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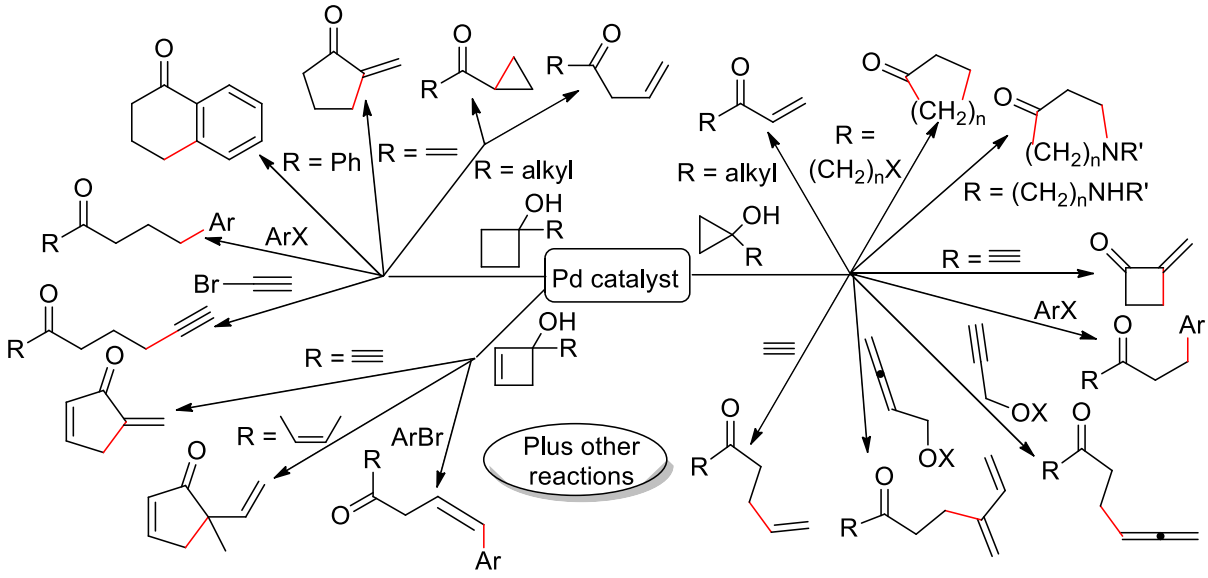
Graphical abstract.



Abstract. The exploitation of the ring strain of cyclopropanols, cyclobutanols and cyclobutenols has led to a variety of Pd-catalyzed reactions, especially when the ring is substituted with other functions. Cross-coupling and domino reactions have also been reported. The present review gathers together the literature results with special attention to the procedures. Proposed mechanisms are described with, in some cases, personal comments.

Keywords: Palladium, Catalysis; Strained cycla(e)nols; Ring expansion; Ring contraction; Domino reactions

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1. Introduction

Cyclopropanols, cyclobutanols and cyclobutenols undergo a variety of reactions depending on the nature of substituents and reactants.[1] Their ring-opening is favored by the high strain energy of these small carbocycles (Figure 1).[2] The tendency of the cyclopropane to coordinate with transition metals resembles with the property of unsaturated compounds to act as π-ligands.[3] The π character of the ring is exemplified by the ultra-violet properties of α-cyclopropylketones which are closer to those of conjugated enones than of saturated ketones.[4] Cyclobutane is often considered as the "big brother" of cyclopropane, with similar properties and reactivity.[1e] Consequently, cyclopropanols, cyclobutanols and cyclobutenols could be considered like di-functionalized compounds. Their reactivity under palladium catalysis led to a number of reports and remains the subject of an active research. The present review highlights these Pd-catalyzed transformations,[5] and is organized according to the nature of the substrate and the intra- or intermolecular participation of other reactive entities. Similar reactions have been sometimes reported from siloxycyclopropanes and siloxycyclobutanes; they are included in the review.

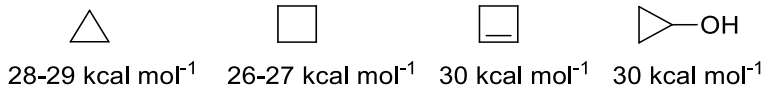


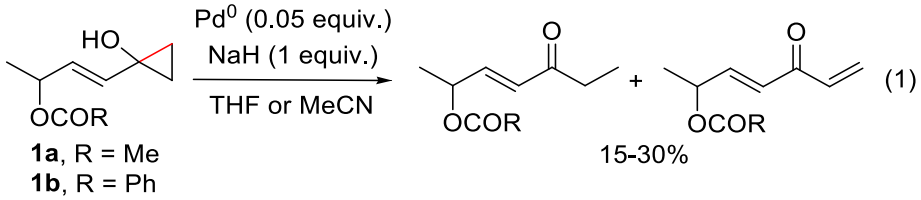
Figure 1. Ring strain energy of cyclopropane, cyclobutane, cyclobutene and cyclopropanol.

2. Cyclopropanols

In the presence of a palladium catalyst, cyclopropanols undergo rearrangement to enones or reaction with a function belonging either to a ring substituent or to another partner.

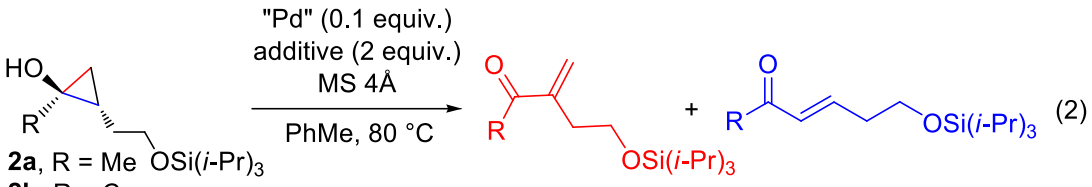
2.1. Conversion to enones

This subchapter is devoted to the formation of enones without participation of any other function.
In 1990, Meijere, Salaün and co-workers isolated low yields of a 1:1 mixture of conjugated enones and dienones from the treatment of (*E*)-4-(1-hydroxycyclopropyl)but-3-en-2-yl acetate (**1a**) or benzoate (**1b**) with NaH and a Pd^0 catalyst *in situ* prepared from $Pd(OAc)_2$ or $Pd(dba)_2$ and dppe (Eq. 1).[6]



Effective procedures for the transformation of the cyclopropanols **1c**-**1f** and **2a**-**2c** into the corresponding α,β-enones have been reported in 2000 by the teams of Cha and Okumoto

(Eqs 2 to 4).[7,8] Cha's team obtained the best yields in toluene using $Pd(OAc)_2$ as the catalyst and DMSO as the additive under oxygen (Eq. 2).[7] The ability of the DMSO/O_2 association to regenerate Pd^{II} from Pd^0 has been revealed by Larock and Hightower.[9-11] Nevertheless, the authors also obtained an efficient reaction under nitrogen atmosphere (Eq. 2). According to Okumoto's team, $Pd(dba)_2$ in MeCN was the optimum system for the reaction of **1c-1f** and **2c** but may lead to the saturated ketone as side-product (Eqs 3 and 4).[8] The latter was selectively produced with $PdCl_2$ in MeCN (Eq. 3).

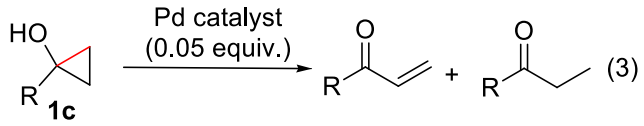


(2)

2a, R = Me
2b, R = Cy

From **2a**	$Pd(OAc)_2$, pyridine, O_2, 4 h:	69%	18%
	$Pd(OAc)_2$, DMSO, O_2, 1.5 h:	75%	18%
	$Pd_2(dba)_3$, DMSO, O_2, 1 h:	60%	17%
	$Pd_2(dba)_3$, BQ,[a] O_2, 1 h:	79%	0%
From **2b**	$Pd(OAc)_2$,[b] DMSO, N_2, 4 h:	73%	11%
	$Pd_2(dba)_3$, BQ,[a] O_2, 1 h:	76%	0%

[a]BQ = 1,4 benzoquinone
[b]Using 0.2 equiv. of $Pd(OAc)_2$.



(3)

1c, R = $BnCH_2$
in MeCN at 50 °C for 20 h

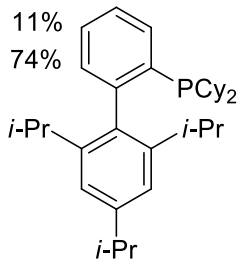
$Pd(OAc)_2$:	78%	16%
$PdCl_2$:	0%	99%
$Pd(dba)_2$:	98%	1%
5% Pd/C:	71%	11%

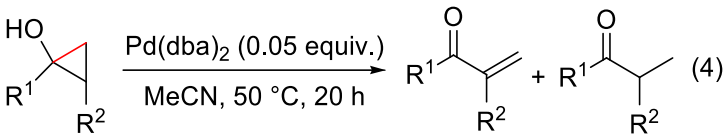
1g, R = Bn
with XPhos (0.1 equiv.) in PhMe at 25 °C for 16 h

$Pd(dba)_2$:[a]		2%
$Pd(OAc)_2$:[b]	4%	11%
$Pd(OAc)_2$, MeONa (1 equiv.):		74%

[a]2% conversion.
[b]34% conversion.

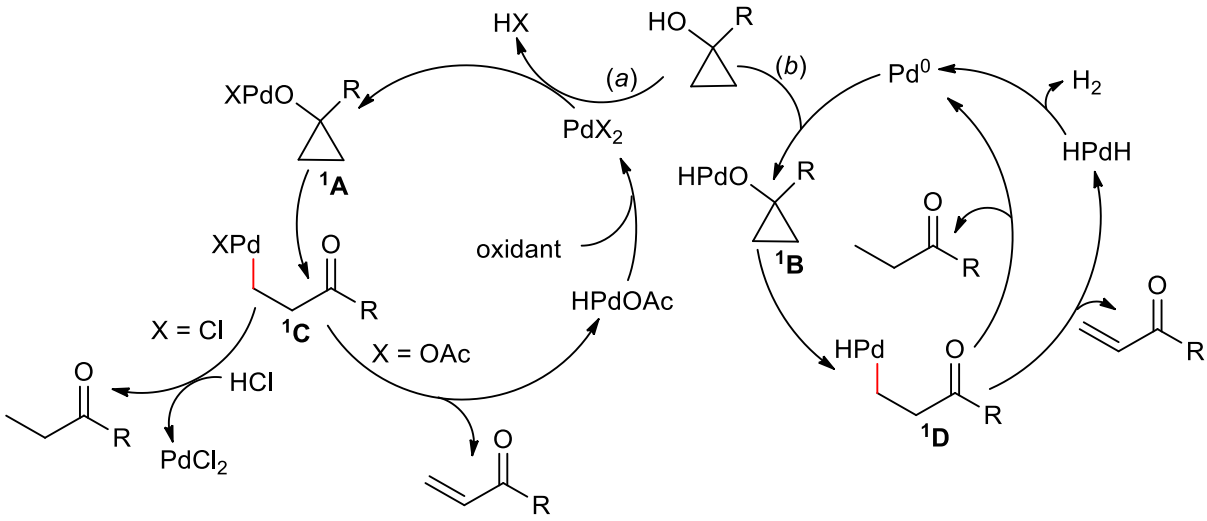
XPhos:





1d, R^1 = $BzO(CH_2)_3$, R^2 = H:	31%	22%
1e, R^1 = Ph, R^2 = H:	48%	6%
1f, R^1 = 3-cyclohexenyl, R^2 = H:	46%	2%
2c, R^1 = $BnCH_2$, R^2 = Me:	77%	5%

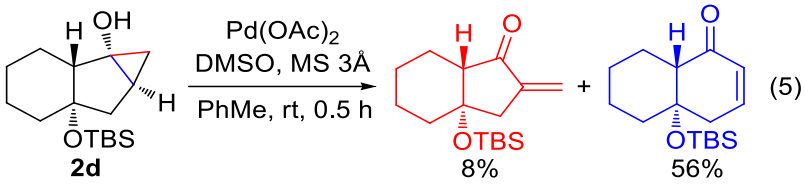
Two catalytic cycles depending on the Pd oxidation state have been proposed (Scheme 1, paths *a*[7] and *b*).[8] Reaction of palladium with the O-H bond leads to either ^{1}**A** or ^{1}**B**. Subsequent cleavage of the C-C bond provides ^{1}**C** and ^{1}**D**, respectively. Theses intermediates may undergo β-H elimination to deliver the enone and either HPdOAc or HPdH. $Pd(OAc)_2$ is regenerated from HPdOAc with the oxidant, while expulsion of H_2 from HPdH leads to Pd^0. The saturated ketone is obtained either from protonolysis of ^{1}**C**, or from ^{1}**D** via reductive elimination of Pd^0. Note that under Pt-catalysis, a platinacyclobutane ring formed from oxidative insertion of Pt into the cyclopropyl unit is assumed as a key intermediate.[3]

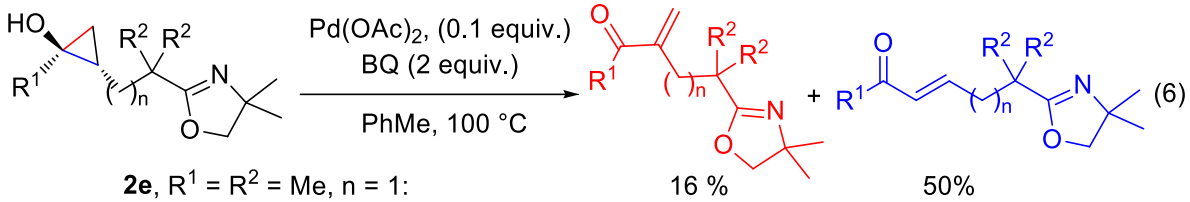


Scheme 1

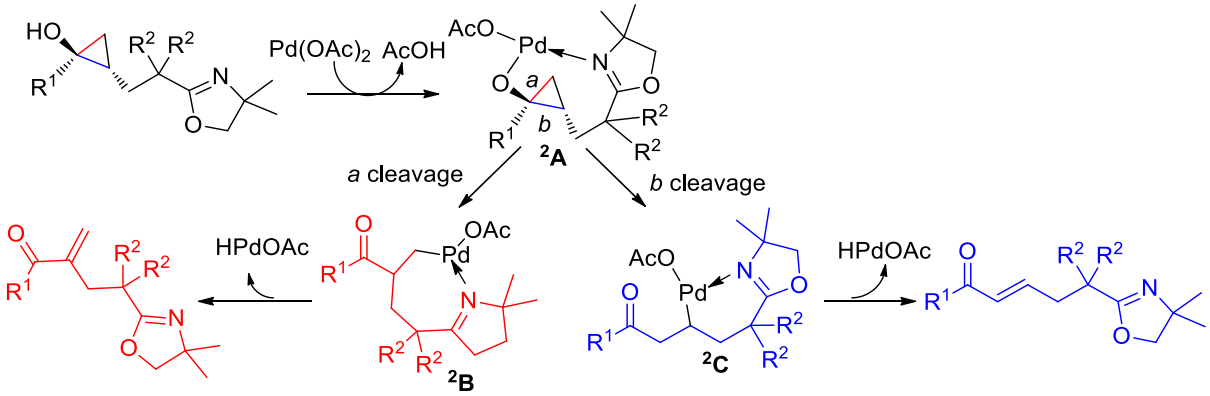
In the course of mechanism studies of Pd^0-catalyzed cross-coupling reactions (see Subchapter 2.3.4.), Ma's team studied the reactivity of 1-benzylcyclopropanol (**1g**) using $Pd(dba)_2$ or $Pd(OAc)_2$ and a Buchwald ligand – 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl (XPhos)[12] – (Eq. 3).[13] After 16 h in toluene at 25 °C, 98% of **1g** was recovered with the first association whereas the second led to a better conversion with formation of an approximatively 3:1 mixture of 1-phenylbutan-2-one and 1-phenylbut-3-en-2-one. The former was selectively obtained with MeONa as additive. We however suspect that, under these last conditions, the tautomerization would be due to the basic media[1a,1b] rather than Pd catalysis. The reaction of trisubstituted cyclopropanols **2a**-**2c** mainly or selectively involved the cleavage of the less substituted C-C bond, whereas that of the more substituted C-C bond of tricyclic substrate **2d** (Eq. 5)[7] or oxazoline-tethered cyclopropanols **2e**-**2i** (Eq. 6)[14] was preferred. From **2e**-**2i**, the selectivity towards the β-substituted α,β-unsaturated ketone would be due to the directing role of the oxazoline (Scheme 2): the *a* cleavage of alkoxypalladium intermediate ^{2}**A**

leads to the seven-membered palladacycle ^{2}**B** whereas the *b* cleavage provides the more favorable six-membered palladacycle ^{2}**C**.[14] From **2j**, the distance between the oxazoline and the three-membered ring (Eq. 6, n = 2) precludes efficient N/Pd interactions, hence the cleavage of the less substituted C-C bond to afford the α-substituted α,β-unsaturated ketone.



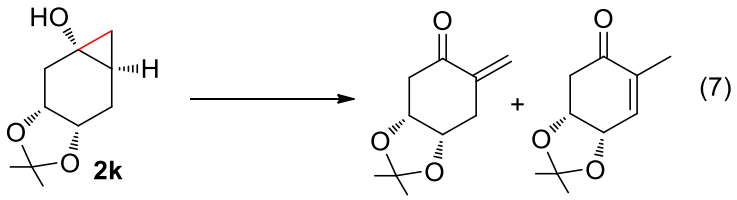


2e, $R^1 = R^2$ = Me, n = 1:	16 %	50%
2f, R^1 = *i*-Pr, R^2 = Me, n = 1:	6%	57%
2g, $R^1 = (CH_2)_2Ph$, R^2 = Me, n = 1:	9%	41%
2h, $R^1 = (CH_2)_3Cl$, R^2 = Me, n = 1:	6 %	42%
2i, R^1 = Me, R^2 = H, n = 1:	13%	22%
2j, $R^1 = R^2$ = Me, n = 2:	58%	<1%

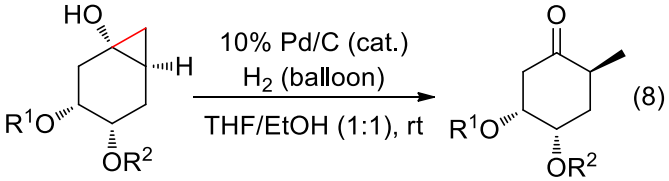


Scheme 2

The reaction of **2k** with a stoichiometric amount of $Pd(OAc)_2$ and 2 equiv. of pyridine in toluene at 80 °C provided a mixture of *exo*- and *endo*-cyclohexenones (Eq. 7).[15] With benzoquinone (BQ) as additive or with Pd/C as the catalyst in THF/EtOH at room temperature, the reaction led selectively to the *exo*-compound (Eq. 7). Under hydrogen atmosphere, these last conditions produced cyclohexanones from **2k** and **2l** (Eq. 8).[16]

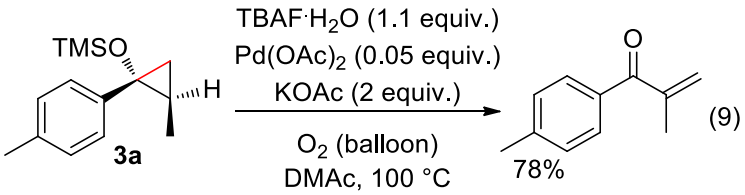


- $Pd(OAc)_2$ (1.04 equiv.), pyridine (2 equiv.), PhMe, 80 °C, 3 h: *exo* (31 %) + *endo* (55%)
- $Pd(OAc)_2$ (1.2 equiv.), pyridine (2.2 equiv.), BQ (2 equiv.), PhMe, 80 °C, 3 h: *exo* (70 %) + **2k** (10%)
- 10% Pd/C (1.1 equiv.), THF/EtOH (1:1), rt, 24 h: *exo* exclusively



2k, R^1-R^2 = CMe_2, 12 h: 80%
2l, R^1 = R^2 = H, 5 h: 82%

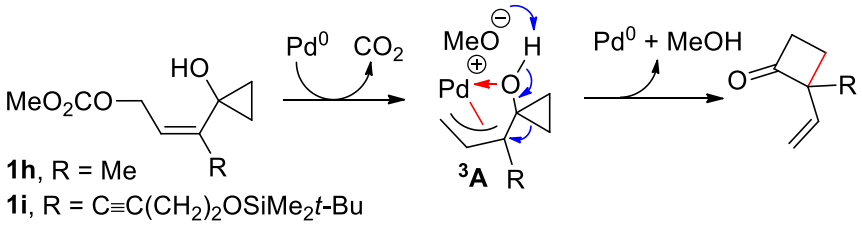
Under Pd^{II} catalysis and oxygen atmosphere, the domino deprotection/rearrangement reaction of TMS-protected cyclopropanol **3a** occurred at 100 °C in dimethyl acetamide containing both $TBAF{\cdot}H_2O$ and KOAc, leading selectively to the corresponding α,β-unsaturated ketone (Eq. 9).[17]



2.2. Intramolecular reactions

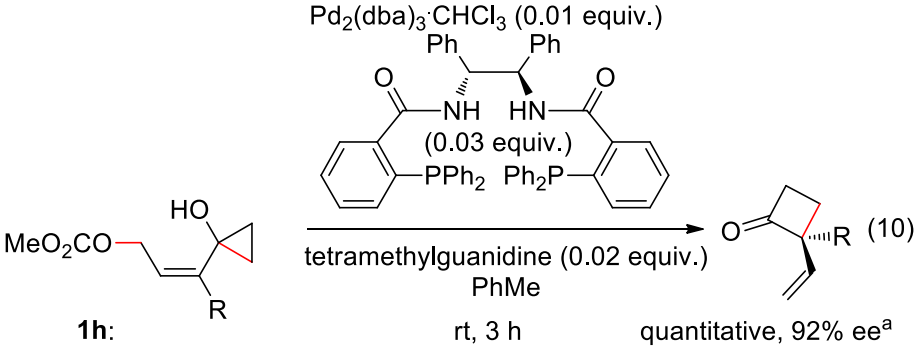
2.2.1. With an allyl carbonate

Trost and Yasukata disclosed Pd^0-catalyzed efficient C-3 → C-4 ring expansions of 1-(1-substituted-3-methoxycarbonyloxy-1-propenyl)cyclopropanols **1h** and **1i**, that occurred via η^3-allylpalladium ^{3}**A** (Scheme 3).[18] Enantioselective reactions were performed using chiral ligands with efficiency improved in the presence of a base, especially tetramethylguanidine (Eq. 10). This ring expansion contrasts with the rearrangement of **1a** and **1b** previously reported by Salaün and co-workers (Eq. 1). Contrary to **1a** and **1b**, the C=C bond of **1h** and **1i** has a *Z*-configuration, and the sp^2 carbon in α-position of the cyclopropanol is disubstituted. We suggest that the *cis*-relationship between the cyclopropanoyl unit and the leaving group makes easier the coordination of the hydroxy group to palladium depicted in ^{3}**A**. This facilitates the O-H bond cleavage, while the disubstitution promotes the subsequent carbon-to-carbon 1,2-migration to the tertiary terminus.



1h, R = Me
1i, R = C≡C(CH$_2$)$_2$OSiMe$_2$*t*-Bu

Scheme 3

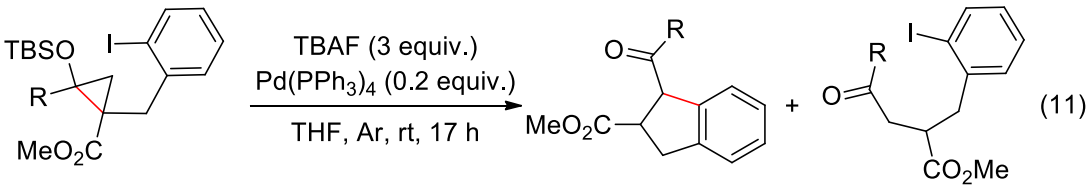


1h:	rt, 3 h	quantitative, 92% ee[a]
1i:	0 °C, 8 h	91%, 89% ee

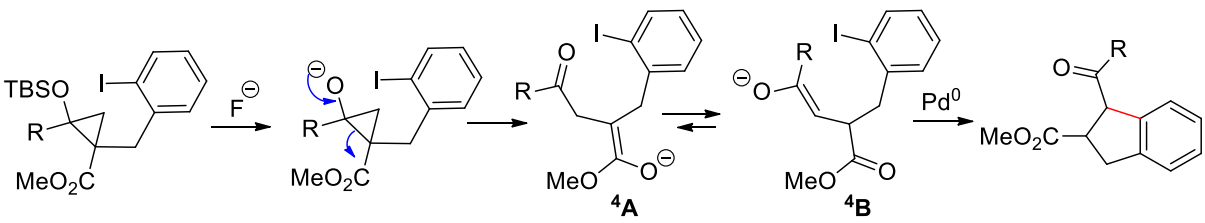
[a]85% ee in the absence of tetramethylguanidine.

2.2.2. With an arylating entity

In 1996, Reissig's team disclosed the Pd-catalyzed transformations mediated with CsF or TBAF of *t*-butyldimethylsilyl ethers of *o*-iodobenzyl-tethered cyclopropanols **4a**-**4d** into indane derivatives (Eq. 11).[19,20] According to the authors, treatment of the substrate by -fluoride leads to ester enolate ^{4}**A** via cleavage of the more substituted bond of the small ring (Scheme 4).[21] Equilibration to more stable ketone enolate ^{4}**B**[20] is followed by Pd-catalyzed intramolecular enolate arylation.[22] The formation of the ring-opened product (Eq. 11) obtained as side-product from **4d** or selectively from **4e** consolidates this proposal.

