenation of derivative (-)-**22a** (Scheme 5b).

Scheme 5. Scale-up experiment and transformations of product (-)-22a.

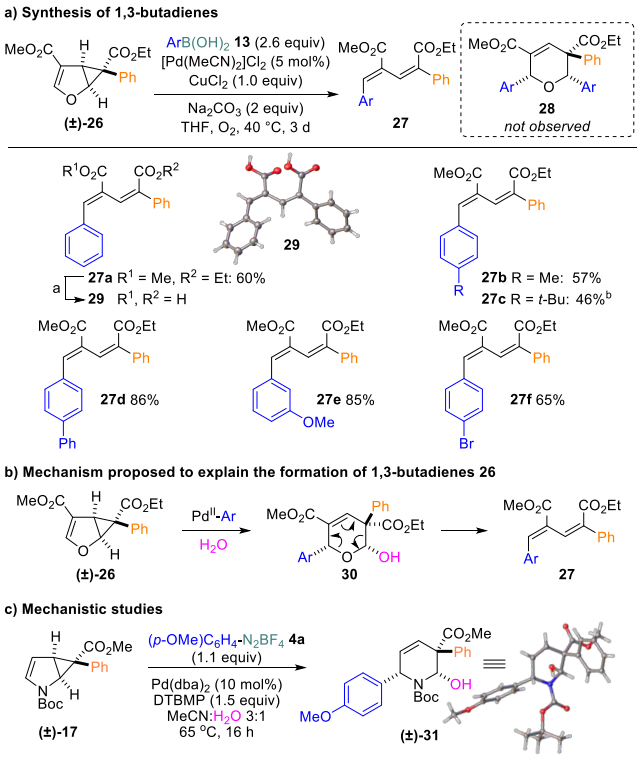


a) *m*-CPBA (2.0 equiv), DCM, 25 °C, 2 h, 77%, b) NH_4CO_2H (40.0 equiv), Pd/C (10 mol%), MeOH, 25 °C, 18 h, 88% c) $K_2OsO_4{\cdot}2H_2O$ (5 mol%), NMO (2.0 equiv), acetone:H_2O 2:1, 48 h, 68%. Stereochemistry of compounds **23** and **25** could not be determined. *Trans*-selectivity was tentatively assigned in analogy to literature.[15]

Finally, we examined arylation of cyclopropanated furan **26**. After preliminary attempts similar to pyrrole **17** using reductive Heck conditions (Scheme 4a) remained to be unsuccessful, we returned to the oxidative approach. In principle, this procedure would allow us to generate doubly arylated pyrans **28** by undergoing a second transmetalation with aryl boronic acid during the organo-palladium intermediate of type **B'** (*cf.* Scheme 4a). Surprisingly, subjecting **26** to reactions conditions resulted in the formation of highly substituted butadienes **27** instead(Scheme 6a). All reactions proceeded with complete stereoselectivity, whereby the yield varied between 46% and 86%. The configuration of the diene system was confirmed by X-Ray crystallography after saponification of **27a** to dicarboxylic acid **29**.

The clean diastereoselectivity as well as the nature of the products indicate that the reaction might involve a formal retro-Diels-Alder fragmentation pathway *via* intermediate **30** (Scheme 6b). This species could result, in turn, from trapping of the generated six-membered organopalladium intermediate by water formed in stochiometric amounts during the course of the reaction (Pd^{II}-Cu^{I}-O_2). The postulated formation of intermediate **30** is supported by the isolation of lactamol **31** from the reaction of pyrrole **17** in aqueous CH_3CN (Scheme 6c). A retro-Diels-Alder type fragmentation from **28** as a potential intermediate can be ruled out as no benzaldehydes or their corresponding carboxylic acids were observed as byproducts.

Scheme 6. Synthesis of 1,3-Butadiens 27 from cyclopropanated furan 26

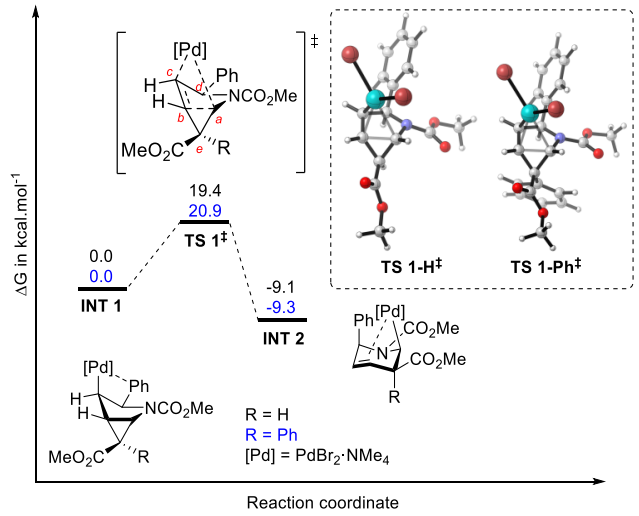


a) LiOH (40 equiv), THF:H_2O 1:1, reflux, 18 h, 97%. [b] Reaction performed at 55 °C.