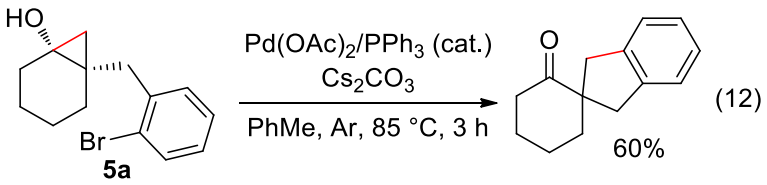


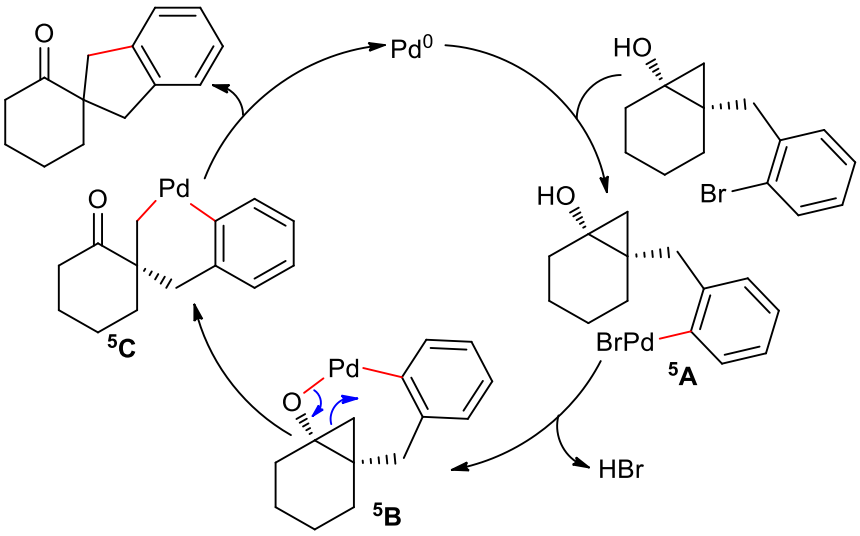
4a, R = Ph:	61%	
4b, R = Me:	51%	
4c, R = *t*-Bu:	68%	
4d, R = 1-cyclohexenyl:	33%	17%
4e, R = isopropenyl:	0%	24%



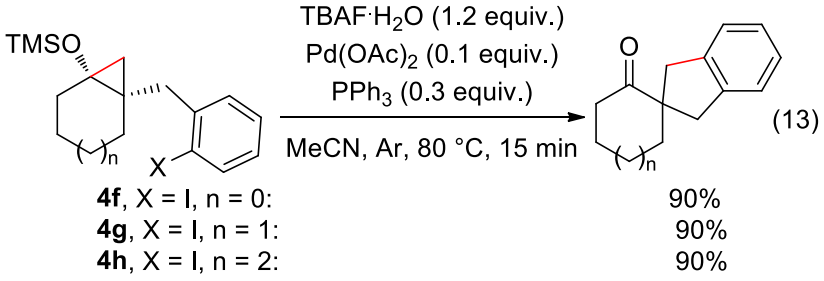
Scheme 4

Five years later, an indane derivative was also obtained by Orellana and Rosa from the Pd-catalyzed reaction of *o*-bromobenzyl-tethered cyclopropanol **5a**, but via the cleavage of the less substituted HOC-C bond of the ring (Eq. 12).[23] The proposed mechanism implicates the oxidative addition of palladium to the aryl bromide leading to ^{5}**A** (Scheme 5). Reaction of ^{5}**A** with the hydroxyl gives the alkoxypalladium complex ^{5}**B**, which undergoes three-membered ring cleavage leading to ^{5}**C**. Subsequent reductive elimination of Pd^{0} delivers the spirocyclic ketone. The authors speculated that the modest yield obtained from **5a** could be due to the decomposition of the cyclopropanol under the reaction conditions. Thus, the authors, who apparently were not aware of Reissig's paper, studied the reaction starting with trimethylsilyl ethers **4f-4h**. Screening various fluoride sources and solvents provided the best results with TBAF·H_2O and MeCN (Eq. 13). The reaction of **4f-4h** could occur similarly to that of **5a** (Scheme 5).[23] We propose an alternative reaction pathway consisting in the intramolecular arylation of the homoenolate formed from fluoride-mediated ring opening of the substrate



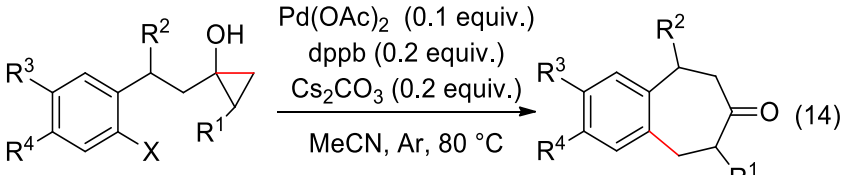


Scheme 5



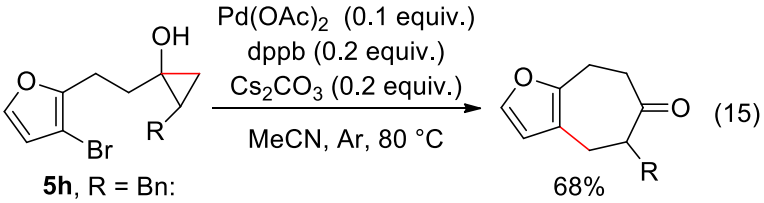
Cha and Ydham extended the annulation process to the synthesis of seven-membered carbocycles from the intramolecular reaction of *tert*-cyclopropanols tethered with (hetero)aryl

bromides or triflates (Eqs 14 and 15).[24] The yield was highly sensitive to the nature of the ligand (Eq. 14).



(14)

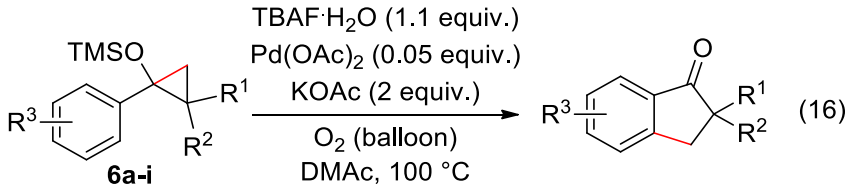
5b, X = Br, $R^1 = R^2 = R^3 = R^4 = H$: 95%[a]
5c, X = Br, $R^1 = R^2 = R^4 = H$, R^3 = OMe: 96%
5d, X = OTf, $R^1 = R^2 = R^3 = H$, R^4 = OMe: 95%
5e, X = OTf, $R^2 = R^3 = R^4 = H$, R^1 = Bn: 88%
5f, X = OTf, $R^2 = R^3 = R^4 = H$, R^1 = Et: 89%
5g, X = OTf, $R^1 = R^3 = R^4 = H$, R^2 = Me: 92%
[a]Other ligands, PPh_3: 59%, dppp: 67%, dppe: 79%.



(15)

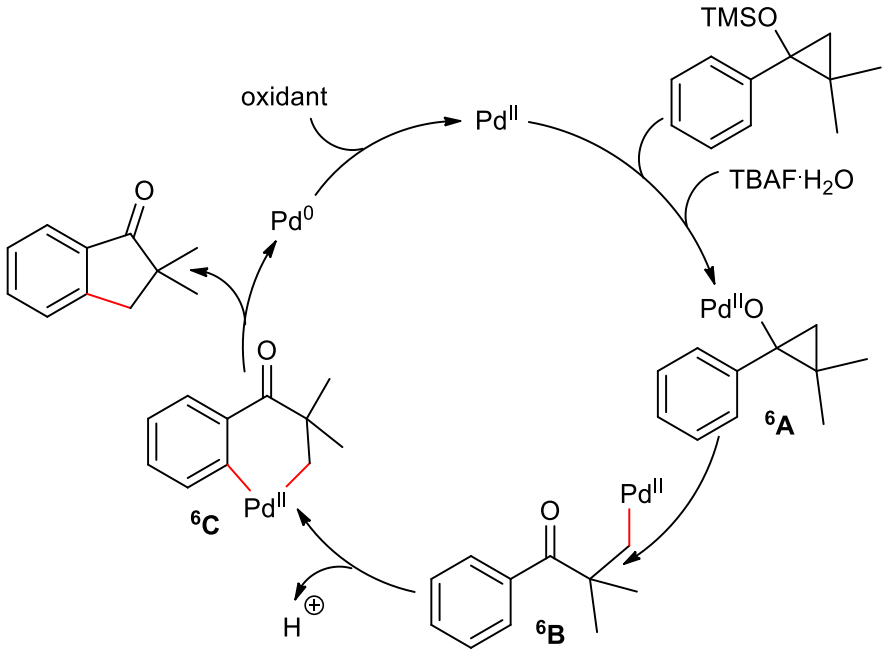
5h, R = Bn: 68%
5i, R = $(CH_2)_2$OTIPS: 64%

While TMS-protected cyclopropanol **3a** underwent the domino deprotection/rearrangement reaction leading to an enone (Eq. 9), the highly substituted silylated substrates **6a-6i** suffered a domino deprotection/cyclization reaction (Eq. 16).[17] As from **3a**, the reaction occurs via an alkoxypalladium intermediate (Scheme 6). Cleavage of the strained carbocycle of [6]**A** provides palladium homoenolate [6]**B**. The absence of available hydrogen in β-position favors activation of the aromatic *ortho*-C-H bond to afford [6]**C**, which undergoes reductive elimination of palladium to liberate the indanone.



(16)

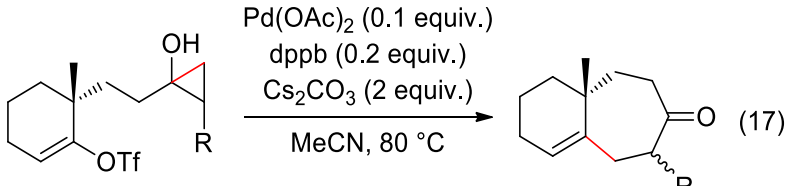
$R^1 = R^2$ = Me, R^3 = *o*-OMe (**a**: 78%), *m*-OMe (**b**: 70%), *p*-OMe (**c**: 75%), *p*-Cl (**d**: 73%), *p*-F (**e**: 84%), *p*-CF_3 (**f**: 84%), *m*-CO_2Me (**g**: 88%), *p*-CO_2Me (**h**: 84%)
R^1-R^2 = $(CH_2)_5$, R^3 = *p*-Me (**i**: 78%)



Scheme 6

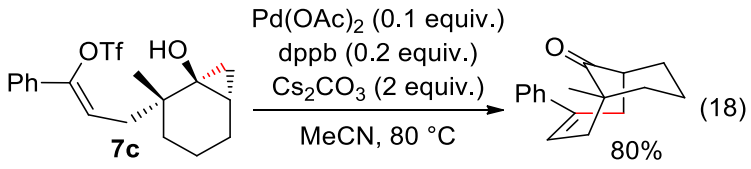
2.2.3. With an alkenylating entity

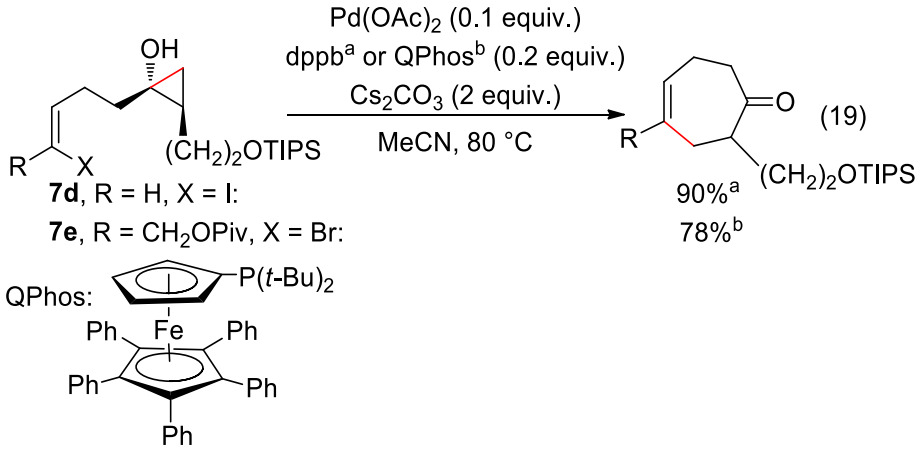
Seven-membered carbocycles were also synthetized using *tert*-cyclopropanols tethered with an alkenyl triflate, iodide or bromide under above Cha's conditions (Eqs 17 to 19), via a mechanism similar to that depicted in Scheme 5.[24] A Hartwig ligand – di-*tert*-butylphosphino pentaphenylferrocene (Qphos)[25]– was used for the reaction of the bromo substrate (Eq. 19).



7a, R = H: 82%

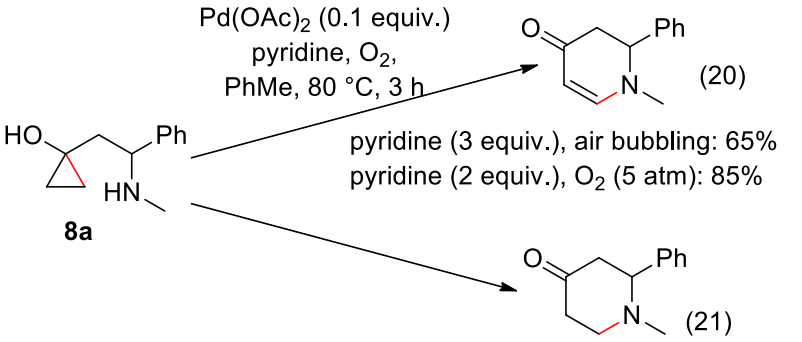
7b, $(CH_2)_2$OTIPS: 76%

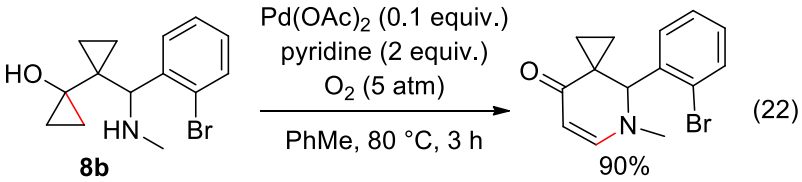


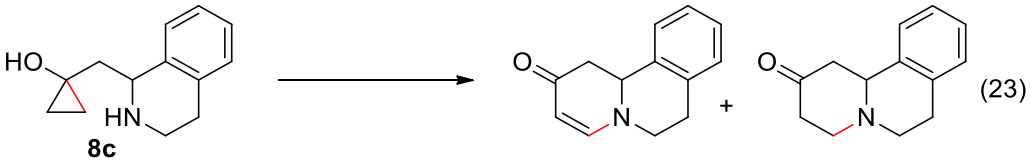


2.2.4. With an amino group

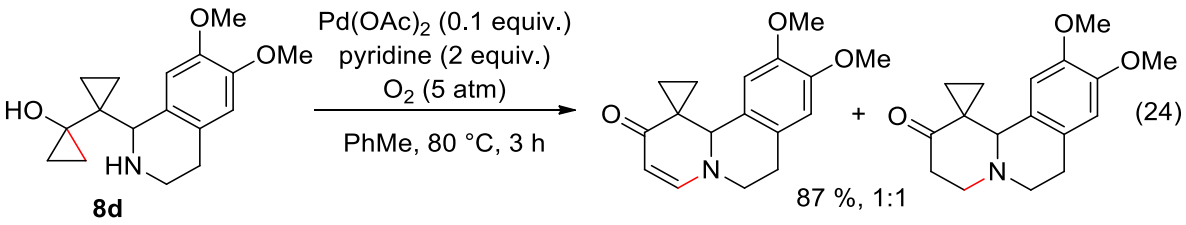
The Pd-catalyzed transformation of *tert*-cyclopropanols into enones urged Brandi's team to carry out domino reactions of β-aminocyclopropanols leading to 2,3-dihydro-1*H*-pyridin-4-ones and tetrahydropyridin-4-ones (Eqs 20 to 26). The former were selectively obtained from **8a** and **8b** under $Pd(OAc)_2$ catalysis in the presence of pyridine and oxygen in toluene at 80 °C (Eqs 20[26,27] and 22[28]), whereas mixtures of the two heterocycles were isolated from **8c** to **8f** (Eqs 23,[27] 24 and 25[28]). In contrast to the above examples, the cyclization of the primary amine **8g** occurred in a low yield (Eq. 26).[27] Surprisingly, use of $Cu(OAc)_2$ instead of oxygen to regenerate the catalyst favored the formation of the saturated heterocycle (Eqs 21[26,27] and 23[27]). This latter was also the main product under Pd^0 catalysis (Eqs 21 and 23).[27]

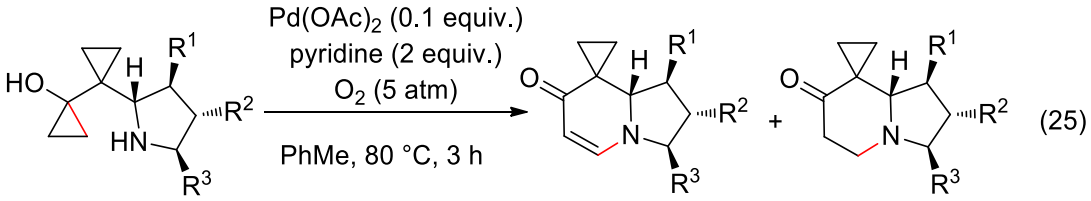




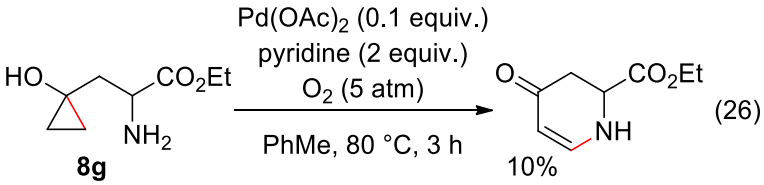


$Pd(OAc)_2$ (0.1 equiv.), pyridine (2 equiv.), O_2 (5 atm), PhMe, 80 °C, 3 h: 90%, 5:1
$Pd(OAc)_2$ (0.1 equiv.), $Cu(OAc)_2$ (2 equiv.), LiOAc (3 equiv.), DMF, 100 °C, 3 h: 75%, 1:5
$Pd(dba)_2$ (0.1 equiv.), MeCN, 50 °C, 20 h: 90%, 1:5

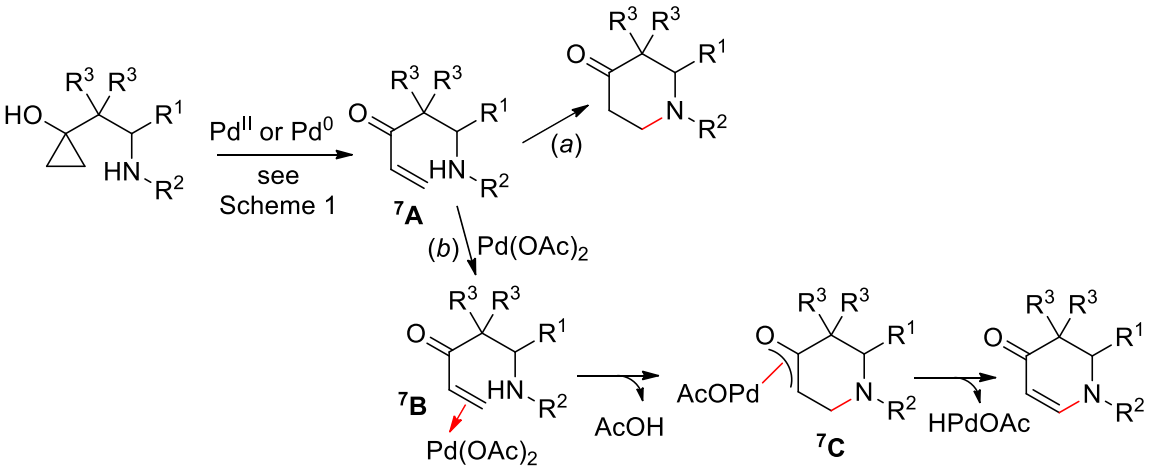




8e, R^1 = O*t*-Bu, R^2 = R^3 = H: 75%, 1:1
8f, R^1 = R^2 = OBn, R^3 = CH_2OBn: 95%, 1:1



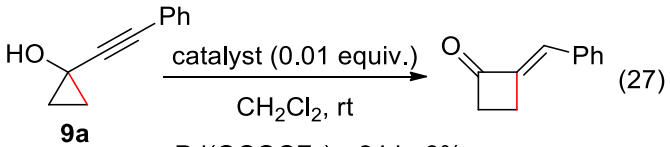
The reaction of the β-aminocyclopropanol with Pd^{II} or Pd^0 catalyst would lead to enone ^{7}**A** (Scheme 7). The aza-Michael reaction of ^{7}**A** affords the tetrahydropyridin-4-one (path *a*). In the presence of $Pd(OAc)_2$, coordination of ^{7}**A** leads to ^{7}**B** which undergoes intramolecular addition of the amino group to provide the oxo-η^3-allylpalladium complex ^{7}**C** (path *b*). Subsequent elimination of HPdOAc delivers the 2,3-dihydro-1*H*-pyridin-4-one. The ratio between the two pathways depends on the substrate substitution. Brandi and co-workers suggested that the use of $Cu(OAc)_2$ (Eqs 21 and 23) leads to "a Cu enolate which competes with the Pd enolate", hydrolysis of the former leading to the tetrahydropyridin-4-one.[27]



Scheme 7

2.2.5. With a C≡C bond

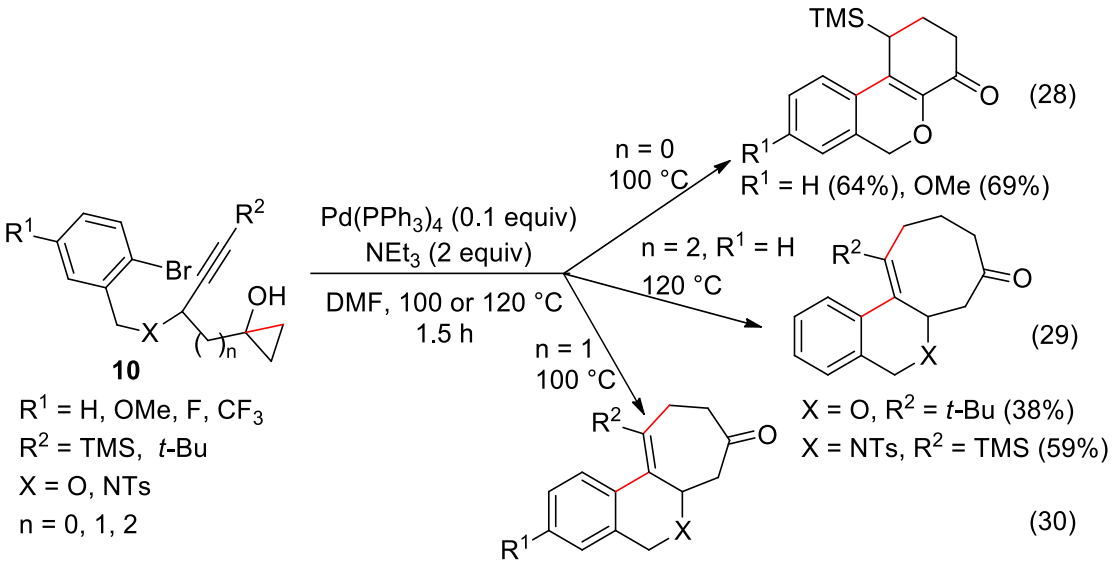
The treatment of alkynylcyclopropanol **9a** with a catalytic amount of $Pd(OCOCF_3)_2$ afforded (*E*)-2-benzylidenecyclobutanone in low yield (Eq. 27). Such a ring expansion occurred efficiently under Au-catalysis (Eq. 27).[29] 1-Phenylpent-1-yn-3-one was obtained as side-product under different conditions (see Subchapter 2.4.2.).[30]

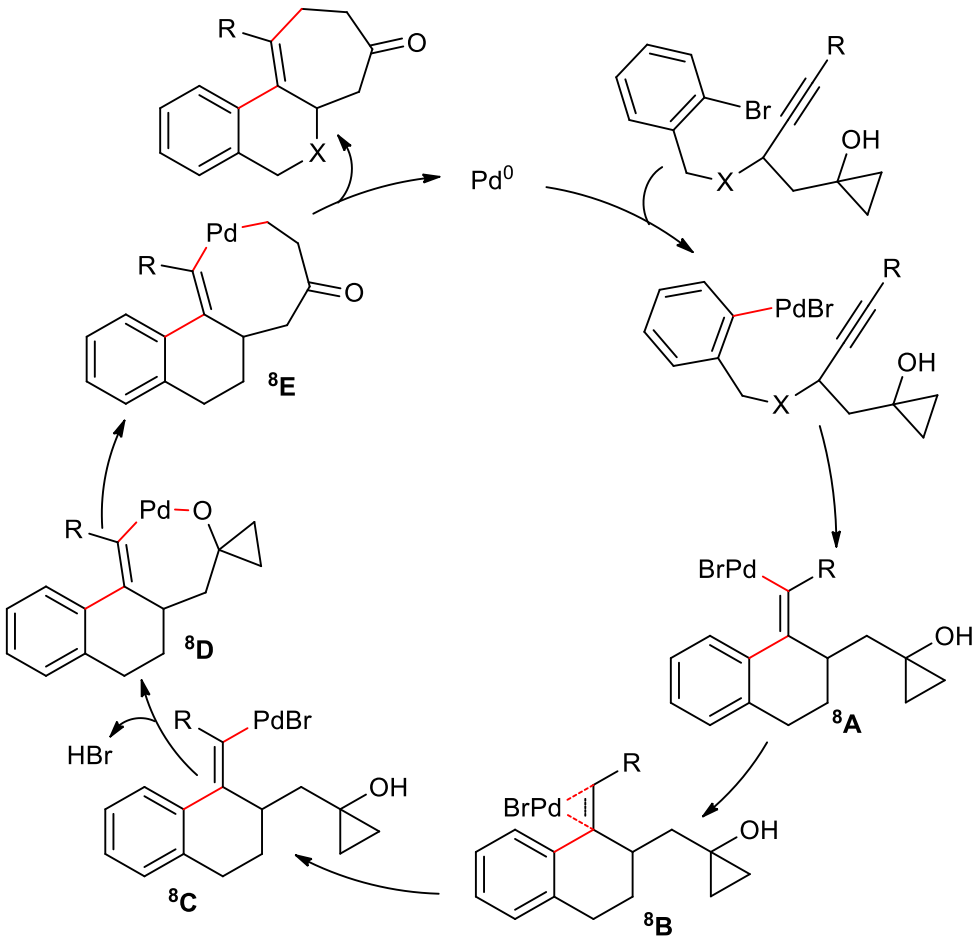


$Pd(OCOCF_3)_2$, 24 h: 8%
$Pd(MeCN)_4(BF_4)_2$, 24 h: 0%
$AuP(C_6H_4\text{-}p\text{-}CF_3)_3(SbF_6)$, 25 min: 99%

2.2.6. With an aryl bromide and a C≡C bond

The Pd^0-catalyzed reaction of cyclopropanols **10** at 100-120 °C with NEt_3 as the base produced the tricyclic unsaturated ketones depicted in Eqs 28 to 30.[31] The first step of this domino reaction is the oxidative addition of the catalyst into the C−Br bond of the substrate (Scheme 8). Subsequent *syn*-carbopalladation of the alkyne affords the η^1-vinyl-palladium species ^{8}**A** which undergoes cis/trans isomerization via the η^2-vinyl complex ^{8}**B**, giving ^{8}**C**. Intramolecular palladation of the hydroxyl group leads to palladacycle ^{8}**D**. β-Carbon elimination opens the three-membered carbocycle, giving ^{8}**E** which leads to the product via reductive elimination of palladium.



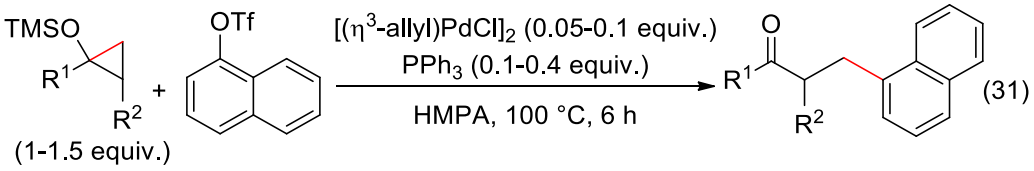


Scheme 8

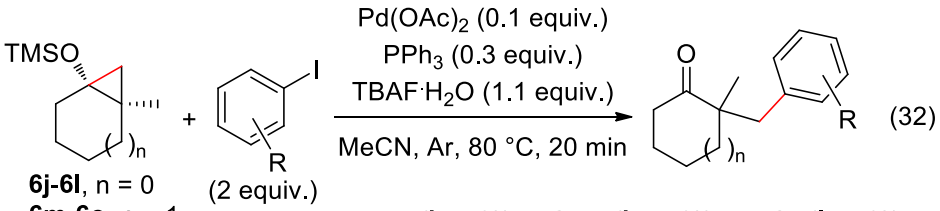
2.3. Intermolecular reactions

2.3.1. With (hetero)aryl halides or triflates

In 1988, Nakamura, Kuwajima and co-workers disclosed the Pd^0-catalyzed cross-coupling of TMS-protected cyclopropanols **3b**-**3e** with naphthalen-1-yl trifluoromethanesulfonate (Eq. 31).[32] More than 20 years later, Orellana and Rosa reported the cross-coupling of TMS-protected cyclopropanols **6j**-**6o** with aryl iodides in yields improved by addition of a fluoride source (Eq. 32).[23]



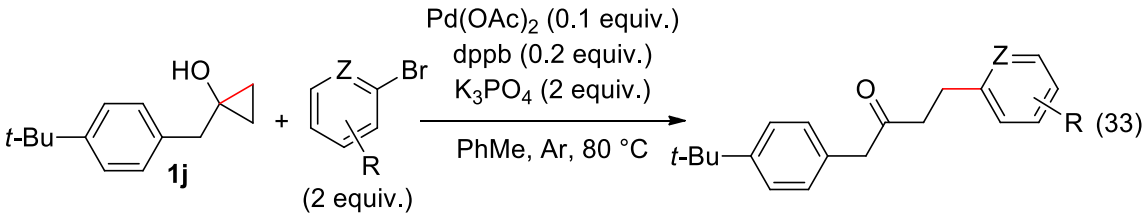
3b, R^1-R^2 = $(CH_2)_4$: 68-84%
3c, R^1 = Et, R^2 = Me: 46-56%
3d, R^1 = H, R^2 = $(CH_2)_6Me$: 58%
3e, R^1 = *p*-$MeOC_6H_4$, R^2 = H: 69%



6j-6l, n = 0
6m-6o, n = 1

n = 0, R = H (**j**, 57%), *p*-OMe (**k**, 49%), *o*-NO_2 (**l**, 65%)
n = 1, R = H (**m**, 57%), *p*-OMe (**n**, 55%), *o*-NO_2 (**p**, 76%)

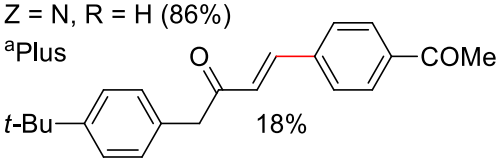
Subsequently, Orellana and Rosa cross-coupled *tert*-cyclopropanols with (hetero)arylbromides, the best results being obtained with the $Pd(OAc)_2$/1,4-bis(diphenylphosphino)butane (dppb)[33] catalytic system associated to K_3PO_4 or Cs_2CO_3 as the base (Eqs 33 to 35).[34] Selective cleavage of the less substituted cyclopropane bond occurred except from the fused bicyclic cyclopropanols **2n** and **2o**. The mechanism of these cross-couplings (Scheme 9, path *a*) is similar to that of the intramolecular arylations depicted in Scheme 5. The β-aryl-α,β-unsaturated ketone isolated as side-product in a few cases (Eqs 33 and 35) could be produced via Heck reaction of α,β-unsaturated ketone ^{9}**B** formed from ^{9}**A** by β-H elimination (path *b*). However, control experiments showed its formation from dehydrogenation of the β-arylketone (path *c*).[34-36] The reluctance of the β-H elimination from ^{9}**A** would be due to the bidentate phosphine which occupies "two coordination sites on palladium, thereby retarding β-hydride elimination relative to reductive elimination".[34,37]



Z = CH, R = *o*-OMe (82%), *m*-OMe (82%), *p*-OMe (83%), *p*-CO_2Me (87%),
p-COMe (66%[a,b]), *p*-CN (91%), *p*-CF_3 (90%), *p*-NMe_2 (81%), *m*-Cl (70%[c])

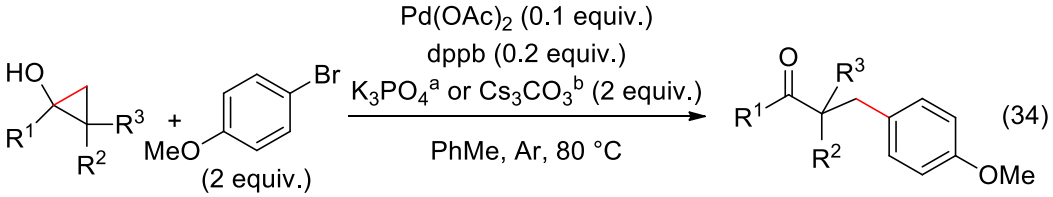
Z = N, R = H (86%)

[a]Plus



[b]87% using Cs_2CO_3 instead of K_3PO_4.

[c]86% using Cs_2CO_3 instead of K_3PO_4.



1c, $R^2 = R^3 = H$, $R^1 = BnCH_2$: 93%[a]

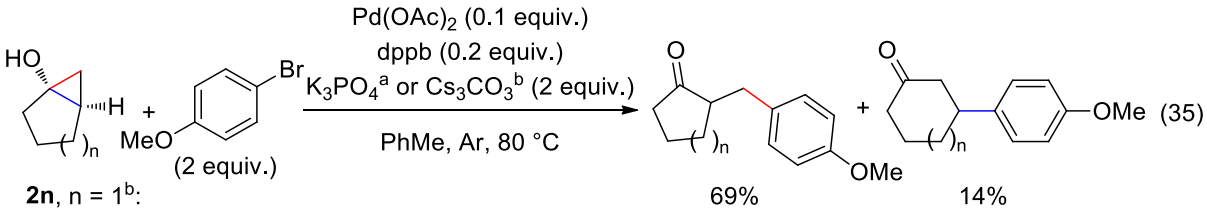
1k, $R^2 = R^3 = H$, $R^1 = CyCH_2$: 88%[b]

1l, $R^2 = R^3 = H$, $R^1 = TBSO(CH_2)_5$: 86%[b]

1m, $R^2 = R^3 = H$, R^1 = (1-cyclohexenyl)CH_2: 77%[b]

2m, $R^3 = H$, $R^1 = p$-(*t*-Bu)$C_6H_4CH_2$, $R^2 = p$-$MeOC_6H_4CH_2$: 77%[b]

11, $R^2 = R^3 = Me$, $R^1 = p$-$F_3CC_6H_4$: 76%[a]

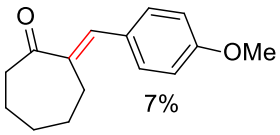


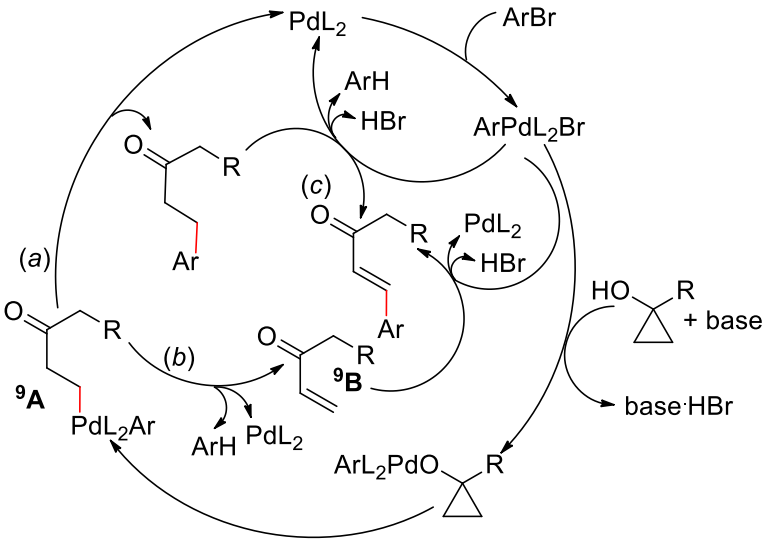
2n, n = 1[b]: 69% 14%

2o, n = 2[a]: 54% 23%

2p, n = 3[b]: 74%[c]

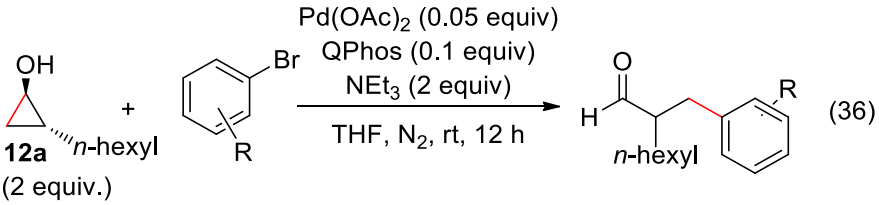
[c]Plus





Scheme 9

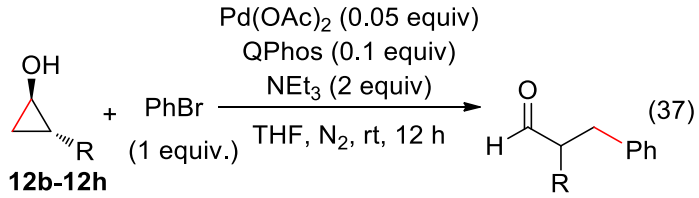
The synthesis efficiency of β-arylated aldehydes from secondary cyclopropanols **12a-h** and aryl bromides is very sensitive to the nature of the ligand.[38] The best yields were obtained with QPhos as the ligand and NEt_3 as the base (Eqs 36 and 37). A mechanism similar to Scheme 9, path *a* was proposed.[38] Although QPhos was a monodentate phosphine (see Eq. 19), the β-hydride elimination (from an intermediate corresponding to ^{9}**A**) was also not observed, but according to Hartwig's team, this sterically hindered ligand "suppress, at least partially, β-hydrogen elimination".[25]



R = H (86%[a,b]), *o*-Me (59%), *m*-OMe (81%), *p*-OMe (80%), *p*-NO_2 (79%), *p*-Cl (83%), *p*-NMe_2 (73%), *p*-CH_2OH (84%), *p*-CO_2Me (79%)

[a]14 and 12% with PPh_3 and dppf, respectively.

[b]95% ee using enantioenriched (96% ee) cyclopropanol.

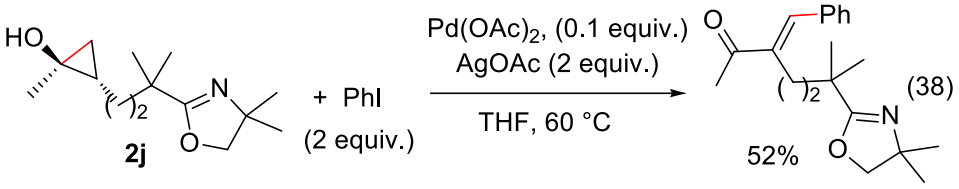


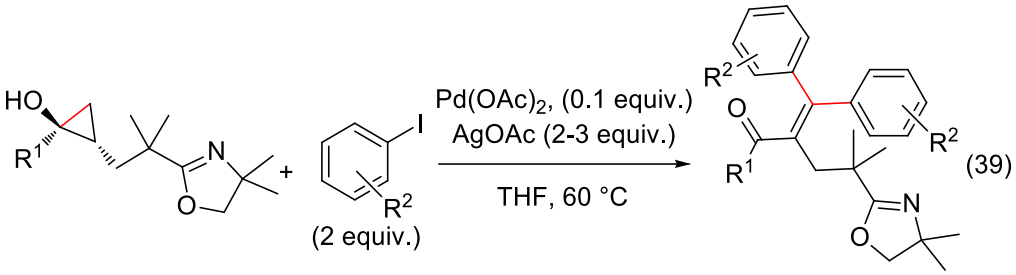
R = **b**, *n*-Bu (93%); **c**, Cy (88%); **d**, $TBSO(CH_2)_3$ (83%); **e**, $TIPSOCH_2$ (59%[a]); **f**, $TBDPSOCH_2$ (73%[a]); **g**, CH_2OCPh_3 (71%); **h**, $(CH_2)_3OCPh_3$ (73%)

[a]Using $Pd(OAc)_2$ (0.1 equiv.) and QPhos (0.2 equiv.).

The ligand-free arylation of oxazoline-tethered cyclopropanol **2j** selectively led to a β-aryl-α,β-unsaturated ketone (Eq. 38), whereas **2e-2g** afforded β-diaryl-α,β-unsaturated ketones (Eq. 39).[14] Instead of the above mechanism (Scheme 9, paths *a* and *c*), that is formation of the

β-arylketone followed by dehydrogenation, Hurski and Novikau proposed the formation of the α,β-unsaturated ketone followed by a Heck reaction (path *b*).[36] They did not mention and, consequently, discuss the 2013 Orellana report,[34] but performed experiments agreeing with their proposal. The absence of β-aryl ketones is also in accord with the proposed mechanism. We suggest that the absence of added ligand promotes the β-hydride elimination and explains this difference of reactivity.





2e, R^1 = Me: R^2 = H (51%[a]), *p*-Me (51%), *p*-OMe (57%), *p*-CO_2Me (59%), *p*-Br (54%), *p*-NO_2 (45%), *m*-Cl (51%), *m*-CF_3 (46%)

2f, R^1 = *i*-Pr: R^2 = *p*-Me (54%[b])

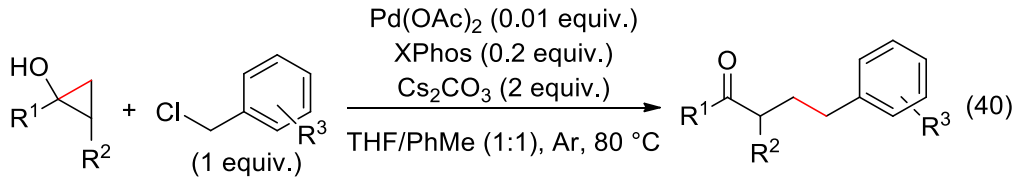
2g, R^1 = $(CH_2)_2$Ph: R^2 = *p*-Me (48%)

[a]Monoarylation product (31%) in DMF.

[b]In *t*-AmOH at 100 °C.

2.3.2. With benzyl halides

For the cross-coupling of benzylic chlorides with tertiary cyclopropanols, Orellana and Nithiy chose the $Pd(OAc)_2$/XPhos catalytic system with Cs_2CO_3 as the base (Eq. 40).[39] This base was selected "since it does not promote base-catalyzed ring-opening of the cyclopropanol to the corresponding ketone, even at elevated temperatures".[39] Benzyl bromide and benzyl iodide led to lower yields than benzyl chloride (Eq. 40). The reaction mechanism would be similar to that of Scheme 9, path *a*,[39] and we suspect that the bulky ligand prevents the β-H elimination. The cross-coupling did not occur with chloromethylpyridines and 3-(chloromethyl)-5-phenyl-1,2,4-oxadiazole; according to a competition experiment, this inability "is not a result of catalyst poisoning".[39]



(40)

1c, R^1 = CH_2Bn, R^2 = H: R^3 = H (94%), *p*-Me (87%[a]), *p*-OMe (84%), *p*-F (59%, 68%[b]), *p*-CF_3 (46%, 54%[b]), *o*-CF_3 (11%, 26%[b]), *m*-NO_2 (0%, 45%[b]), *p*-NO_2 (0%, 0%[b])

1k, R^1 = CH_2Cy, R^2 = H: R^3 = *p*-Me (65%)

1l, R^1 = $(CH_2)_5OTBS$, R^2 = H: R^3 = *p*-Me (72%)

1m, R^1 = CH_2(1-cyclohexenyl), R^2 = H: R^3 = *p*-Me (74%)

2n, R^1-R^2 = $(CH_2)_3$: R^3 = *p*-Me (79%)

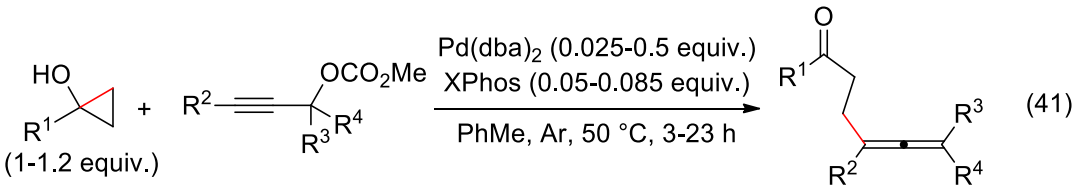
2o, R^1-R^2 = $(CH_2)_4$: R^3 = *p*-Me (66%)

[a]67% and 72% with $PhCH_2Br$ and $PhCH_2I$, respectively.

[b]dioxane as the solvent.

2.3.3. With propargylic carbonates or acetates

XPhos was also an effective ligand for the reaction of tertiary cyclopropanols with propargylic carbonates, especially when $Pd(dba)_2$ was the catalyst (Eq. 41).[40] Interestingly, optically active propargylic carbonates provided the allene with high chirality transfer (Eq. 42). That led Ma's team to propose the mechanism depicted in Scheme 10. S_N2'-type *anti*-oxidative addition of the catalyst to the propargylic carbonate affords the allenyl palladium methoxide intermediate **[10]A**, which undergoes ligand exchange with the cyclopropanol leading to **[10]B**. β-C elimination from **[10]B** gives **[10]C**, which suffers reductive elimination delivering the product. We like to point out that the role of XPhos, a bulky ligand, to prevent β-hydride elimination from **[10]C** is highlighted with the reaction of benzylcyclopropanol **1g** in the presence of PPh_3 instead of XPhos, which afforded 13% of the cross-coupling product and 51% of the methylene ketone (Eq. 41).



(41)

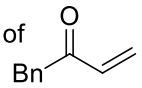
1g, R^1 = Bn: $R^2 = R^3$ = Ph, R^4 = H (84%[a,b,c,d])
R^4 = H, R^3 = Ph, R^2 = *n*-Bu (79%), *n*-Hex (76%), $Ph(CH_2)_2$ (81%), allyl (62%), *p*-$MeCOC_6H_4$ (70%), *o*-ClC_6H_4 (55%), H (20%)
R^2 = *n*-Bu, R^4 = H, R^3 = *p*-NCC_6H_4 (79%), *p*-$MeOCOC_6H_4$ (56%)
R^2 = *n*-Hex, $R^3 = R^4$ = Me (54%[e])
R^2 = *n*-Pent, R^3 = *n*-Pr, R^4 = Me (48%[e])

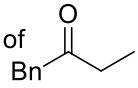
1n, R^1 = Cy: R^2 = *n*-Bu, R^3 = Ph, R^4 = H (74%)

1o, R^1 = CH_2OPh: $R^2 = R^3$ = Ph, R^4 = H (71%)

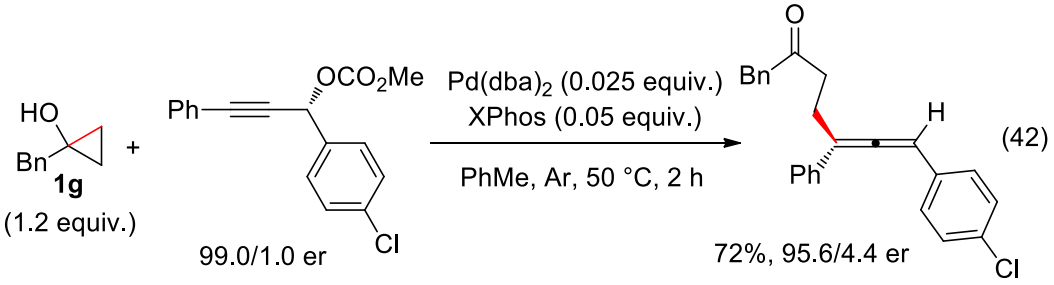
[a]Using $Pd(dba)_2$ (0.025 equiv.) and XPhos (0.05 equiv.).

[b]73% using $Pd(OAc)_2$ (0.05 equiv.) and XPhos (0.085 equiv.).

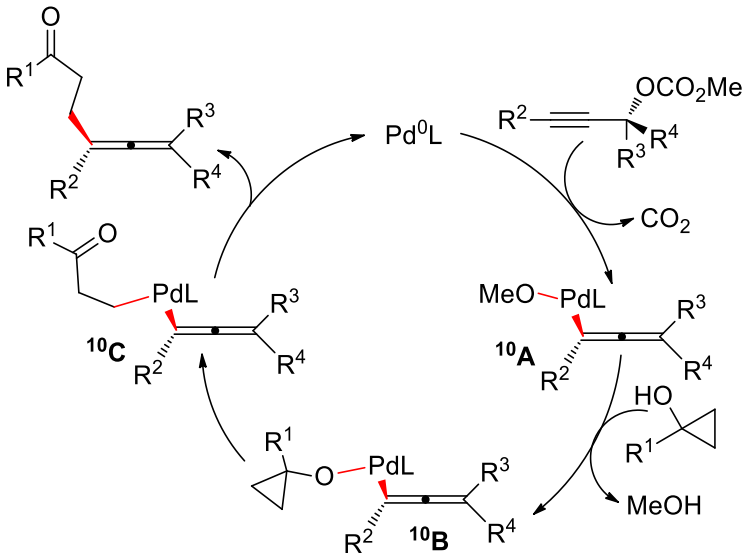
[c]13% using $Pd(dba)_2$ (0.05 equiv.) and PPh_3 (0.01 equiv.) with formation of  (51%).

[d]26% from the propargylic acetate with formation of  (35%).

[e]With $K_3PO_4 \cdot 3H_2O$ (1 equiv.) as additive.



(42)



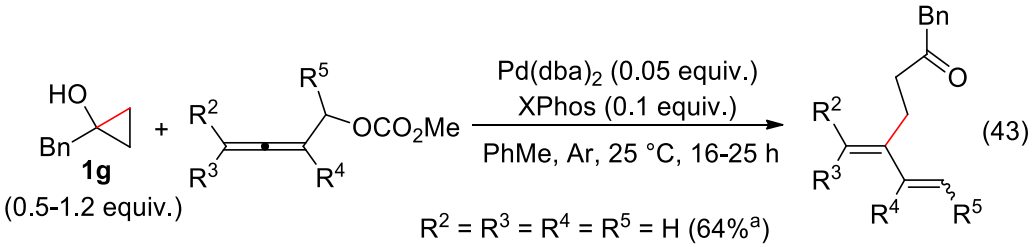
Scheme 10

With 1,3-diphenylprop-2-yn-1-yl acetate as the coupling partner of **1g**, the $Pd(dba)_2$/XPhos-catalyzed reaction was sluggish leading to only 26% of the adduct, 1-phenylbutan-2-one being

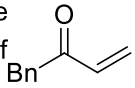
the main product (Eq. 41). We suspect that the in-situ formed AcOH was prejudicial to the cross-coupling.

2.3.4. With 2,3-allenylic carbonates

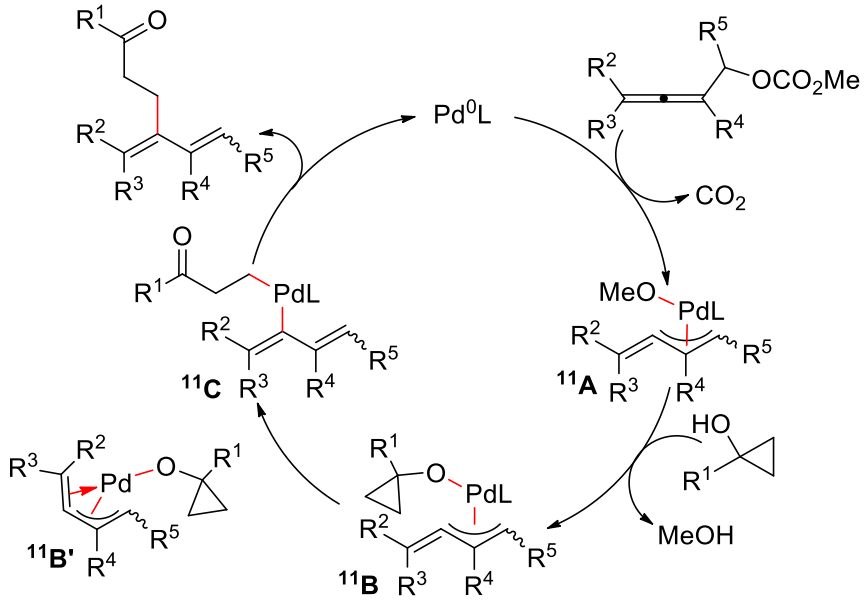
Ma's team again used the $Pd(dba)_2$/XPhos association for the reaction of *tert*-cyclopropanols with 2,3-allenylic carbonates (Eq. 43).[13] The yield was higher from methyl buta-2,3-dienyl carbonate than from benzyl buta-2,3-dienyl carbonate. Moreover, the latter afforded 27% of 1-phenylbut-3-en-2-one (Eq. 43).



(43)

$R^2 = R^3 = R^4 = R^5 = H$ (64%[a])
$R^2 = R^3 = R^5 = H$, R^4 = Ph (68%), *n*-Bu (76%)
$R^2 = R^3 = R^4 = H$, R^5 = Ph (63%), *n*-Pent (68%)
$R^2 = R^4 = R^5 = H$, R^3 = Ph (73%), *n*-Hex (78%)
$R^2 = R^3$ = Me, $R^4 = R^5 = H$ (33%)
[a]58% from the benzyl carbonate with formation of  (27%).