Theoretical Part

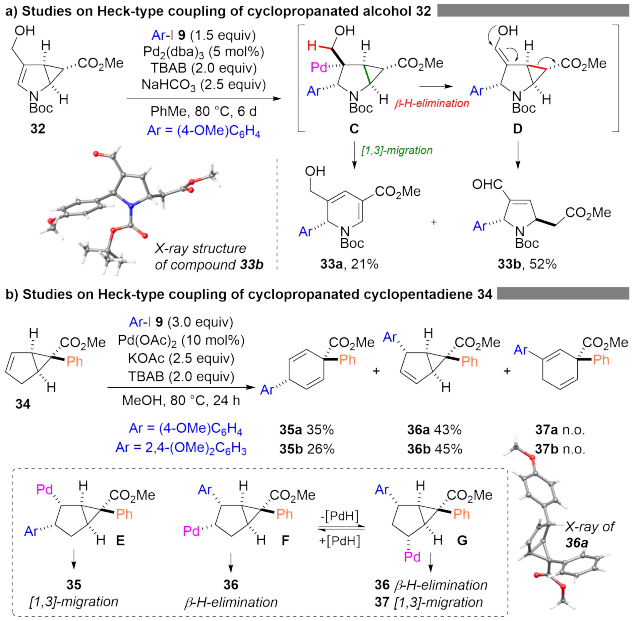
The key mechanistic step of the Pd-migration under simultaneous ring-opening of the cyclopropyl ring was evaluated for the transformation of cyclopropyl substrates (**1**, **17**) via DFT calculations (Scheme 7, details see SI). Based on these computational results the cyclopropyl ring opening starting, after addition of $ArPd^+$ to **1** or **17**, at compounds **INT-1** is accompanied by the migration of the Pd from position *c* to position *a*. For cationic Pd-complexes **INT-1** obtained after the carbopalladation this step exhibits a low energy barrier ($\Delta G^{\ddagger}$ = 19.4 kcal/mol for **1**, $\Delta G^{\ddagger}$ = 20.9 kcal/mol for **17**, Scheme 7). The associated transition state structure is characterized by an elongation of the *a*-*b* bond by 10%, of the Pd-C^c-bond by 1.5% and by a shortening of the Pd-C^a bond by 11%. The envelope conformation of the five membered ring system enables the approach of palladium to the C^a-C^b-σ-bond being cleaved. The dihedral angle defined by C^a-C^b-C^c-Pd is approximately 66° in contrast to the roughly planar transition states for the migratory insertion of aryl palladium complexes in alkenes and typical *ß-syn*-hydride eliminations.[16] In relation to the usual activation barriers within the Heck-cycle like the oxidative addition, carbo-palladation and the base-assisted asynchronous E2-eliminations of the Pd leading to the final product, the barrier of the ring-enlargement/Pd-migration is clearly not turn-over-limiting.[17]

Scheme 7. Mechanistic key step featuring the ring-opening – Pd-migration.



This low-lying energy barrier became also apparent subjecting pyrrole **32** to Heck conditions (Scheme 8a). After initial addition of ArPdY to **C**, this intermediate can undergo β-H-elimination to **D**, thus competing with the [1,3]-Pd migration leading to endocyclic ring-opening. Indeed, both products **33a**:**33b** could be isolated in a ratio of approximately 1:2.5 illustrating that the β-H-elimination offers only a minor energetic advantage.

Scheme 8. Mechanistic experiments – [1,3]-migration vs. β-H-elimination



Further mechanistic studies were performed subjecting carbocycle **34** to the title reaction (Scheme 8b). An interesting feature of this substrate is the fact that also "wrong" adduct **F** may, after palladium migration[18] to **G**, undergo opening of the endocyclic cyclopropane bond. However, regardless of the employed conditions, arylation of bicycle **34** provided compound **36** as the major product, while the formation of isomer **37** was not observed. In contrast, formation of **35** was observed in moderate yields, which must have arisen from **E**, indicating that in this case the β-H-elimination outcompetes the palladium migration.

In summary, we have developed highly comprehensive protocols for the Heck-reaction-triggered endocyclic ring-opening of cyclopropanated hetero- and carbocycles including pyrroles, piperidines, furans as well as cyclopentadienes to grant access to the corresponding 1,2-dihydropyridines, 2*H*-pyrans, 2,3-dihydro-1*H*-azepines, 1,4-cyclohexadienes and 1,3-butadienes. The robustness of this approach was demonstrated with an extensive substrate scope featuring variously substituted aryl and vinyl residues and the synthetic utility was showcased by gram scale experiments as well as representative synthetic transformations of the obtained products. Noteworthy protocols could be developed that allowed to activate *gem*-disubstituted cyclopropanated pyrroles and furans, being readily available starting materials using donor-acceptor diazo acetates.[19] Surprisingly, *gem*-disubstituted cyclopropanated furans resulted in the diastereoselective formation of highly, asymmetrically substituted dienes. Lastly, we demonstrated by DFT calculations as well as complementary mechanistic studies that the [1,3]-palladium migration with concomitant opening of the endocyclic bond as mechanic key step only bears a low energy barrier therefore driving the reaction.

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Notes

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