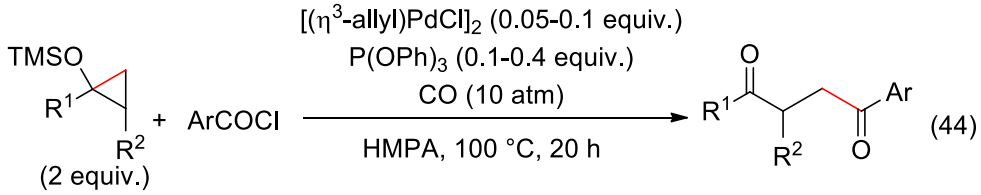
According to the authors, the oxidative addition of the catalyst to the allenyl carbonate affords the methylene (η^3-allyl) palladium methoxide complex **[11]A** (Scheme 11). Exchange of the methoxy of **[11]A** for the cyclopropyloxy provides **[11]B**, which undergoes β-C elimination leading to **[11]C**. Subsequent reductive elimination of palladium delivers the product. The cross-coupling compound corresponding to addition to the other extremity of the η^3-allyl moiety of **[11]B** has never been observed, but no explanation was proposed by the authors. We suspect that coordination of the pendant ethylenic bond of the η^3-allyl moiety leading to an intermediate like **[11]B'** could direct the reaction.



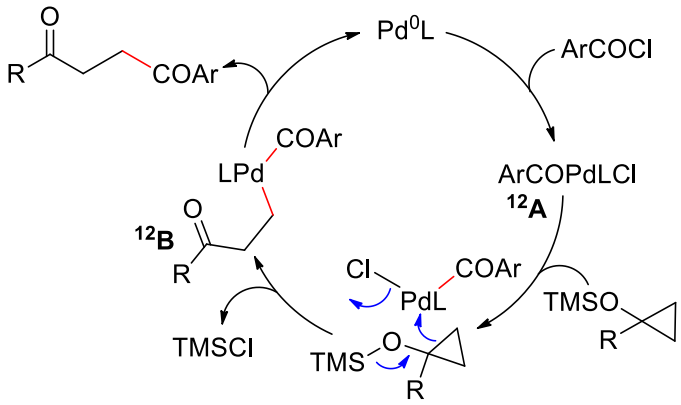
Scheme 11

2.3.5. With acylating reagents

In 1989, Nakamura, Kuwajima and co-workers reported the Pd-catalyzed reaction of siloxycyclopropanes with aromatic acid chlorides at 100 °C in HMPA under CO atmosphere (Eq. 44).[41,42] A plausible catalytic cycle is shown in Scheme 12. Cleavage of the cyclopropyl ring by aroylpalladium chloride **[12]A**[43] leads to TMSCl and β-aroylpalladium ketone **[12]B** (Scheme 12).[42] Reductive elimination of palladium from **[12]B** affords the product. CO atmosphere was required to preclude the decarbonylation of the aroylpalladium intermediate.[42] We suspect that CO as supplementary ligand of palladium could also contribute to prevent β-H elimination from **[12]B**. No 1,4-diketone was obtained from aliphatic acid chlorides.

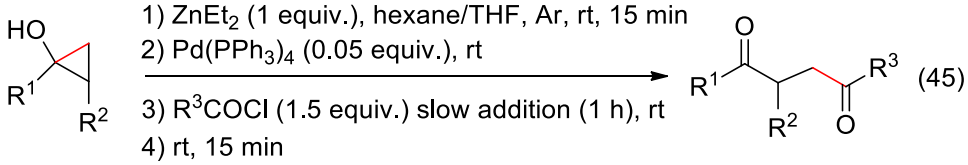


3b, R^1-R^2 = $(CH_2)_4$: Ar = 1-naphthyl (46%)
3e, R^1 = *p*-$MeOC_6H_4$, R^2 = H: Ar = Ph (75%)
3f, R^1 = 2-furyl, R^2 = H: Ar = *m*-MeC_6H_4 (52%)



Scheme 12

More than 20 years later, Cha's team disclosed a new synthesis of 1,4-diketones from *tert*-cyclopropanols (Eq. 45).[44,45] The process would implicate a zinc cyclopropyloxide.[44] We suspect a trans-metalation reaction[46] with an acetylpalladium complex leading, after cleavage of a ring bond, to a Pd species similar to **[12]B**. The method was used to prepare an intermediate of the total synthesis of (+)-myrmicarin 217 from **2s** and but-2-enoyl chloride (Scheme 13).[44]

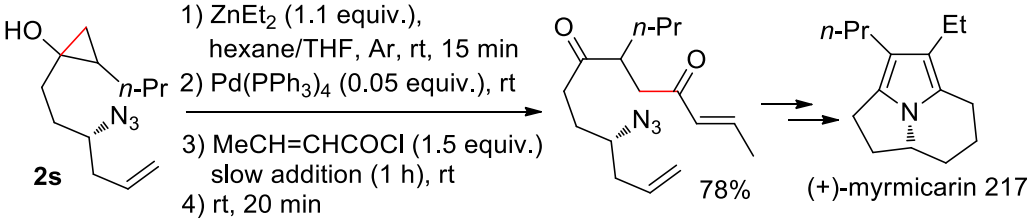


1g, R^1 = Bn, R^2 = H: R^3 = *i*-Pr (67%[a]), CH_2OMe (70%[a]), CH=CHPh (68%[a])

2q, R^1 = Me, R^2 = Bn: R^3 = *i*-Pr (60%), *i*-Bu (75%), CH_2OMe (62%), CH_2OBn (51%), CH=CHMe (60%), CH=CHPh (70%), $(CH_2)_4CH=CH_2$ (70%)

2r, R^1 = Me, R^2 = $(CH_2)_2OTIPS$: R^3 = *i*-Pr (65%), *i*-Bu (73%), *t*-Bu (64%), CH_2OMe (65%), CH_2Ph (57%), CH=CHMe (65%)

[a]Plus BnCOEt (8-13%).

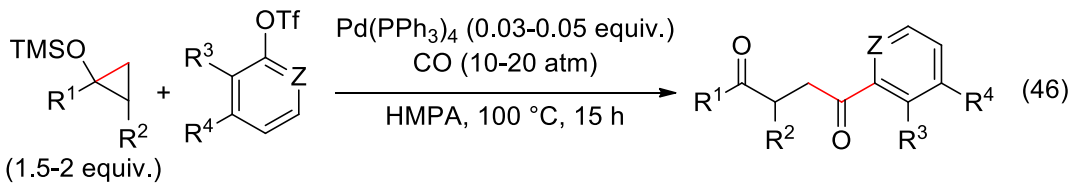


Scheme 13

2.3.6. With carbon monoxide and (hetero)aryl triflates

Another Pd-catalyzed procedure leading to 1,4-diketones is the carbonylative arylation of siloxycyclopropanes depicted in Eq. 46.[47] Nakamura and Aoki proposed the neutral aroylpalladium species **[14]A** as intermediate leading to the product (Scheme 14, path *a*).[47] Surprisingly, an unsaturated ester was obtained with a vinyl triflate (Eq. 47).[47] Given the use of aryl and vinyl triflates, we suspect the formation of the cationic palladium intermediate

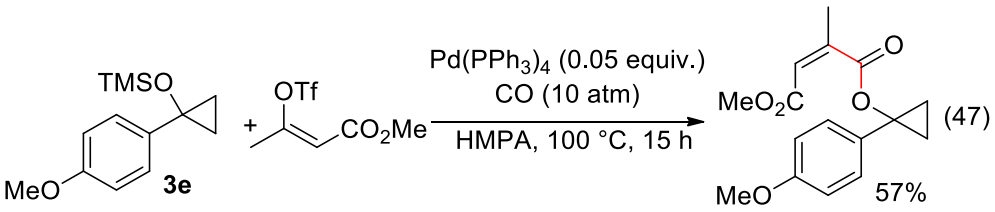
14B.[48] Trans-metalation of **14B** with the siloxycyclopropane affords **14C**, which evolves towards the diketone (path *b*) or the ester (path *c*), depending on the nature of the acyl group.



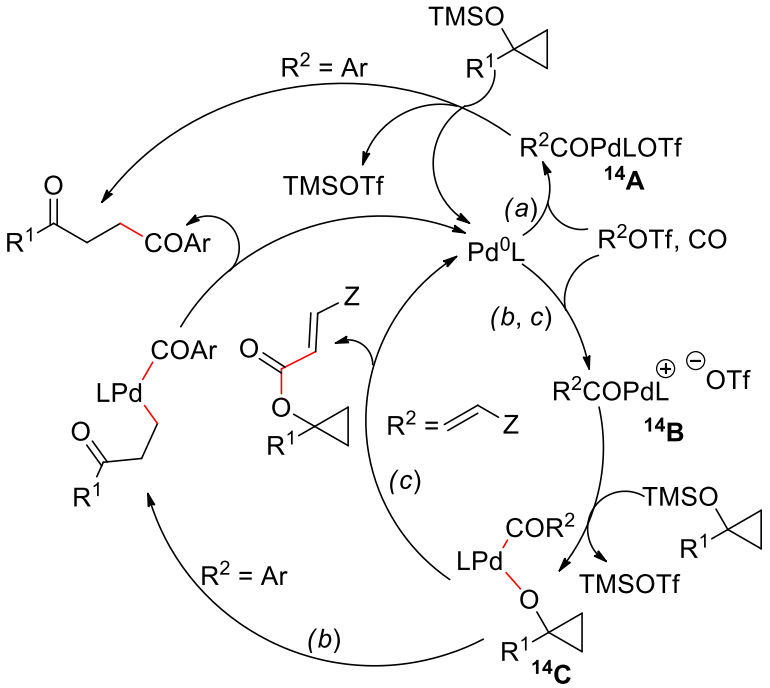
(46)

3b, R^1-R^2 = $(CH_2)_4$:
3c, R^1 = Et, R^2 = Me:
3e, R^1 = *p*-$MeOC_6H_4$, R^2 = H:

Z = CH, R^3-R^4 = $(CH)_4$: 59%
Z = CH, R^3 = F, R^4 = H: 36%
Z = CH, R^3 = R^4 = H: 55%
Z = CH, R^3-R^4 = $(CH)_4$: 73%
Z = CH, R^3 = H, R^4 = OMe: 61%
Z = CH, R^3 = F, R^4 = H: 43%
Z = N, R^3 = R^4 = H: 27%



(47)

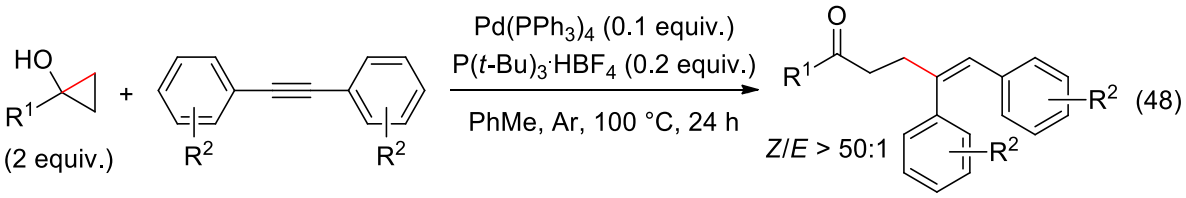


Scheme 14

2.3.7. With alkynes

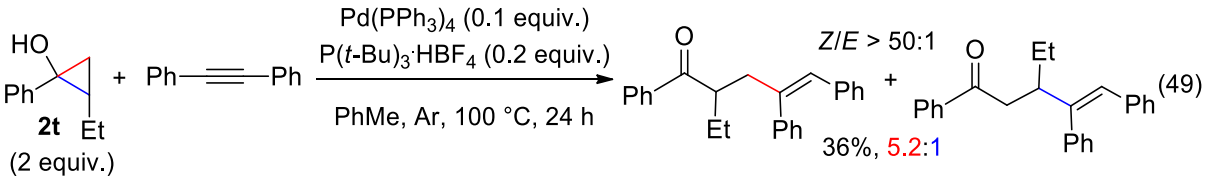
The team of Lin and Yao recently disclosed access to γ,δ- unsaturated ketones from the Pd-catalyzed hydroalkylation of alkynes with *tert*-cyclopropanols (Eqs 48 to 50).[49] The efficiency

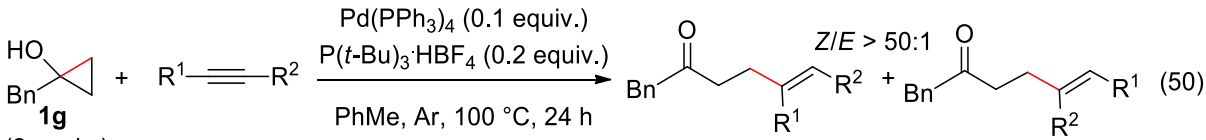
greatly depended on the catalytic system, the best results being delivered with the $Pd(PPh_3)_4/P(t\text{-}Bu)_3{\cdot}HBF_4$ association (Eq. 48).



1c, $R^1 = BnCH_2$: R^2 = H (77%)
1e, R^1 = Ph: R^2 = H (86%)
1g, R^1 = Bn: R^2 = H (92%[a,b]), *o*-OMe (65%), *m*-Me (59%), *p*-Me (74%), *p*-OMe (85%), *p*-F (70%), *p*-Cl (63%), *p*-CF_3 (75%), *p*-NO_2 (45%)
1n, R^1 = Cy: R^2 = H (72%)
1o, $R^1 = PhOCH_2$: R^2 = H (71%)

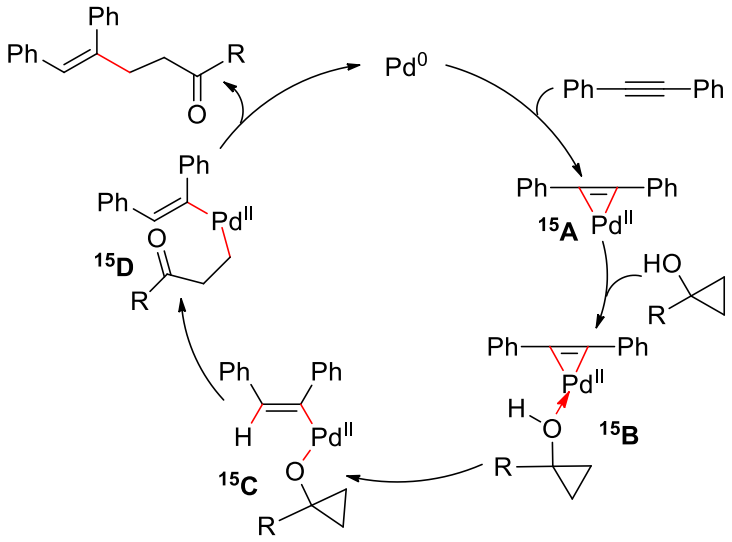
[a]Other ligands: PPh_3 (55%), dppm (<1%), dppb (<10%), PCy_3 (89%).
[b]Other catalysts: $Pd(OAc)_2$ (14%), $Pd(OCOCF_3)_2$ (21%), $PdCl_2(PPh_3)_2$ (<10%).





R^1 = Me, R^2 = Ph: 46%, 1.2:1
R^1 = Ph, $R^2 = CO_2Me$: 86%, 5.9:1
R^1 = Bn, R^2 = H: 54%, 1.7:1

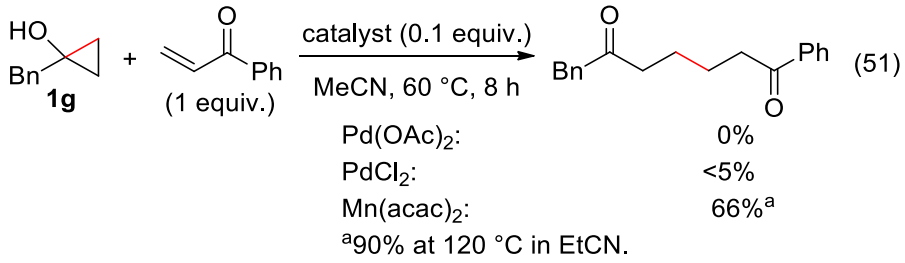
A catalytic cycle (Scheme 15) was proposed on the basis of deuterium-labeling experiments.[49] Oxidative ligation of the alkyne to the catalyst generates the Pd^{II} complex ^{15}**A**. Coordination of the cyclopropanol to ^{15}**A** provides ^{15}**B**, which undergoes hydrogen transfer leading to vinylpalladium species ^{15}**C**. Subsequent β-carbon elimination affords ^{15}**D**, which gives the enone via reductive elimination of palladium.



Scheme 15

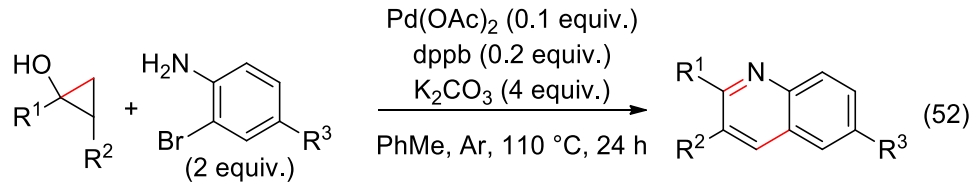
2.3.8. With enones

Looking for the synthesis of 1,6-diketones, Loh and co-workers carried out the reaction of **1g** with 1-phenylprop-2-en-1-one in the presence of various catalysts.[50] 1,7-Diphenylheptane-1,6-dione was isolated with $PdCl_2$ in a very low yield, but not with $Pd(OAc)_2$ (Eq. 51). The expected compound was effectively obtained under $Mn(acac)_2$ catalysis via a radical pathway.



2.3.9. With *ortho*-bromoanilines

Quinolines were prepared from the Pd-catalyzed domino reaction of tertiary and even secondary cyclopropanols with an excess of *ortho*-bromoanilines (Eq. 52).[51] The *ortho*-bromoaniline is not only involved in the cross-coupling partner but also in the dehydrogenation reaction (Scheme 16, cycles *1* and *2*).



1j, $R^1 = CH_2(C_6H_4t\text{-Bu})$, R^2 = H: R^3 = H (76%), Me (75%), Cl (84%), F (88%), CF_3 (76%), CO_2Me (89%), SO_2NMe_2 (65%)

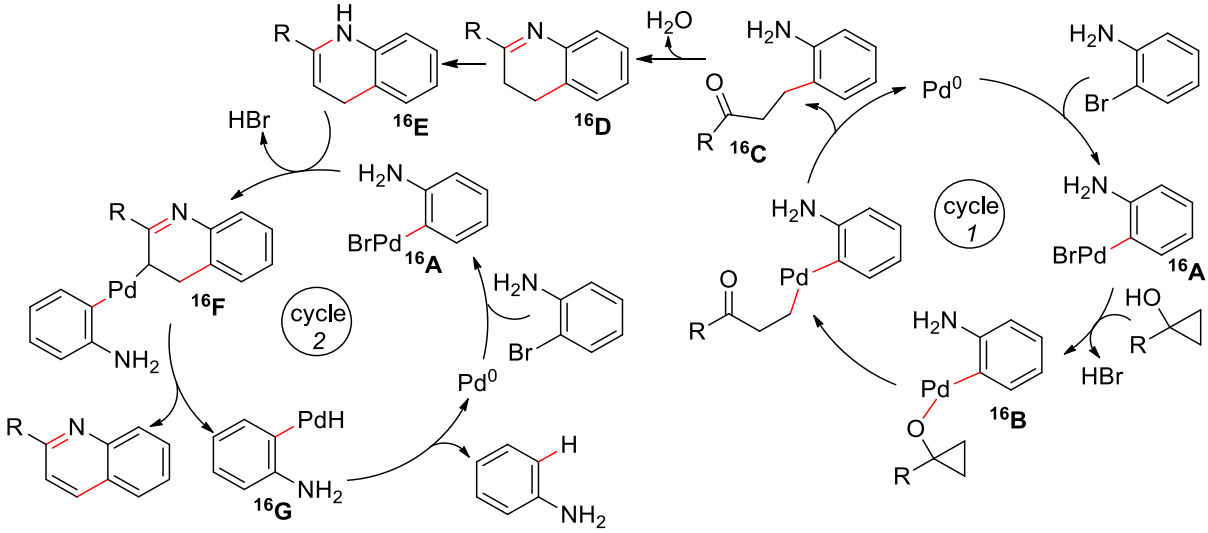
1k, $R^1 = CH_2Cy$, R^2 = H: R^3 = H (77%)

1m, $R^1 = CH_2$(1-cyclohexenyl), R^2 = H: R^3 = H (41%)

2n, R^1-$R^2 = (CH_2)_3$: R^3 = H (48%)

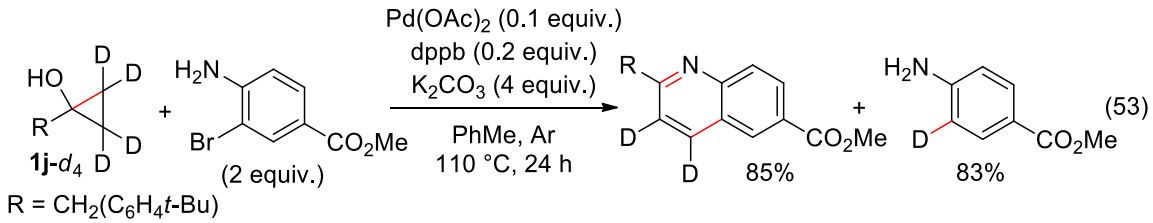
2o, R^1-$R^2 = (CH_2)_4$: R^3 = H (51%)

12a, R^1 = H, $R^2 = (CH_2)_5Me$: R^3 = H (80%)



Scheme 16

The proposed mechanism (Scheme 16) is consistent with the results of the cross-coupling of deuterated cyclopropanol **1j**-d_4 (Eq. 53). Cycle *1* concerns the reaction of aryl palladium complex ^{16}**A** with the cyclopropanol to afford ^{16}**B**, which leads to acyclic ketoaniline ^{16}**C** via C-C cleavage and reductive elimination. Cyclization of ^{16}**C** provides imine ^{16}**D**. Cycle *2* involves the reaction of ^{16}**E**, that is the enamine tautomer of ^{16}**D**, with ^{16}**A** to produce ^{16}**F**. Subsequent β-H-elimination gives palladium hydride intermediate ^{16}**G**, which undergoes reductive elimination leading to the quinoline.

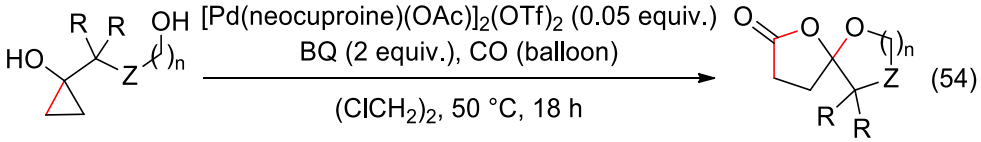


R = $CH_2(C_6H_4t\text{-Bu})$

2.4. Intermolecular reactions of functionalized cyclopropanols

2.4.1. Hydroxyl-tethered cyclopropanols with carbon monoxide

The teams of Dai and Waymouth disclosed the efficient carbonylative spirolactonization of hydroxycyclopropanols **13** under [Pd(neocuproine)(OAc)]$_2$(OTf)$_2$-catalysis and carbon monoxide atmosphere (Eq. 54).[52] The yields decreased with other Pd^{II} catalysts such as Pd(OAc)$_2$ and Pd(OCOCF$_3$)$_2$, or with O$_2$ instead of BQ to regenerate the catalyst.



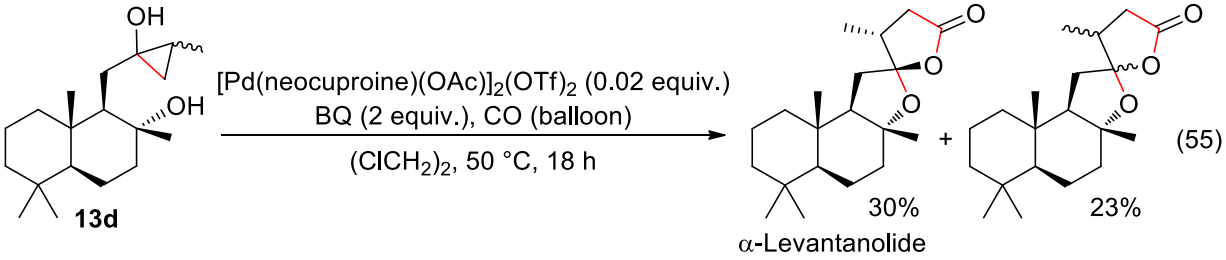
(54)

13a, Z = CH_2, n = 1: R = Ph (89%), *p*-$MeOC_6H_4CH_2$ (99%), *p*-$FC_6H_4CH_2$ (94%), *p*-$BrC_6H_4CH_2$ (71%), Bn (81%)

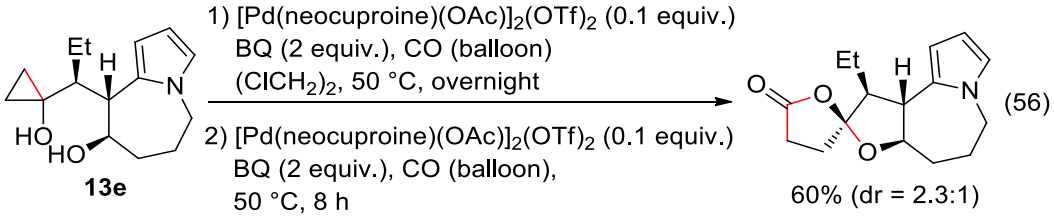
13b, Z = CH_2, n = 2: R = *p*-$MeOC_6H_4CH_2$ (81%)

13c, Z = NBoc, n = 2: R = H (58%)

The method was used for the synthesis of α-levantonolide (Eq. 55)[52] and a precursor of both bisdehydroneostemoninine and bisdehydrostemoninine (Eq. 56).[53]

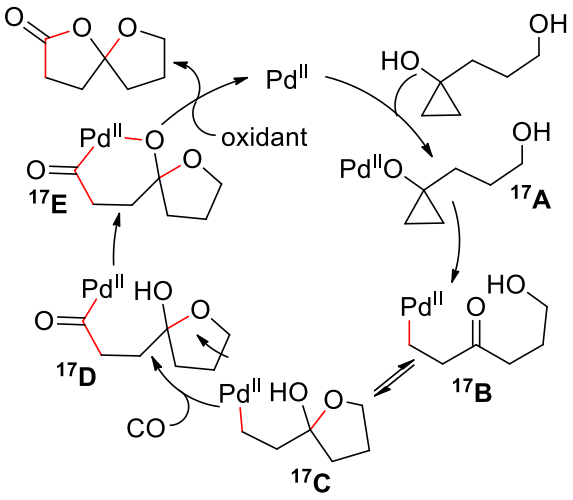


(55)



(56)

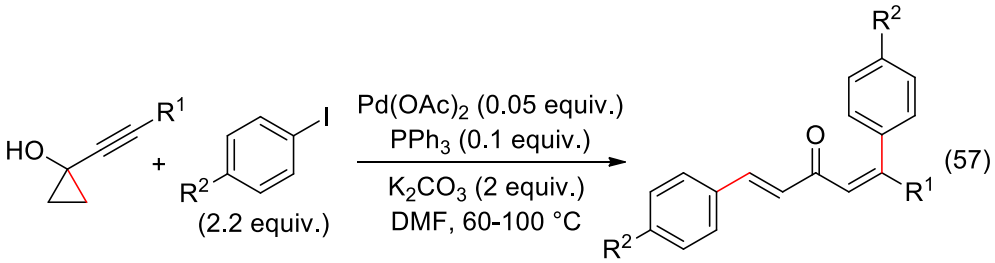
A simplified catalytic cycle is proposed in Scheme 17. The C-C cleavage of the cyclopropyl ring of ^{17}**A** affords ^{17}**B** which is in equilibrium with hemiketal ^{17}**C**. Subsequent insertion of carbon monoxide into the C-Pd bond gives ^{17}**D**, from which the oxaspirolactone is formed by intramolecular trapping by the hydroxyl, possibly through the formation of palladacycle ^{17}**E**.[54] Several key intermediates have been identified from high-resolution electrospray ionization mass spectrometry monitoring of the reaction.[52]



Scheme 17

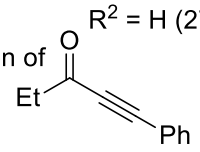
2.4.2. 1-Alkynylcyclopropanols

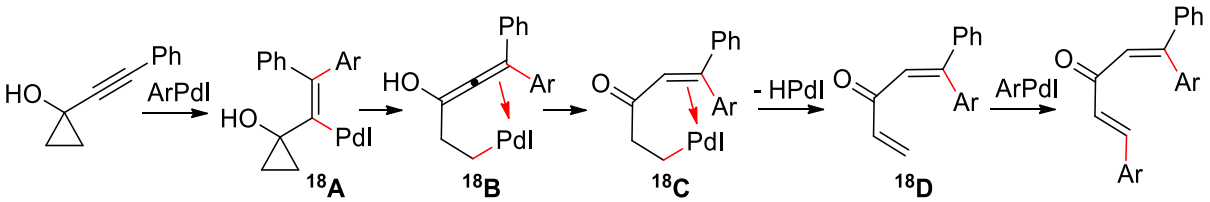
In contrast to the very low efficiency of the additive-free Pd^{II}-catalyzed reaction of **9a** (Eq. 27), such substrates underwent Pd^{0}-catalyzed cross-coupling with aryl iodides in basic media to afford 1,1,5-trisubstituted-penta-1,4-dien-3-ones in yields up to 79% (Eq. 57).[30] The reaction would involve the regioselective cis-carbopalladation of the triple bond of the substrate, leading to ^{18}**A**, which undergoes ring opening to afford the allenic species ^{18}**B** (Scheme 18). The latter evolves to ^{18}**C**. Subsequent β-H elimination is followed by Heck reaction of ^{18}**D**, giving the di-addition product.



9a, R^1 = Ph, 100 °C: R^2 = H (70%[a]), Me (63%), OMe (53%)
9b, R^1 = *p*-MeC_6H_4, 100 °C: R^2 = H (56%), Me (79%)
9c, R^1 = *p*-$MeOC_6H_4$, 60 °C: R^2 = H (51%)
9d, R^1 = CH_2Bn, 80 °C: R^2 = H (27%)

[a]12% at 80 °C in the absence of base and formation of

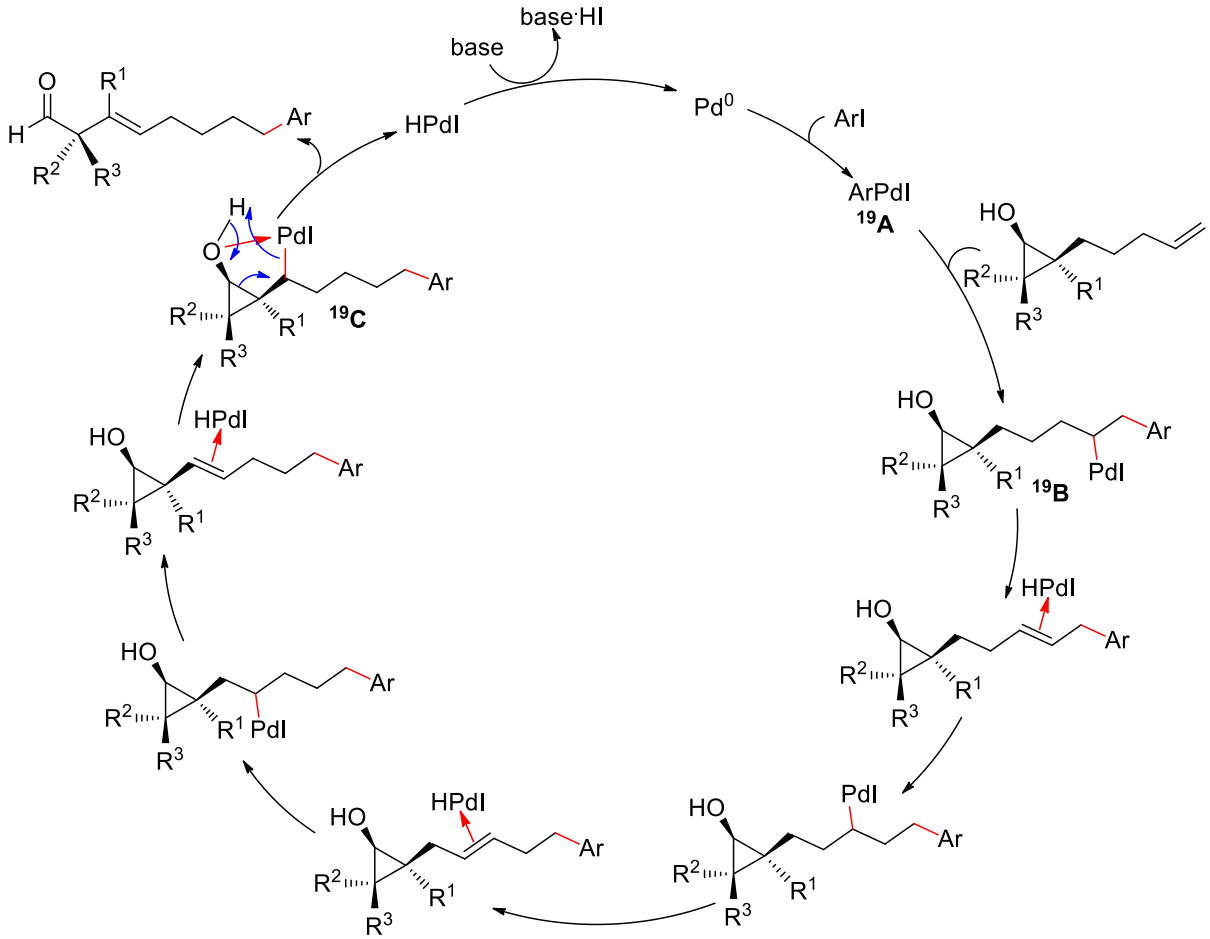




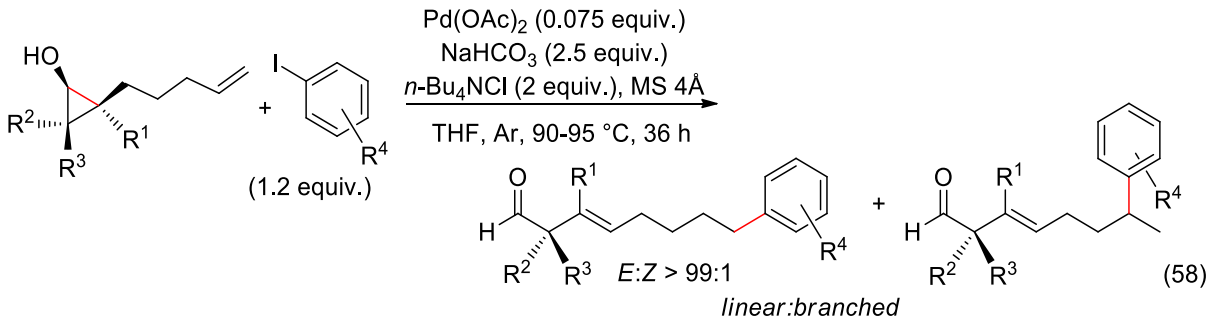
Scheme 18

2.4.3. Olefin-tethered cyclopropanols

The Heck reaction of secondary cyclopropanols substituted with a long ethylenic tether led, via a "palladium walk" (Scheme 19), to fragmentation of the remote ring producing aryl β,γ-unsaturated aldehydes (Eq. 58).[55] Addition of aryl palladium species **[19]A** to the C=C bond of the substrate affords **[19]B**, which undergoes a series of β-H elimination/HPdI addition to produce **[19]C**. According to Marek's team, the *syn*-periplanar relationship between the hydroxyl and the palladium favors the ring cleavage, giving the aldehyde.



Scheme 19



14a, R^1 = H, R^2 = Ph, R^3 = Me: R^4 = H (67%, *5.7:1*), *m*-OMe (62%, *5.7:1*)

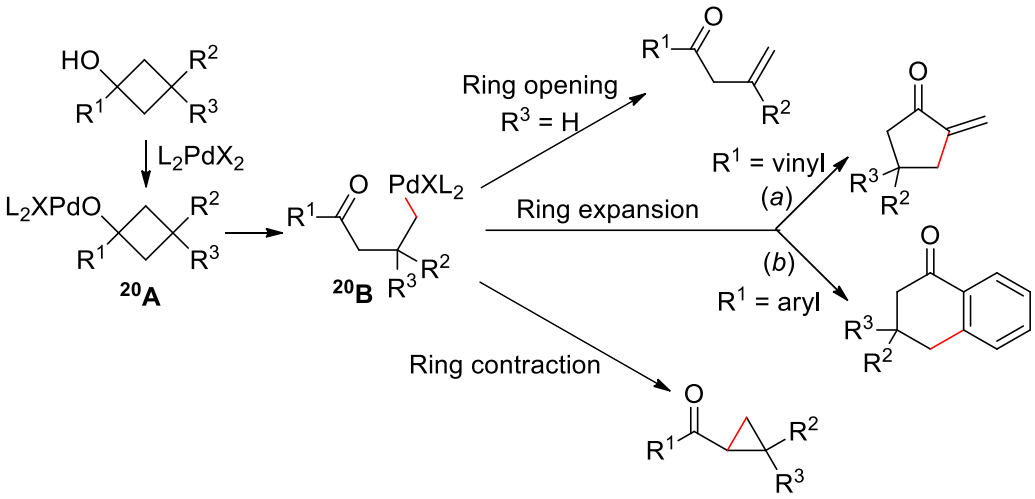
14b, R^1 = H, R^2 = *p*-MeC_6H_4, R^3 = Me: R^4 = H (61%, *8.1:1*), *m*-OMe (60%, *9:1*), *p*-Cl (70%, *7.3:1*)

14c, R^1 = *n*-hexyl, R^2 = Me, R^3 = CH_2OMe: R^4 = H (86%, *5.7:1*), *o*-Cl (78%, *7.3:1*)

14d, R^1 = *n*-Bu, R^2 = Ph, R^3 = CH_2OMe: R^4 = H (67%, *5.7:1*), *o*-Cl (64%, *5.7:1*), *p*-OMe (62%, *4.5:1*)

3. Cyclobutanols

In 2001, Uemura and co-workers considered three types of Pd-catalyzed intramolecular reactions of *tert*-cyclobutanols.[56] The authors hypothesized that they occur from the organopalladium intermediate **[20]B** formed from alkoxypalladium complex **[20]A** via β-carbon elimination (Scheme 20). Then, **[20]B** leads to dehydrogenation products through pathways depending on the substituents. When a β-H elimination is possible, **[20]B** may afford the β,γ-unsaturated ketone. When formed from a 1-vinyl or 1-phenylcyclobutanol, **[20]B** may lead to a ring expansion, especially if no β-H is available. The third type of reaction mode is the ring contraction leading to the α-cyclopropyl ketone. Subsequent reports revealed that the ring expansion may also occur with an allenyl substituent or be a step of a domino intramolecular reaction. Cyclobutanols may also undergo intermolecular domino reactions.

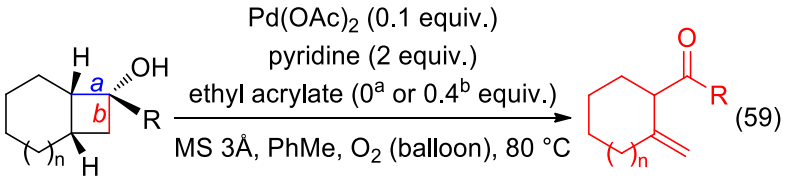


Scheme 20

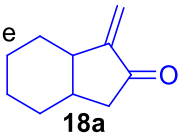
3.1. Intramolecular reactions

3.1.1. Unsaturated ketones from ring opening

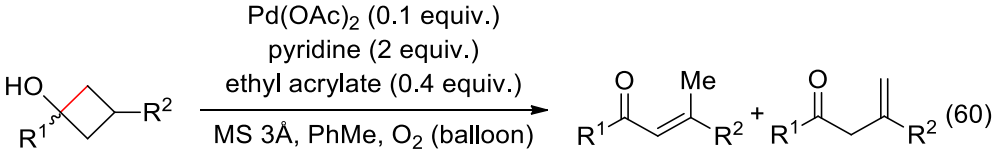
While 1-methylcyclobutanol would be stable at 0°C under Pd^{II}-catalyzed oxidation conditions,[57] Uemura's team reported, in 1999-2001, the formation of β,γ- or/and α,β-unsaturated ketones from the Pd^{II}-catalyzed rearrangement of 1-butylcyclobutanols **15a-15c**, 1-vinylcyclobutanols **16a**, **16b** and 1-phenylcyclobutanols **17a-17d** at 80 °C in benzene containing pyridine (Eqs 59 and 60).[56,58] Except from **16a** and **16b**, the yield was improved in the presence of ethyl acrylate (Eq. 59) but its role remains unclear.[56] The catalytic cycle would be similar to the one depicted in Scheme 1, path *a*.[56,58] The α,β-unsaturated ketones would be formed from isomerization of the β,γ-unsaturated ketones via addition/elimination sequences of the in-situ produced HPd species.[56] An excess of pyridine was required for the selective cleavage of bond *b* of vinylcyclobutanol **16a**. Indeed, a substoichiometric amount led to the competitive cleavage of bond *a* giving 1-methylenehexahydroindan-2-one (**18a**)[58] (Eq. 59). The dependence of the reaction course of **16a** on the experimental conditions is discussed in Subchapter 3.1.2.



15a, R = *n*-Bu, n = 1, 38 h:[b] 71%
16a, R = CH=CH$_2$, n = 1, 20 h:[a,c] 56%
16b, R = CH=CH$_2$, n = 2, 23 h:[a] 52%
17a, R = Ph, n = 1, 48 h:[a] 60%
17a, R = Ph, n = 1, 16 h:[b] 97%
17b, R = Ph, n = 2, 21 h:[b] 93%

[c]30% with 0.2 equiv. of pyridine and formation of  (21%)

18a

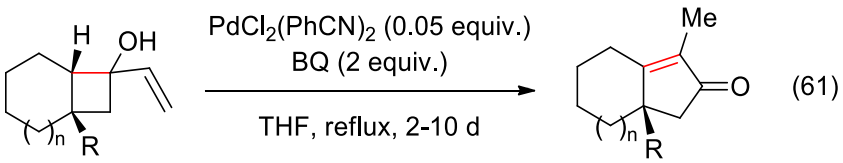


15b, R^1 = *n*-Bu, R^2 = *n*-hexyl: 41% 21%
15c, R^1 = *n*-Bu, R^2 = *t*-Bu: 20% 49%
17c, R^1 = Ph, R^2 = *n*-hexyl: 57% 3%
17d, R^1 = Ph, R^2 = *t*-Bu: 33% 43%

3.1.2. Ring expansion

3.1.2.1. Via a Heck-type reaction

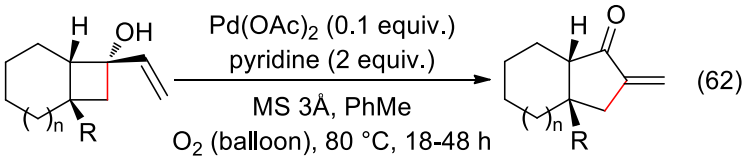
Prior to Uemura's team, Clark's team also discloses the Pd^{II}-catalyzed ring-expansion of **16a** but with formation of the intracyclic enone **19a** (Eq. 61)[59] instead of the exocyclic enone **18a** (Eq. 59). The Clark procedure, which uses $PdCl_2(PhCN)_2$ and benzoquinone, also led to intracyclic enones from **16b**, **16c** and **16d** (Eq. 61). Although both teams prepared **16a** from Grignard reaction of the corresponding butanone,[58,59] the C-OH configuration center could differ;[60] the configuration is not indicated in Clark's report (Eq. 61).[59] We propose that the difference is rather ascribable to the different experimental conditions of Eqs 59 and 61.



16a, R = H, n = 1: **19a**, 67%
16b, R = H, n = 2: **19b**, 53%
16c, R = H, n = 0: **19c**, 58%
16d, R = Me, n = 1: **19d**, 67%

The above difference in the structure of the ring-expansion product was not commented by Uemura and co-workers. Under $Pd(OAc)_2$/pyridine conditions, **16d**, **16e** and **16f** led to 2-

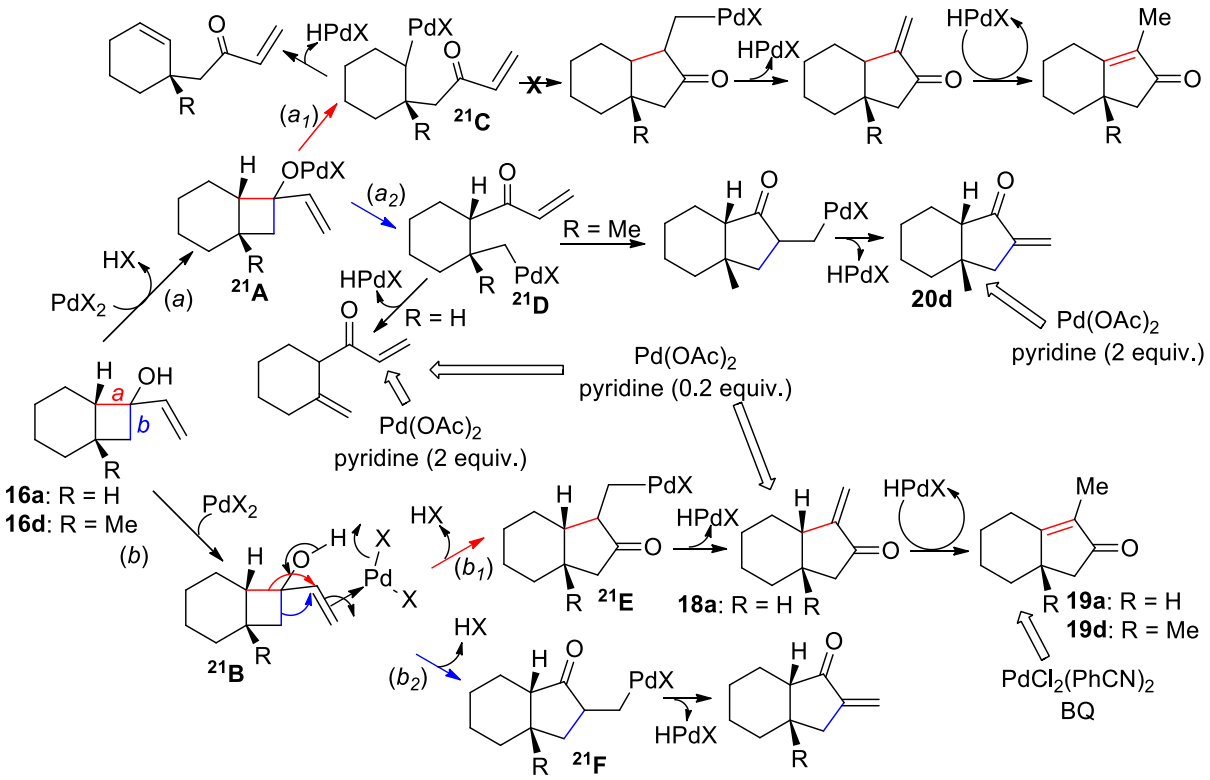
methylenehexahydroindan-1-ones **20d-20f** (Eq. 62), while **16a** provided 1-methylenehexahydroindan-2-one (**18a**) (Eq. 59).[56]



(62)

16d, R = Me, n = 1: **20d**, 67%
16e, R = Ph, n = 0: **20e**, 67%
16f, R = Ph, n = 1: **20f**, 62%

In Scheme 21, we consider the different plausible reaction paths of **16a** and **16d**. Reaction of the substrate with the Pd^{II} catalyst leads to either alkoxypalladium ^{21}**A** (path *a*) or η^2-vinylpalladium ^{21}**B** (path *b*). Cleavage of the bond *a* of ^{22}**A** (path a_1) would afford alkylpalladium intermediate ^{21}**C** which would undergo β-H elimination leading to the cyclohexenyl derivative, rather than Heck reaction. Cleavage of the bond *b* of ^{21}**A** (path a_2) would provide ^{21}**D** which gives the ring-cleavage product if R = H, or 2-methylenehexahydroindan-1-one if R = Me. Rearrangement of ^{21}**B** could afford alkylpalladium intermediates ^{21}**E** (path b_1) or ^{21}**F** (path b_2). β-H elimination from ^{21}**E** gives the 1-methylenehexahydroindan-2-one which may evolve towards the intracyclic enone. As for ^{21}**F**, it would lead to 2-methylenehexahydroindan-1-one if R = Me.

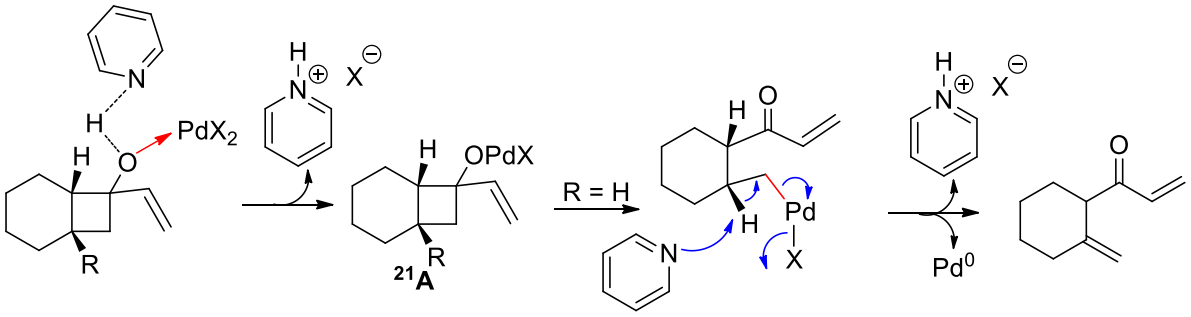


Scheme 21

We propose that pyridine promotes path *a* via i) activation of the OH bond[61,62] leading to the decrease of the energy required for the formation of alkoxypalladium intermediate ^{21}**A** and ii) trapping of HX (Scheme 22). Path a_1 being above discarded, path a_2 leads to the ring-opening

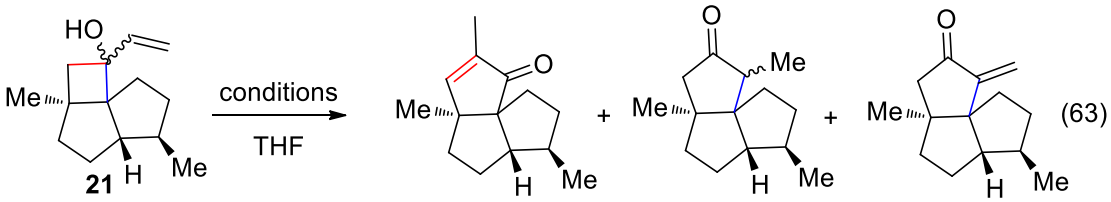
or ring-expansion product, depending on the nature of R. When R = H, pyridine may assist the β-H elimination[61,62] (Scheme 22). Decreasing the amount of pyridine makes less easy the formation of ^{21}**A**, hence the occurrence of the competitive path *b* which affords **18a** as side-product from **16a**.

Coordination to the catalyst of a ligand with a π-acid character such as benzoquinone increases the electron-deficiency of the palladium center, favoring the coordination of the C=C bond of the substrate[63,64] to selectively afford ^{21}**B** (Scheme 21, path *b*). Subsequent cleavage of bond *a* affords **19a** and **19d** from **16a** and **16d**, respectively (path b_1). It seems required to point out the two roles of BQ: ligand and reoxidant. According to the experimental results, path b_2 would not occur in the presence of BQ.



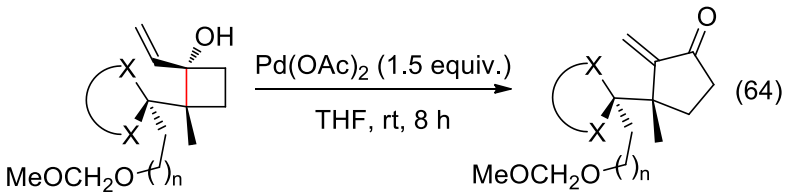
Scheme 22

Pd^{II} compounds in either stoichiometric amounts or catalytic quantities associated to benzoquinones have been used for a variety of ring expansions (Eqs 63,[65] 64[66] and 65 to 67[67]). The expected reaction failed however from **22b** (Eq. 64), probably, according to Nemoto and co-workers, because of "the existence of the double bond close to the reaction site".[68]



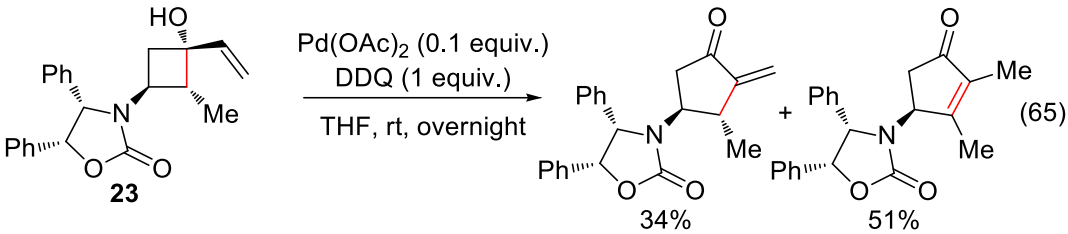
$PdCl_2(PhCN)_2$ (1 equiv.), rt, 1h: 75%, 1:5.5:4

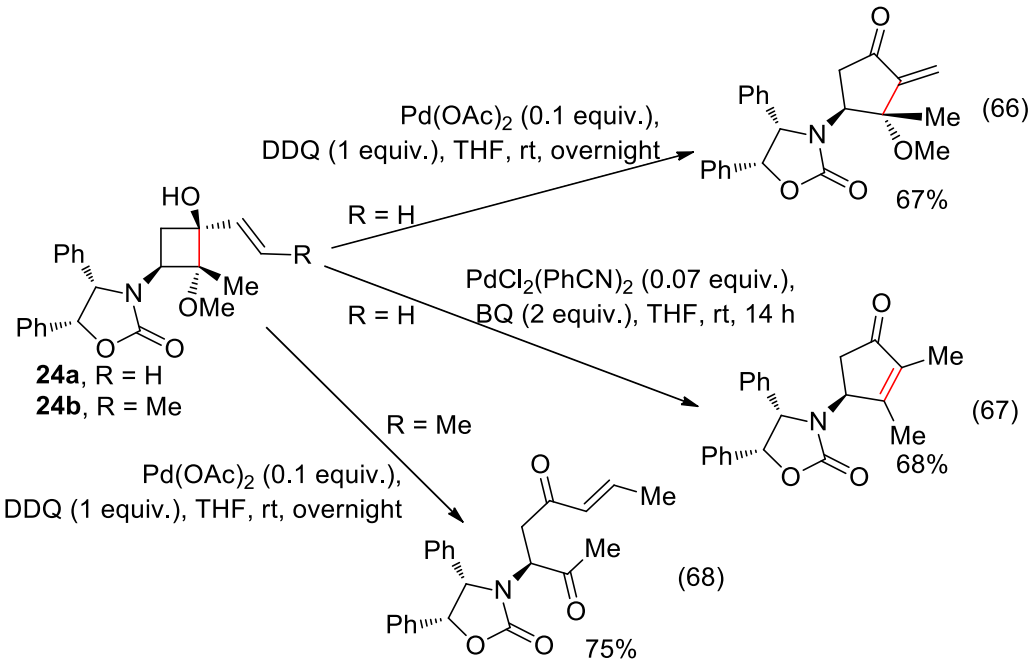
$PdCl_2(PhCN)_2$ (0.05 equiv.), BQ (2 equiv.), reflux, 48 h: 64%, 1:2.2:6



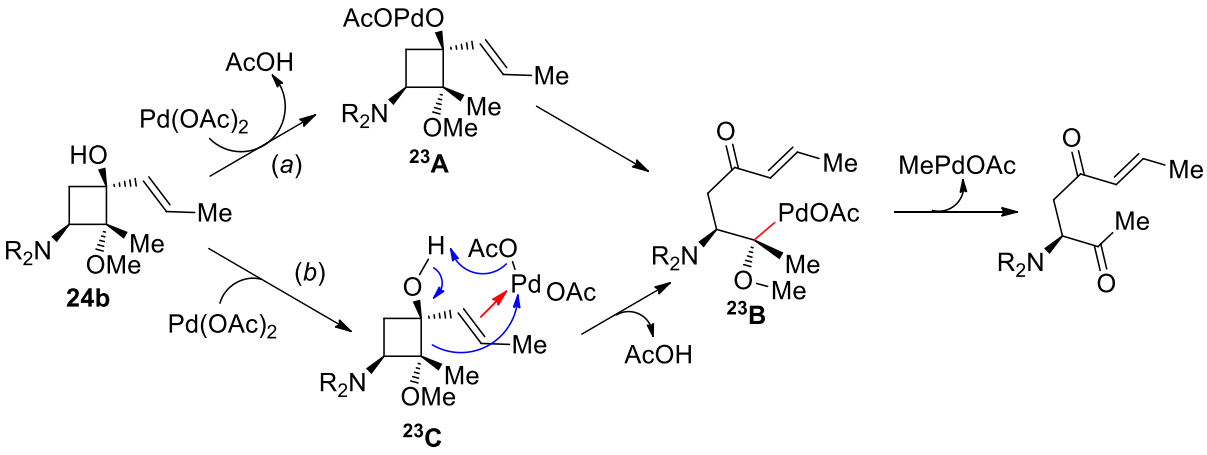
22a, n = 0, X = O, O, CH_2, CH_2 : 79-90%

22b, n = 1, X = CH, CH_2 : 0%



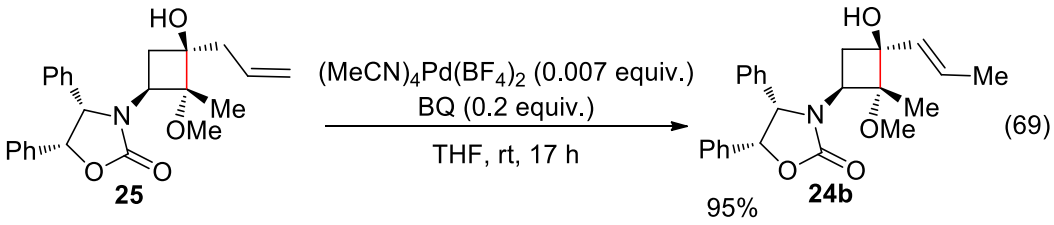


Surprisingly, treatment of **24a** under Clark's conditions led to the elimination of the MeO substituent (Eq. 67) while $Pd(OAc)_2$ associated to 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) afforded the expected methylene ketone (Eq. 66).[67] Hegedus and Ranslow proposed that the elimination product is formed from addition of the in-situ produced HPd species to the C=C bond of the methylene ketone followed by the competitive β-elimination of palladium methoxide.[69] Propenyl cyclobutanol **24b** led to a diketone instead of the ring-expansion product (Eq. 68).[67] The authors presumed that "this ring opening reaction takes place via a β-carbon elimination pathway".[67] This elimination could occur after formation of alkoxypalladium complex ^{23}**A** and subsequent cleavage into ^{23}**B** (Scheme 23, path *a*). The reaction arising in the absence of base, we rather suspect a ring cleavage from ^{23}**C** (Scheme 23, path *b*). Given the preservation of the configuration of the asymmetric carbon center, it seems interesting to note that, from ^{23}**B**, the β-H elimination leading to a vinyl ether as a plausible intermediate towards the diketone did not occur.

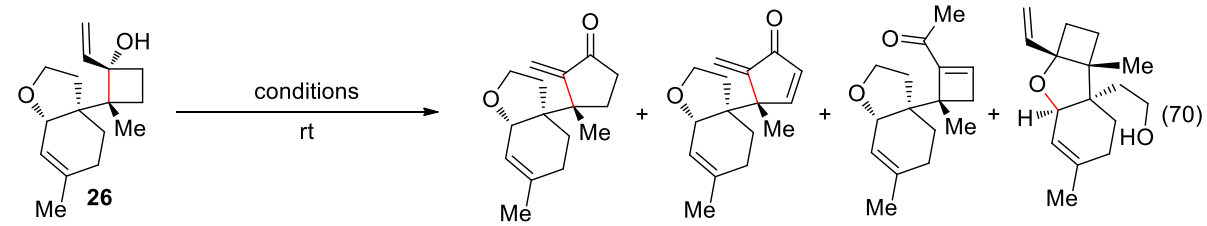


Scheme 23

Hegedus and Ranslow expected the formation of a cyclohexenone from ring expansion of allylcyclobutanol **25**, but treatment with a cationic Pd complex in the presence of BQ only led to efficient migration of the double bond giving **24b** (Eq. 69).[67]



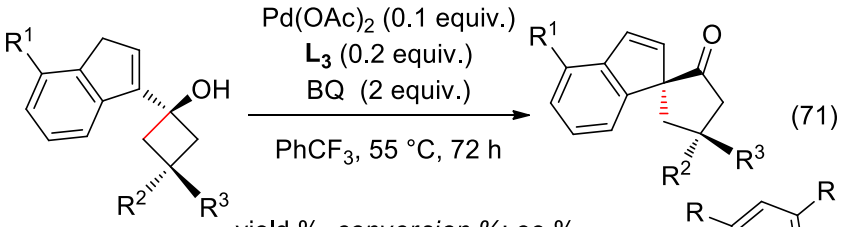
The retrosynthesis of (±)-scirpene designed by Nemoto and co-workers involved the ring-expansion product of **26** as an intermediate.[68] While only a tricyclic compound was obtained using stoichiometric $Pd(OAc)_2$, $PdCl_2(MeCN)_2$ afforded the target product, especially in the presence of BQ, but in decreased yield under catalytic conditions (Eq. 70). An acetylcyclobutene was a notable by-product; the mechanism of its formation is obscure. Slight dehydrogenation of the ring-expansion product was observed.[35]



$Pd(OAc)_2$ (2 equiv.), THF:	0%	0%	0%	50%
$PdCl_2(MeCN)_2$ (1.2 equiv.), DMF:	36%	0%	32%	31%
$PdCl_2(MeCN)_2$ (1 equiv.), BQ (2 equiv.), DMA:	62%	4%	34%	trace
$PdCl_2(MeCN)_2$ (0.1 equiv.), BQ (2 equiv.), DMA:	42%	4%	27%	trace
$PdCl_2(MeCN)_2$ (0.1 equiv.), $CuCl_2$ (2 equiv.), DMA:	43%	0%	41%	trace

Rayney and Chai studied the enantioselective Pd-catalyzed ring expansion of indenyl propanols **27**.[70] Screening a series of BINOL-derived Brønsted acids showed a strong influence of the solvent, traces of water and steric hindrance of the ligand, leading to the best results in $PhCF_3$ with $Pd(OAc)_2$/BQ associated to phosphoric acid $\mathbf{L_3}$ (Eq. 71). Essentially no-conversion of **27a** occurred in the absence of the catalyst or the ligand. Moreover, related

substrates shown on Figure 2 or use of the methyl ether of **27a** failed to undergo the desired reaction or led to low yields. On the basis of these observations and of an intermolecular kinetic isotopic effect experiment, the authors proposed the formation of a η^3-allylpalladium intermediate and the phosphoric acid-assisted cleavage of the four-membered ring. Subsequent computational studies by Sunoi and Jindal led to rather favor a Wacker-type mechanism (Scheme 24)[71] and then, to decipher the origin of the stereoinduction, ^{24}**A** being the stereodetermining transition state.[72]

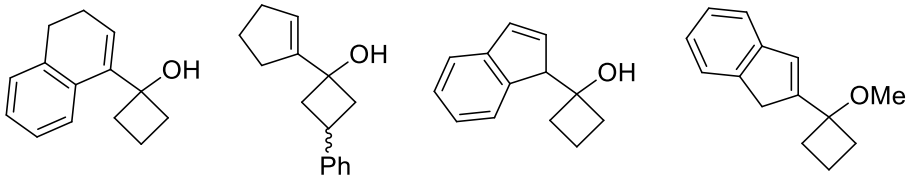


(71)

yield %, *conversion %*; ee %

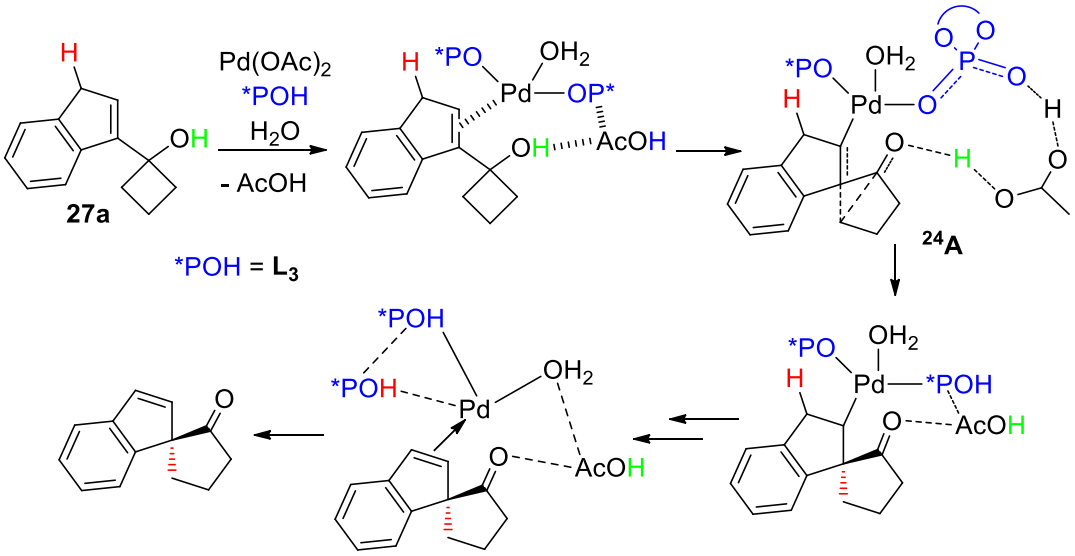
27a, $R^1 = R^2 = H$, $R^3 = H$: 67, *89*, 75[a]
27b, $R^1 = R^2 = H$, $R^3 = Ph$: 59, *70*; 97[b]
27c, $R^1 = R^2 = H$, $R^3 = CH_2OBn$: 43, *74*; 96[c]
27d, $R^1 = R^2 = H$, $R^3 = n$-Bu: 78, *91*; 96[d]
27e, $R^1 = R^2$-$R^3 = (CH_2)_5$: 69, *94*, 77
27f, $R^1 = OBn$, $R^2 = H$, $R^3 = H$: 50, *70*, 84
[a]In PhMe at 60 °C for 48 h: <*10%* conversion using **L**$_1$ and 45, *88*, 34 using **L**$_2$.
[b]Diasteroisomer ratio: 8:1.
[c]Diasteroisomer ratio: 6:1.
[d]Diasteroisomer ratio: 4:1.

L$_1$, R = H
L$_2$, R = Me
L$_3$, R = *i*-Pr



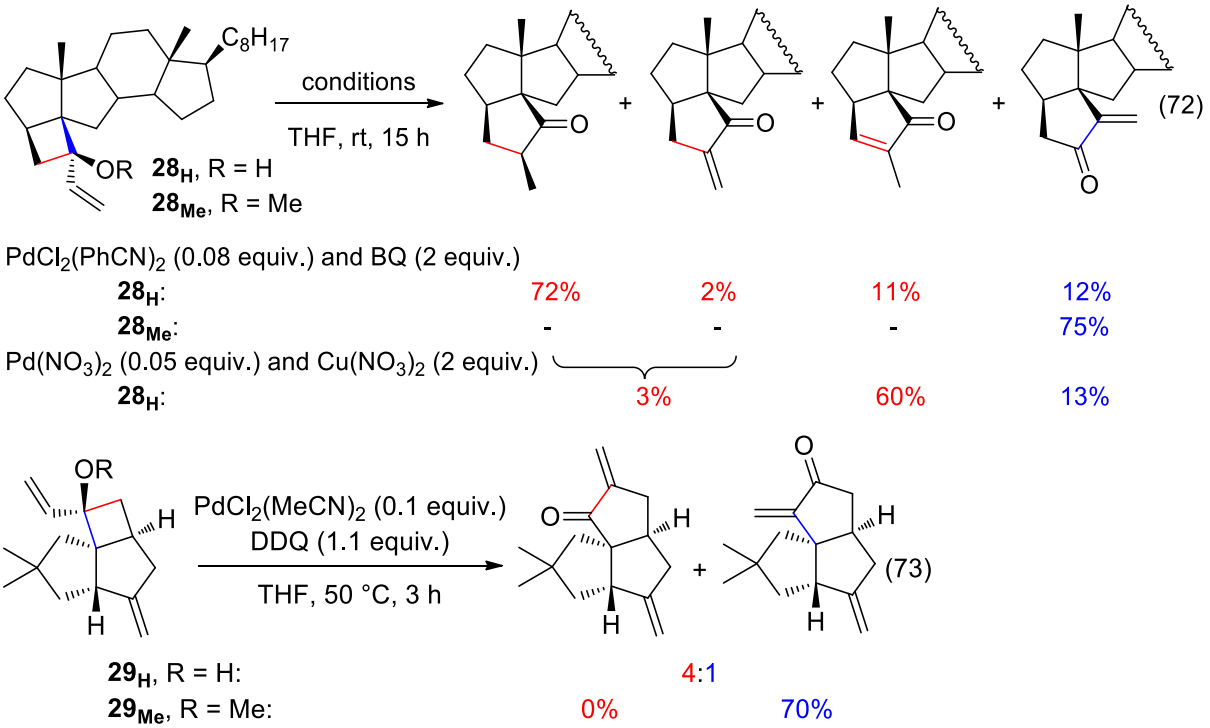
Yield: 0% 0% < 3% 0%

Figure 2

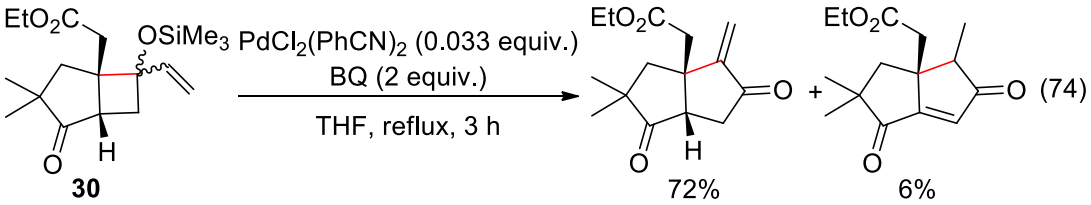


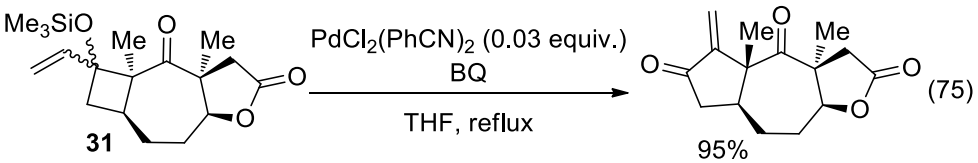
Scheme 24

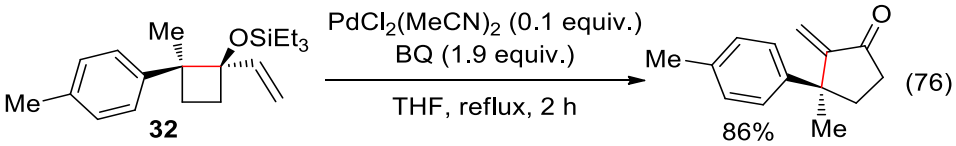
Research on the synthesis of nonlinear triquinane-type building blocks led Kočovský's team to study the Pd^{II}-catalyzed rearrangement of $\mathbf{28_H}$ (Eq. 72).[73] A mixture of ring-expansion products was obtained from cleavage of mainly the less-substituted bond. In contrast, the methyl ether $\mathbf{28_{Me}}$ led to the selective migration of the quaternary carbon. Such a selectivity difference was also observed by Toste and co-workers for the ring-expansion of $\mathbf{29_H}$ compared to that of $\mathbf{29_{Me}}$ (Eq. 73).[74]



Ring expansions have also been reported from trimethyl- and triethylsilyl ethers of vinylcyclobutanols **30-32** (Eqs 74,[75] 75[76] and 76[77]), the deprotection of the silyl ether would be *in situ* Pd mediated.[78] Ionic intermediates have been proposed in order to account for the fortuitous epimerization of the $C(sp^3)$-Me in the course of the reaction of **31**.

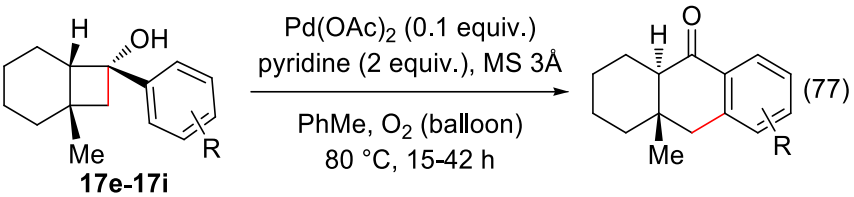






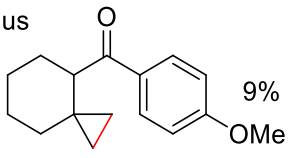
3.1.2.2. Via C-H activation of an aryl group

While arylcyclobutanols **17a-17d** led to ring opening products (Eqs 59 and 60), **17e-17i** afforded hexahydroanthracenones under similar experimental conditions (Eq. 77).[56] This results from the angular methyl substituent of **17e-17i** that leads to no hydrogen available for the β-H elimination of the alkylpalladium intermediate generated from cleavage of the less substituted C-C bond of the four-membered ring. Consequently, this intermediate undergoes intramolecular reaction with the aryl group leading to the oxidative ring expansion product. The epimerization of the angular C-H arises from reversible palladium intermediates in the course of the process, or from the subsequent formation of an oxo-π-allylpalladium complex. A slight amount of a cyclopropyl ketone due to competitive reaction pathway with the methyl substituent of the alkylpalladium, was isolated from **17i**. According to Uemura's team, the formation of this three-membered ring would involve either a Pd^{IV} species obtained by activation of a $C(sp^3)$-H, or addition of a Pd-carbene complex produced by α-H elimination of the alkylpalladium.[56] It seems interesting to point out the strong difference of reactivity of monocyclic arylcyclobutanols **17j-17m** and pinene derivative **17n** (see Section 3.1.3.).



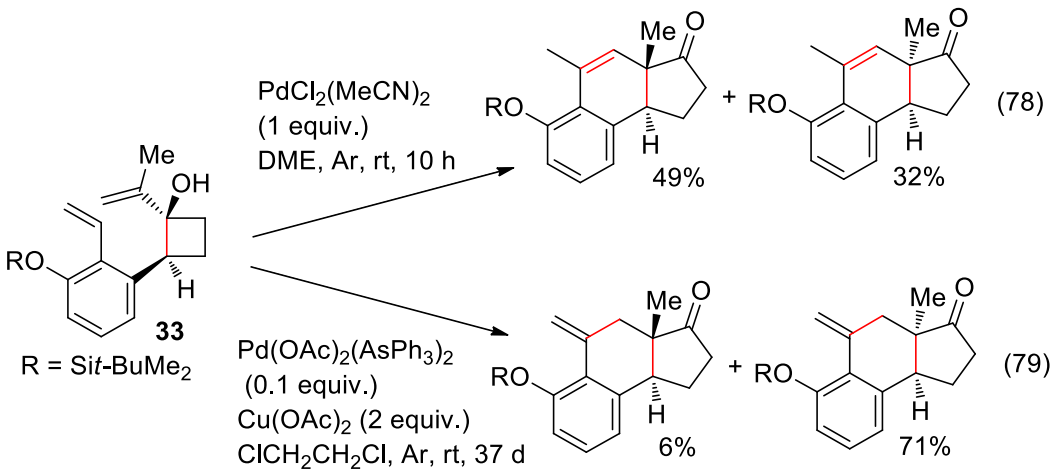
R = H, **e**: 92%; *m*-Cl, **f**: 85%; *p*-Cl, **g**: 93%; *m*-MeO, **h**: 85%; *p*-MeO, **i**: 83%[a]

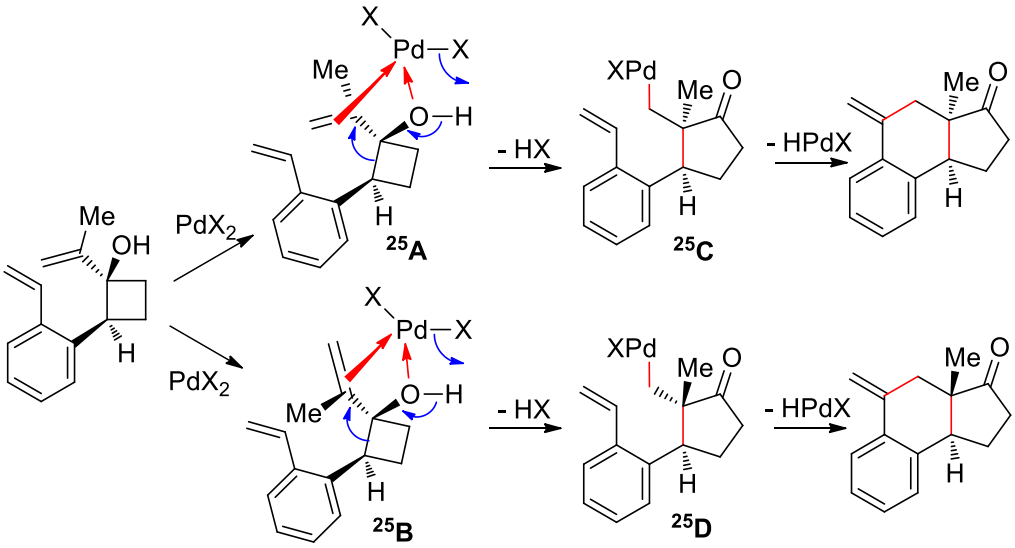
[a]Plus



3.1.2.3. Via two domino Heck-type reactions

Isopropenyl cyclobutanols such as **33**, which bear a chain with a C=C bond in a position suitable for coordination to the alkylpalladium intermediate formed in the course of the ring-expansion, underwent a domino reaction leading to benzo- and naphthohydrindans as reported by Nemoto's team,[79-81] using either stoichiometric amounts of Pd^{II} (Eq. 78) or catalytic conditions (Eq. 79).[80] The formation of diastereoisomers may be explained by different conformations of the isopropenyl group leading to palladium intermediates ^{25}**A** and ^{25}**B** (Scheme 25). Subsequent migration of the cyclobutyl bond via the face opposite to palladium would provide ^{25}**C** and ^{25}**D**, respectively, which undergo Heck reaction to deliver the products. The diastereoisomers ratio may also depend on the solvent polarity.[81]



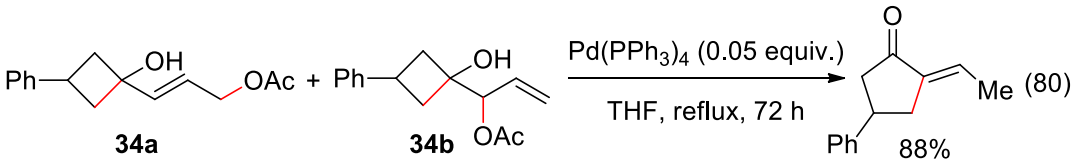


Scheme 25

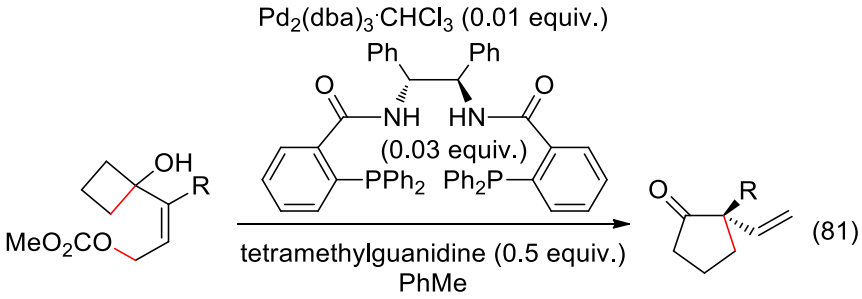
The above domino reactions would be limited to substrates bearing the isopropenyl-type substituent, which lead to alkylpalladium intermediates like ^{25}**C** and ^{25}**D**, without plausible β-H elimination reaction. Indeed, Nemoto and co-workers did not mention the domino reaction from **22b** (Eq. 64).[68]

3.1.2.4. η^3-Allylpalladium-mediated ring expansion

In the course of the study of the Pd^0-catalyzed ring expansion of vinyl oxaspirohexanes, Kim and co-workers isolated a mixture of allyl acetates **34a** and **34b**.[82] A slow reaction of this mixture under Pd^0-catalysis in refluxing THF afforded (*E*)-2-ethylidene-4-phenylcyclopentanone in high yield (Eq. 80).



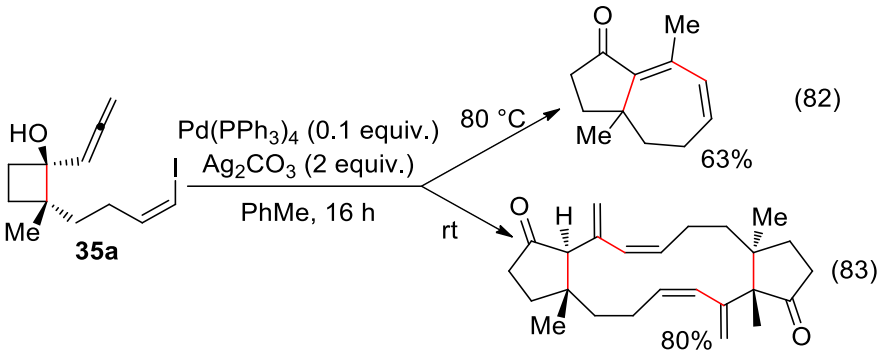
The C-3 → C-4 ring expansion procedure related in Subchapter 2.2.1. also led to the efficient asymmetric C-4 → C-5 ring expansion of allyl carbonates **34c** and **34d** (Eq. 81).[18]

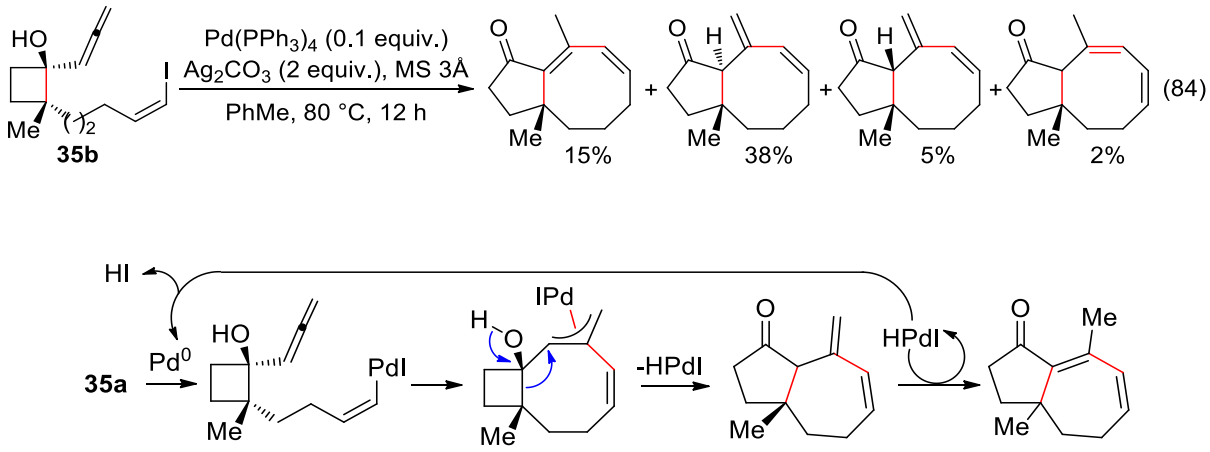


The ring expansions depicted in Eqs 80 and 81 occur through a catalytic cycle similar to that of Scheme 3.

3.1.2.5. Allene carbopalladation-mediated ring-expansion

The Pd^0-catalyzed reaction of 1-allenylcyclobutanols bearing an alkenyliodide tether **35a** and **35b** provided bicyclic compounds at 80 °C (Eqs 82 and 84) through carbopalladation of the allenyl moiety followed by ring expansion of the four-membered ring and isomerization (Scheme 26). In contrast, a bimolecular reaction leading to a tricyclic diketone arose at room temperature from **35a** (Eq. 83).[83]

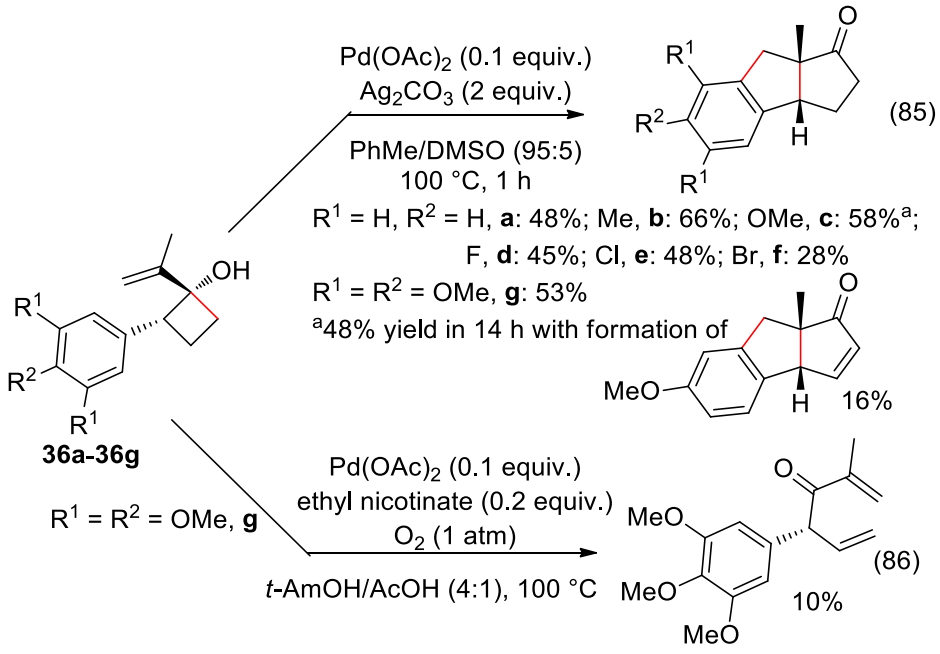




Scheme 26

3.1.2.6. Via Heck-type reaction and C(sp^2)-H activation

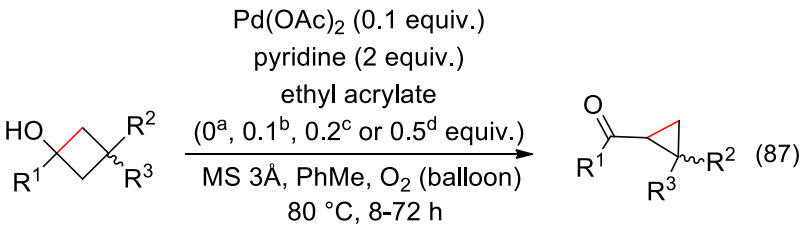
The domino ring expansion/arylation reaction of α-aryl isopropenyl cyclobutanols **36a-36g** leading to benzodiquinanes has been disclosed by Orellana and co-workers, under $Pd(OAc)_2$ catalysis with Ag_2CO_3 as both base and reoxidant.[84] A mixture of PhMe and DMSO as solvent at 100 °C for 1 h would be the optimum conditions (Eq. 85). This domino reaction would occur similarly to Scheme 25 with oxidative addition of the alkylpalladium to an aryl group instead of an olefin. Increasing the reaction time led to dehydrogenation of the cyclopentanone moiety.[35] Changing experimental conditions for those of Stoltz's team used for dehydrogenative Heck reactions[85] led to the ring-cleavage product of **36g** in a low yield (Eq. 86).



3.1.3. Ring contraction

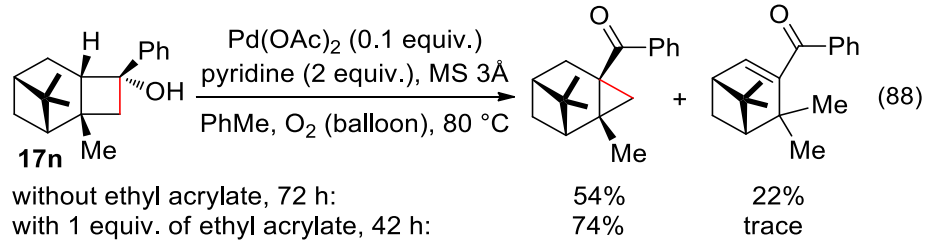
The ring-contraction leading to α,β-cyclopropylketones from 3-disubstituted *tert*-cyclobutanols **15d** and **15e** (Eq. 87)[56] could be due to the absence of available hydrogen for a β-H elimination

in the alkylpalladium intermediate formed from the ring cleavage. However, 3-disubstituted-1-phenylcyclobutanols **17j-17m** also afforded such compounds (Eq. 87).[56] This contrasts to the ring expansion products obtained from 2,3,3-trisubstituted-1-arylcyclobutanols **17e-17i** under similar experimental conditions (Eq. 77).[56]

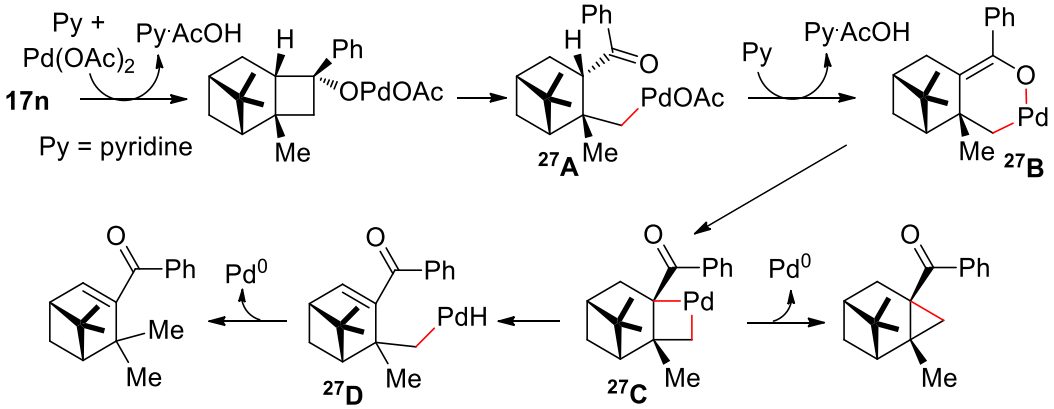


15d, $R^1 = R^2 = R^3 = n$-Bu:	83%[b]
15e, $R^1 = n$-Bu, R^2-$R^3 = (CH_2)_5$:	95%[b]
17j, $R^1 = R^2 = R^3$ = Ph:	47%[a], 65%[c]
17k, R^1 = Ph, $R^2 = R^3 = n$-Bu:	94%[b]
17l, R^1 = Ph, R^2 = Me, R^3 = Ph:	30%[a], 69%[c], 81%[d]
17m, R^1 = Ph, R^2-$R^3 = (CH_2)_5$:	98%[a], 98%[b]

Despite the structure of pinene derivative **17n** more similar to that of **17e-17i** (Eq. 77), the dehydrogenative Heck reaction of Eq. 77 was, like from **17j-17m**, not observed (Eq. 88). The results highly depended on the presence of ethyl acrylate. In its absence, a mixture of the α,β-cyclopropylketone and an unusual α,β-enone was obtained with 96% conversion in 72 h, whereas this additive led to full conversion in 42 h and selective formation of the cyclopropylketone. According to Uemura's team, pyridine converts the alkylpalladium intermediate ^{27}**A** into the palladium enolate ^{27}**B**, which affords the palladacyclobutane ^{27}**C** (Scheme 27). ^{27}**C** undergoes either reductive elimination leading to the cyclopropylketone, or β-H elimination giving the hydridopalladium complex ^{27}**D**. Subsequent reductive elimination delivers the enone.



without ethyl acrylate, 72 h:	54%	22%
with 1 equiv. of ethyl acrylate, 42 h:	74%	trace

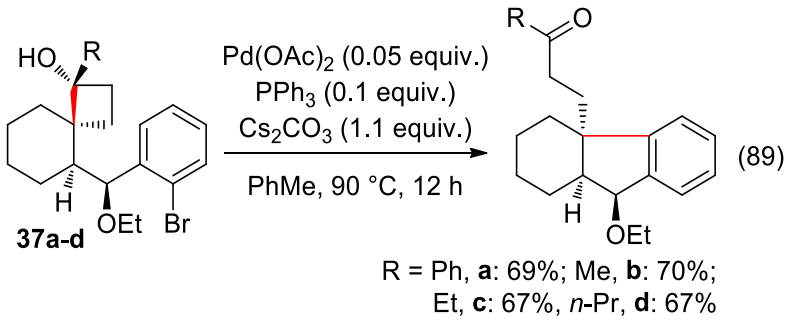


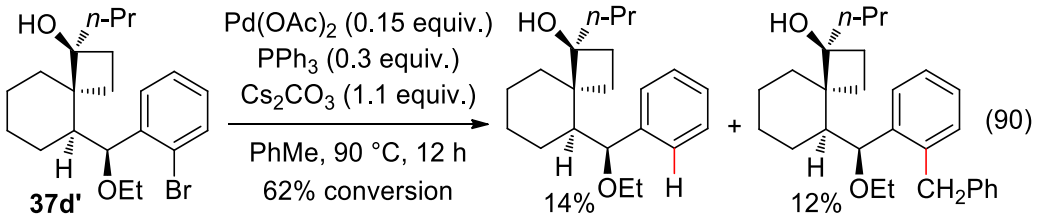
Scheme 27

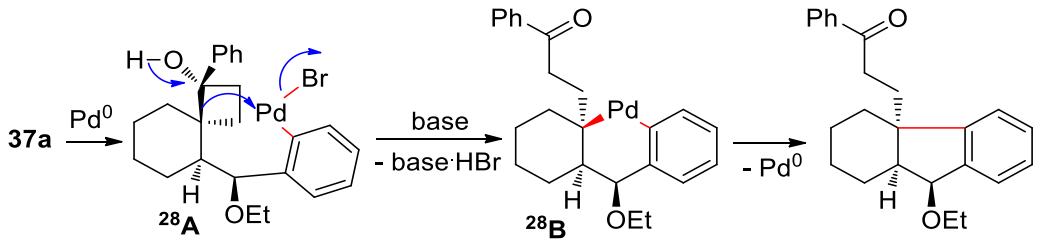
The role of ethyl acrylate on the selectivity (Eq. 88) as well as the absence of the ring expansion product from **17j-17n** remains obscure.

3.1.4. Annelation via arylpalladium^{II}-mediated ring opening

An annelation arose from the Pd^0-catalyzed reaction of *o*-bromophenyl-tethered *tert*-cyclobutanols **37a-37d** leading to five-membered carbocycles (Eq. 89).[86] The reaction course highly depended on the hydroxyl configuration. Indeed, no annulation occurred from **37d'** (Eq. 90). The absence of annulation of the trimethylsilylether of **37a** was also noted. These observations and the stereochemistry of the isolated products led Cha and co-workers to assume the absence of a palladium alcoholate intermediate. That differs from the reaction of bromobenzyl-tethered cyclopropanol **5a** (Scheme 5). Arylpalladium complex ^{28}**A** was proposed as intermediate (Scheme 28). Base-assisted intramolecular electrophilic attack of the four membered ring results in cleavage of the more substituted C-C bond leading to palladacycle ^{28}**B**. Subsequent reductive elimination of Pd^0 releases the product.







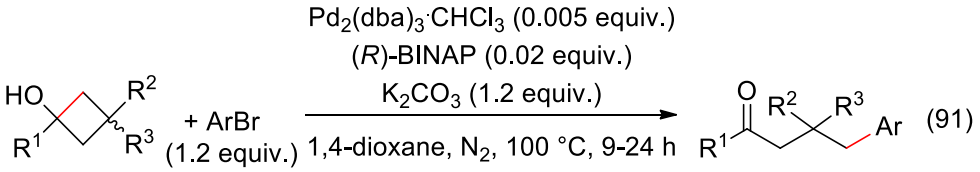
Scheme 28

3.2. Intermolecular reactions of the cyclobutanol core

3.2.1. With aryl halides or triflates

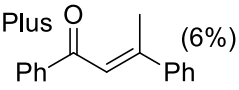
In 1999, Uemura and Nishimura disclosed the synthesis of γ-arylketones from the Pd^0-catalyzed coupling of *tert*-cyclobutanols with aryl bromides (Eqs 91 and 92).[87] In the original paper, (*R*)-(+)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl ((*R*)-BINAP) was superior to other tested

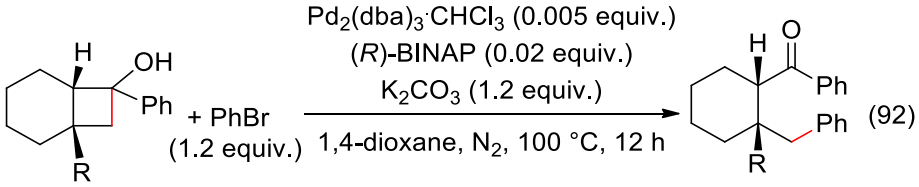
ligands for optimum yields, but did not induce enantioselectivity. These reactions occur in a manner similar to that of *tert*-cyclopropanols (Scheme 9, path *a*). A slight amount of the unsaturated ketone due to β-H elimination instead of reductive elimination was isolated from **17o** (Eq. 91).



(91)

17d, R^1 = Ph, R^2 = *t*-Bu, R^3 = H: Ar = Ph (96%), 2-naphthyl (82%)
17j, R^1 = R^2 = R^3 = Ph: Ar = Ph (94%)
17l, R^1 = Ph, R^2 = Me, R^3 = Ph: Ar = Ph (95%), 2-naphthyl (85%), *p*-ClC_6H_4 (94%)
17o, R^1 = R^2 = Ph, R^3 = H: Ar = Ph (79%)[a]

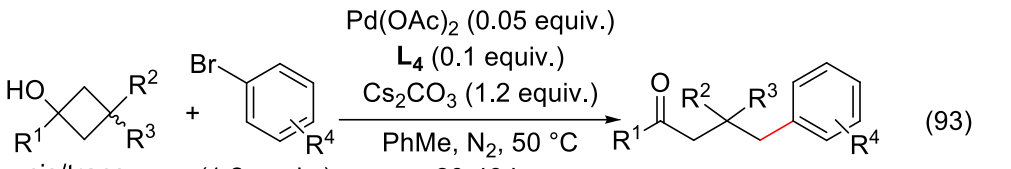
[a]Plus  (6%)



(92)

17a, R = H: 96%
17e, R = Me: 95%

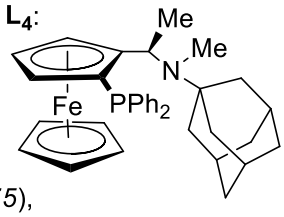
Screening various unichiral ligands,[88] in particular ferrocene-containing N,P-bidentate ligands, led the team to subsequently report *ee's* up to 78%[89] and then 95%[90] (Eq. 93). Aryl bromides seem to afford better enantioselectivities than aryl triflates.[90] The procedure was used for the resolution of racemic tertiary cyclobutanols (Eq. 94).[91]



(93)

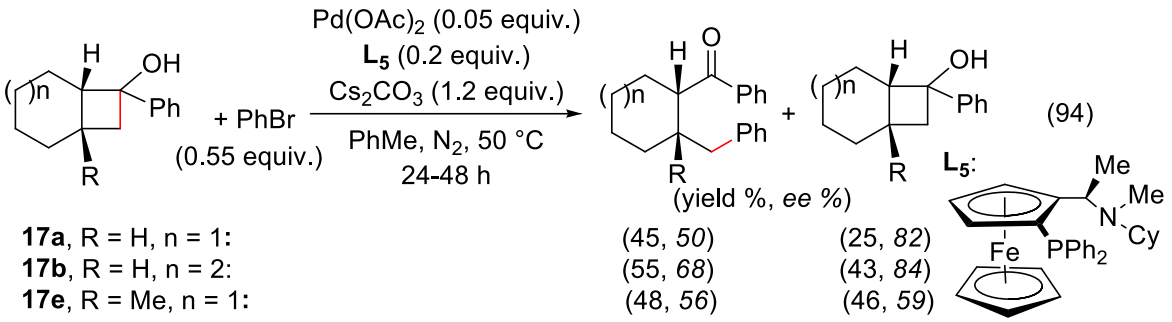
cis/trans = 99:1-96:4
(1.2 equiv.)

L4:

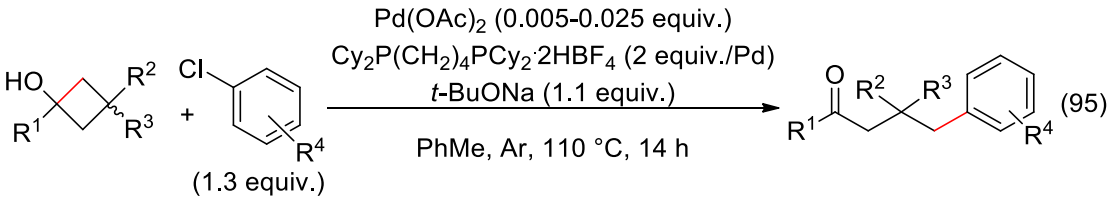


(yield %, *ee* %)

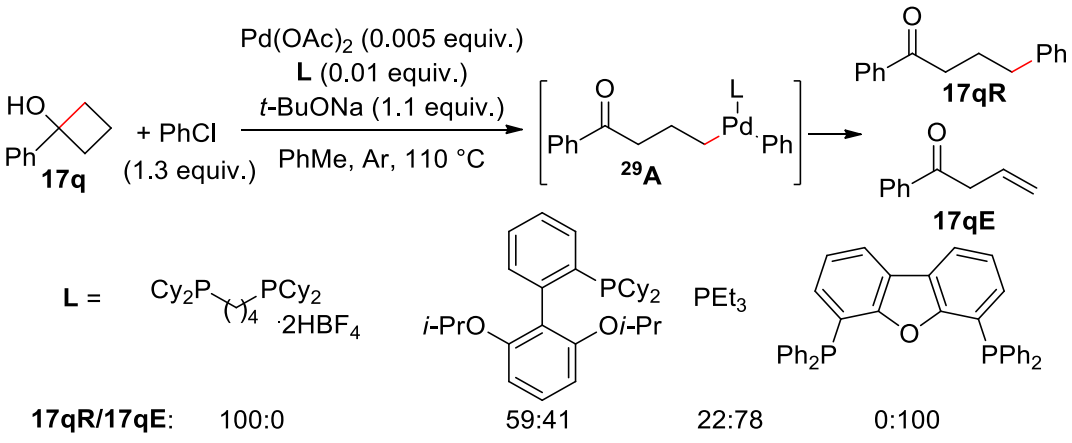
17c, R^1 = Ph, R^2 = *n*-hexyl, R^3 = H: R^4 = H (99, *82*)
17d, R^1 = Ph, R^2 = *t*-Bu, R^3 = H: R^4 = H (99, *75*)
17l, R^1 = Ph, R^2 = Me, R^3 = Ph: R^4 = H (83, *90*)
17o, R^1 = R^2 = Ph, R^3 = H: R^4 = H (93, *91*), *o*-OMe (94, *75*), *m*-OMe (93, *82*), *p*-OMe (87, *90*), *p*-Me (95, *91*), *p*-Cl (97, *88*), *p*-NMe_2 (89, *95*)



In 2012, Martin and Ziadi related the Pd^0-catalyzed arylative ring-opening reaction with much less reactive aryl chlorides using $Cy_2P(CH_2)_4PCy_2{\cdot}2HBF_4$ as the ligand and *t*-BuONa as the base at 110 °C (Eq. 95).[92] Under these conditions, the γ-arylation was efficient even in the absence of 3-substitution of the substrate as demonstrated with **17p**, but did not occur with heteroaromatics such as 2-chloropyridine, 3-chloropyridine and 3-chlorothiophene. The dependence of the selectivity - reductive elimination versus β-H elimination reaction from σ-alkylpalladium intermediate [29]**A** - on the nature of the ligand is exemplified in Scheme 29. The authors proposed that $Cy_2P(CH_2)_4PCy_2{\cdot}2HBF_4$ retards the β-H elimination and enhances the reductive elimination, favoring the formation of the cross-coupling product.

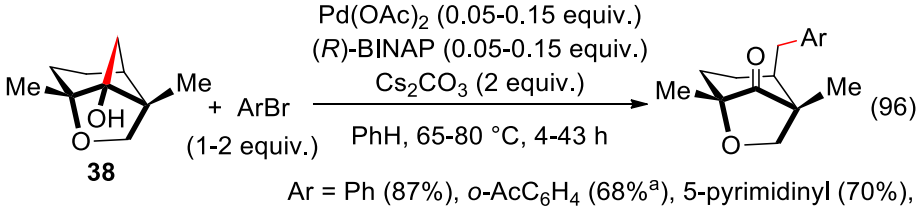


15f, R^1 = Me, R^2 = Me, R^3 = Ph: R^4 = H (90%)
17c, R^1 = Ph, R^2 = *n*-hexyl, R^3 = H: R^4 = H (83%)
17j, R^1 = R^2 = R^3 = Ph R^4 = H (99%)
17l, R^1 = Ph, R^2 = Me, R^3 = Ph: R^4 = H (97%), *p*-(*n*-Bu) (93%), *p*-OMe (75%), *p*-SMe (99%), *p*-CF_3 (99%), *p*-NH_2 (71%), *p*-COMe (88%), *p*-CH=CH_2 (99%), *m*-Cl (82%), *p*-(1-pyrrolyl) (99%), *o*-Me (97%)
17o, R^1 = R^2 = Ph, R^3 = H: R^4 = H (97%),
17p, R^1 = Ph, R^2 = R^3 = H: R^4 = H (83%), *p*-SMe (84%), *p*-CH=CH_2 (86%)



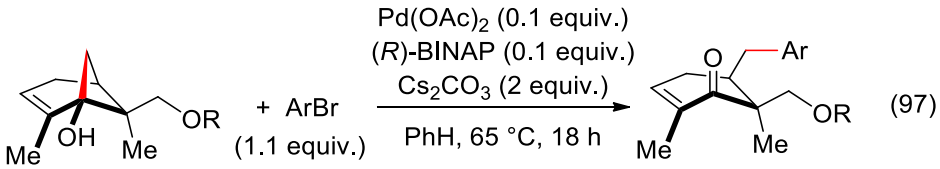
Scheme 29

For the construction of taxol scaffold, Sarpong and co-workers carried out the arylative ring-opening of (+)-carvone derivatives **38** and **39** using the $Pd(OAc)_2$/(*R*)-BINAP procedure (Eqs 96 and 97).[93] In some cases, changing BINAP for P(*t*-Bu)$_3$ led also to effective cross-couplings (Eq. 96).



38

Ar = Ph (87%), *o*-AcC_6H_4 (68%[a]), 5-pyrimidinyl (70%),
2-thienyl (68%), 3-furyl (34%),
2-(*N*-Me)-indolyl (54%), 3-pyridyl (76%)
[a]P(*t*-Bu)$_3$ as the ligand.

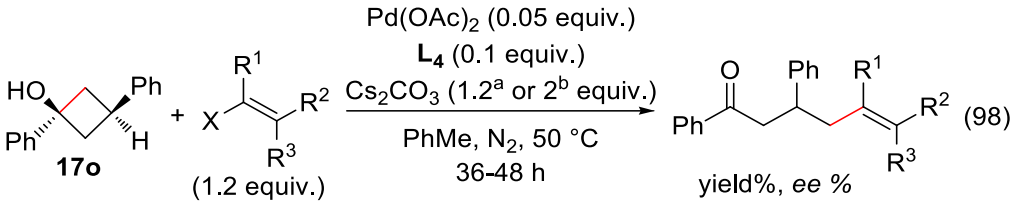


39a: R = H:
39b: R = Ac:

Ar = 2-(*N*-Me)-indolyl (29%)
Ar = Ph (64%), 2-(*N*-Me)-indolyl (59%),
4-(*N*-Boc)-indolyl (81%)

3.2.2. With vinyl halides or triflates

Uemura's team used their enantioselective arylation procedure (Eq. 93) for the enantioselective vinylation of **17o** with vinyl bromides or triflates (Eq. 98).[90]

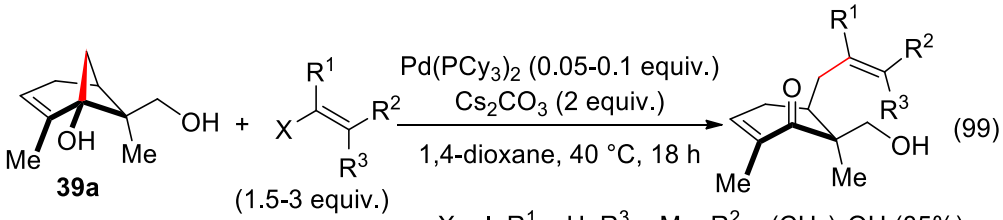


17o

yield%, *ee* %

X = OTf, R^1-R^2 = $(CH_2)_4$, R^3 = H:[a]	65, *88*
X = Br, R^1 = H, R^2 = R^3 = Me:[b]	87, *73*
X = Br, R^1 = R^2 = R^3 = H:[b]	27, *73*
X = Br, R^1 = Ph, R^2 = R^3 = H:[b]	36, *78*

After the cross-coupling of **39a** and **39b** with 2-methylprop-1-en-1-yl bromide under experimental conditions of Eq. 97,[93] Sarpong and co-workers used a variety of vinyl bromides or iodides.[94] Optimization of the reaction conditions led to retain $Pd(PCy_3)_2$ as the catalyst and 1,4-dioxane as the solvent (Eq. 99). The procedure provided an access to an intermediate of the total synthesis of xishacorene B.

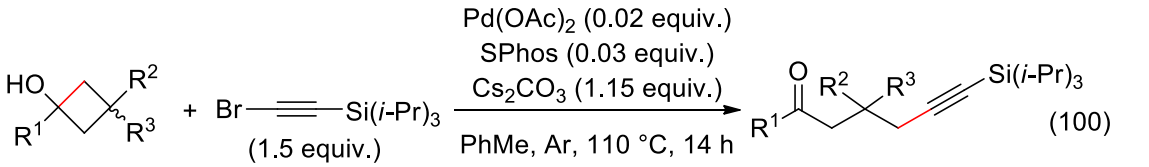


(99)

X = I, R^1 = H, R^3 = Me, R^2 = $(CH_2)_2OH$ (85%),
$(CH_2)_2CH=CMeCH_2OTBS$ (77%)
X = I, R^1 = R^2 = R^3 = H (38%)
X = I, R^1 = H, R^2 = R^3 = Ph (69%)
X = Br, R^1 = H, R^2 = R^3 = Me (89%),
CH_2OTBS (50%)
X = Br, R^2 = R^3 = H, R^1 = Me (68%),
Ph (78%), $(CH_2)_2OH$ (53%)

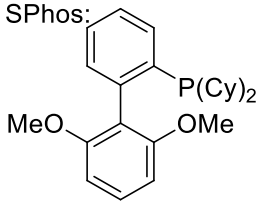
3.2.3. With bromoacetylenes

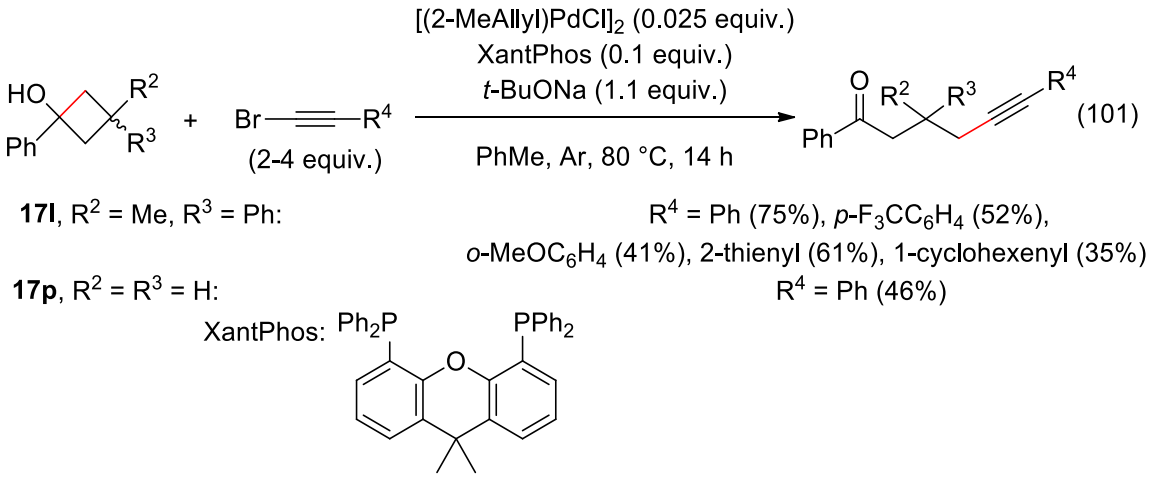
Various conditions were tested by Martin and co-workers for the cross-coupling of *tert*-cyclobutanols with (bromoethynyl)triisopropylsilane.[95] The best system – $Pd(OAc)_2$ with 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl (SPhos) as the ligand and Cs_2CO_3 as the base in toluene at 110 °C – (Eq. 100) was however not efficient for coupling with other bromoacetylenes. Re-optimization led them to use η^3-allylpalladium dimer with 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (Xantphos) and *t*-BuONa at 80 °C (Eq. 101). The reaction of **17l** with (bromoethynyl)triisopropylsilane was briefly examined using an unichiral Sphos derivative leading to a moderate enantioselectivity (22% *ee*).



(100)

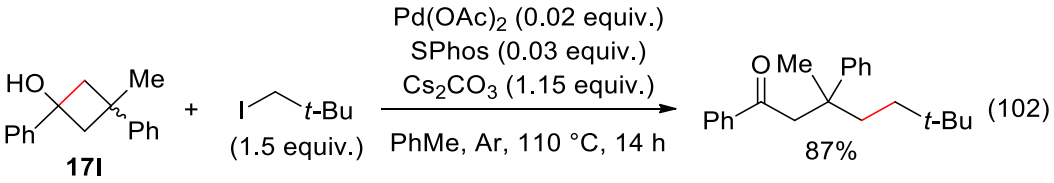
15g, R^1 = $CH_2C(Me)_2Ph$, R^2 = R^3 = H: 86%
17c, R^1 = Ph, R^2 = *n*-hexyl, R^3 = H: 88%[a]
17l, R^1 = Ph, R^2 = Me, R^3 = Ph: 92%
17o, R^1 = R^2 = Ph, R^3 = H: 78%
17p, R^1 = Ph, R^2 = R^3 = H: 82%
[a]$Pd(OAc)_2$ (0.04 equiv.).





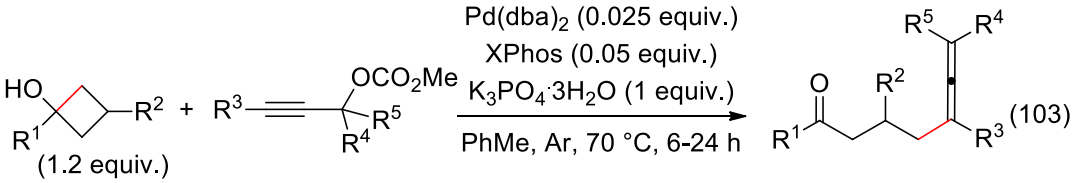
3.2.4. With alkyl halides

Under their $Pd(OAc)_2$/Sphos conditions (Eq. 100), Martin's team carried out the cross-coupling **17l** with neopentyliodide in high yield (Eq. 102).[95,96] The formation of an alkylpalladium intermediate without plausible β-H elimination allowed this efficient reaction. Given the intermolecular Heck reactions of benzyl halides[97] and α-heteroatom-substituted alkyl halides,[98,99] we anticipate that their cross-coupling with *tert*-cyclobutanols could effectively occur.



3.2.5. With propargylic carbonates

Recently, Ma and co-workers disclosed the synthesis of multisubstituted δ-allenyl ketones from the $Pd(dba)_2$/XPhos-catalyzed reaction of *tert*-cyclobutanols with propargylic carbonates (Eq. 103).[100] The reaction efficiency was very sensitive to the experimental conditions – $K_3PO_4 \cdot 3H_2O$ as base in PhMe at 70 °C leading to the best results – and to the substitution of the ring, no coupling taking place with 1-benzyl-3-phenylcyclobutanol **15k** or primary cyclobutanol **15l** (Eq. 103) The reaction cycle starts with the formation of an allenyl palladium methoxide complex and is similar to that of Scheme 10.



15h, R^1 = Cy, R^2 = H: R^5 = H, R^3 = R^4 = Ph (68%)
15i, R^1 = *n*-Bu, R^2 = H: R^5 = H, R^3 = R^4 = Ph (72%)
15j, R^1 = Bn, R^2 = H: R^5 = H, R^3 = R^4 = Ph (65%)
15k, R^1 = Bn, R^2 = Ph: R^5 = H, R^3 = R^4 = Ph (0%)
15l, R^1 = R^2 = H: R^5 = H, R^3 = R^4 = Ph (0%)
17p, R^1 = Ph, R^2 = H: R^5 = H, R^3 = Ph, R^4 = Ph (79%), *p*-ClC_6H_4 (66%), *o*-$MeOC_6H_4$ (80%), H (50%)
R^5 = H, R^3 = *n*-hex, R^4 = Ph (40%)[a]
R^5 = H, R^3 = H, R^4 = Ph (<5%)
R^5 = Me, R^3 = Ph, R^4 = *n*-Pr (53%)

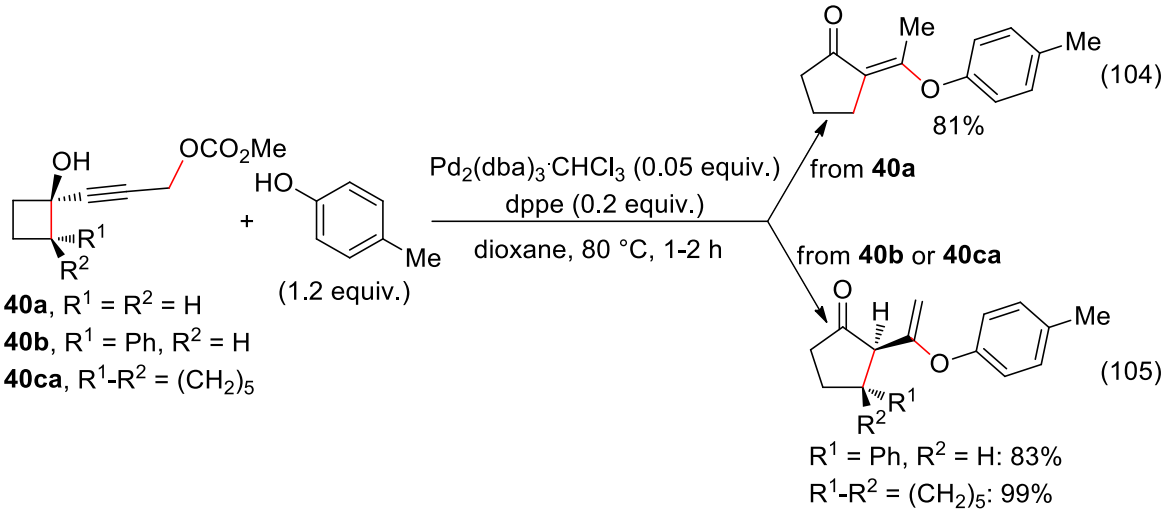
[a]Using 0.66 equiv. of **17p**.

3.3. Intermolecular reactions of functionalized cyclobutanols

3.3.1. Propargylic cyclobutanols

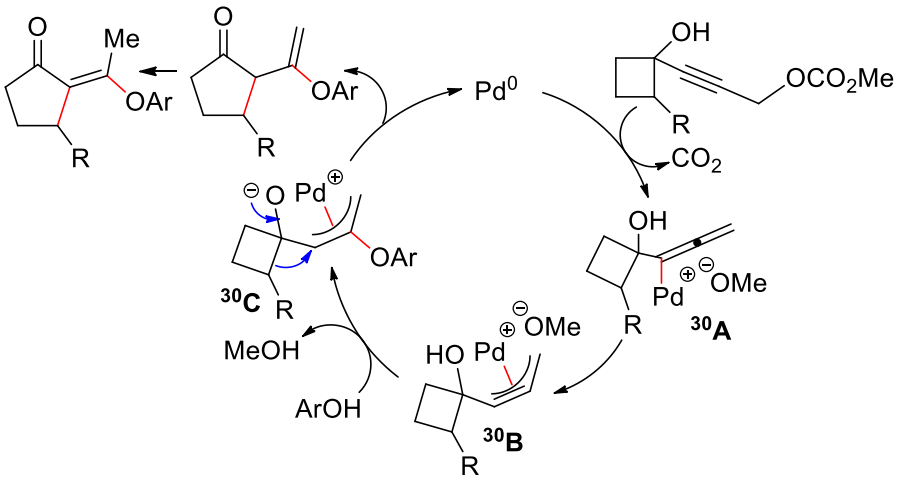
a) with phenols

In 1999, Ihara and co-workers reported the use of $Pd_2(dba)_3{\cdot}CHCl_3$/dppe association for the effective reaction of 1-(3-methoxycarbonyloxy-1-propynyl)cyclobutanols with phenols (Eqs 104 and 105).[101,102] The authors proposed the formation of cationic σ-allenylpalladium complex [30]**A**, "which is regarded as a cationic π-propargylpalladium intermediate" ([30]**B**) (Scheme 30).[102,103] Nucleophilic attack of [30]**B** by ArOH provides [30]**C**, which undergoes ring extension via the cleavage of the more substituted C-C bond. This regenerates the Pd^0 catalyst and affords the *exo*-product, which may isomerize into the *endo*-product.



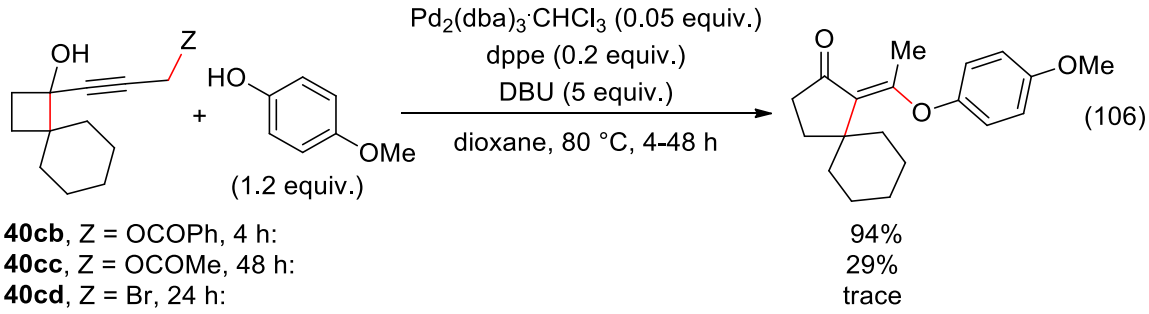
40a, R^1 = R^2 = H
40b, R^1 = Ph, R^2 = H
40ca, R^1-R^2 = $(CH_2)_5$

R^1 = Ph, R^2 = H: 83%
R^1-R^2 = $(CH_2)_5$: 99%



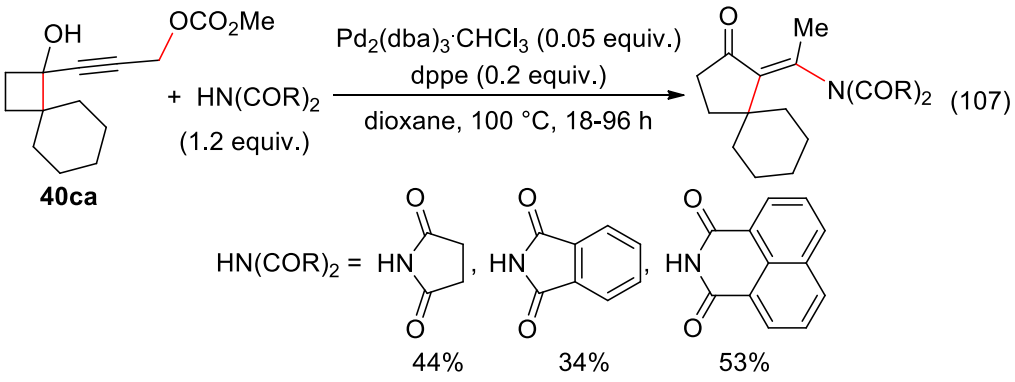
Scheme 30

Benzoate, acetate and bromide have been tested as leaving groups in the presence of DBU to neutralize the in-situ formed acid. The propargylic benzoate **40cb** provided the expected phenoxyketone in high yield whereas the corresponding acetate **40cc** reacted slowly (Eq. 106). As for the bromide **40cd**, it led to a complex mixture containing traces of the ketone.[102]



b) with imides

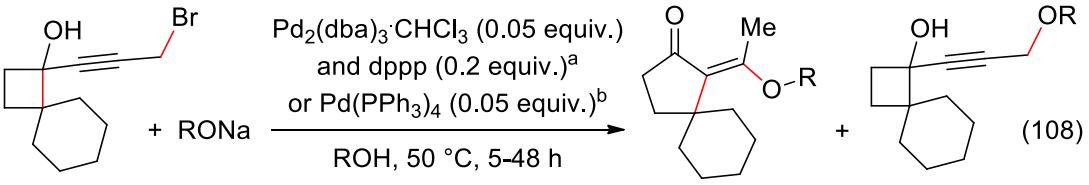
The $Pd_2(dba)_3{\cdot}CHCl_3$/dppe association in dioxane also catalyzed the nucleophilic addition of imides to **40ca** accompanied by the ring expansion (Eq. 107).[102]



c) with alkoxides

Treatment of propargylic bromide **40cd** in methanol with substoichiometric amounts of sodium methoxide and the $Pd_2(dba)_3{\cdot}CHCl_3$/dppe catalytic system led to a low yield of a mixture of

cyclopentanone and propargyl methyl ether showed in Eq. 108.[102] Switching from dppe to dppp increased both selectivity and yield towards the ketone. For the additions of EtONa and BnONa, better results were obtained under $Pd(PPh_3)_4$ catalysis (Eq. 108).



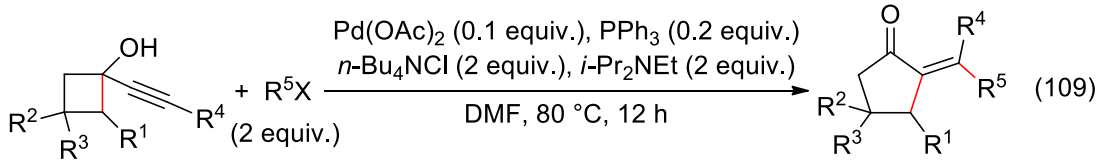
40cd
(4.6 equiv.)

R = Me:	67%[a], 56%[b], 12%[c]	13%[a], 24%[b], 21%[c]
R = Et:	12%[a], 50%[b]	17%[a], 9%[b]
R = Bn:	85%[b]	0%[b]

[c]Using $Pd_2(dba)_3{\cdot}CHCl_3$ and dppe.

3.3.2. 1-Alkynylcyclobutanols

Larock and Reddy disclosed the synthesis of 2-alkylidenecyclopentanones from the Pd^0-catalyzed reaction of 1-(1-alkynyl)cyclobutanols with aryl and vinyl iodides (Eq. 109).[104,105] The cross-coupling also occurred with vinyl triflates but, surprisingly, not with phenyl triflate (Eq. 109). The reaction with aryl iodides was rediscovered by Wu and co-workers (Eq. 110).[106] The catalytic cycle would involve carbopalladation of the triple bond leading to **[31]A** followed by selective cleavage of the more substituted bond of the cyclobutyl to afford palladacycle **[31]B** (Scheme 31). The latter undergoes reductive elimination liberating the product.



41a, $R^1 = R^2 = R^3 = H$, $R^4 = Ph$: R^5X = PhI (70%), *o*-$MeOC_6H_4I$ (74%), (*E*)-*n*-BuCH=CHI (40%), 4-phenylcyclohex-1-enyl triflate (71%)[a], cyclohex-1-enyl triflate (57%)[a], phenyl triflate (0%)

41b, $R^1 = R^2 = R^3 = H$, $R^4 = Me$: R^5X = PhI (60%), (*E*)-*n*-BuCH=CHI (35%)

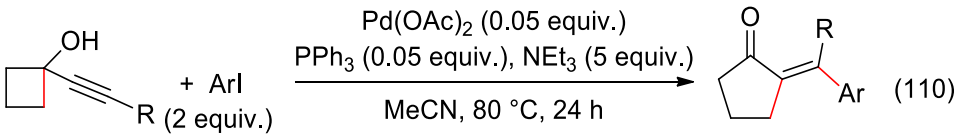
41c, $R^1 = R^2 = H$, $R^3 = R^4 = Ph$: R^5X = *p*-$EtO_2CC_6H_4I$ (64%)

41d, R^1-$R^2 = CH_2CH=CH$, $R^3 = H$, $R^4 = Ph$: R^5X = *o*-$MeOC_6H_4I$ (52%)[b]

41e, R^1-$R^2 = (CH_2)_4$, $R^3 = H$, $R^4 = Ph$: R^5X = PhI (60%)

[a]mixture of stereoisomers.

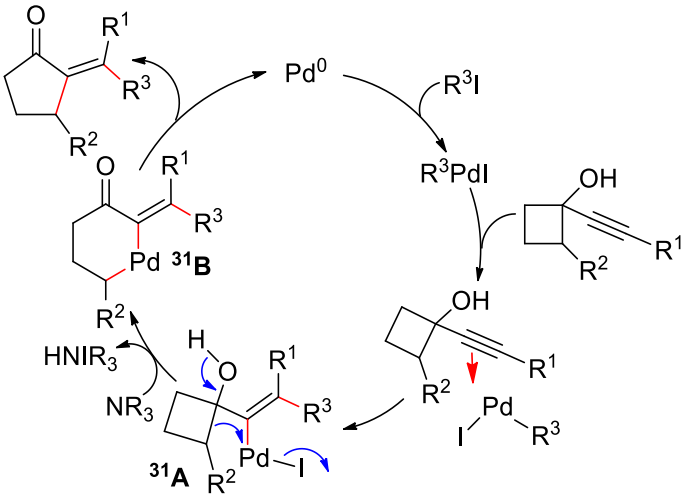
[b]6 h as reaction time.



41a, R = Ph: Ar = Ph (73%), *p*-MeOC$_6$H$_4$ (49%), *p*-MeC$_6$H$_4$ (65%)

41f, R = *n*-Bu: Ar = *p*-MeC$_6$H$_4$ (30%)[a]

[a]48 h as reaction time.

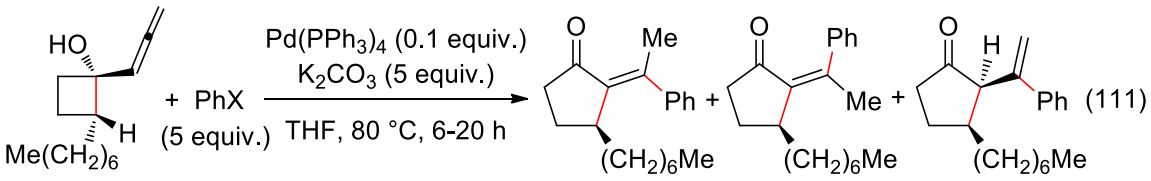


Scheme 31

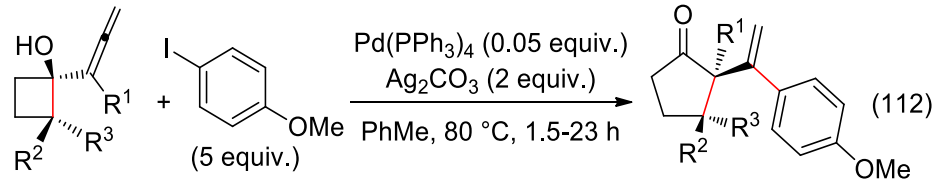
3.3.3. 1-Allenylcyclobutanols

a) carbopalladation

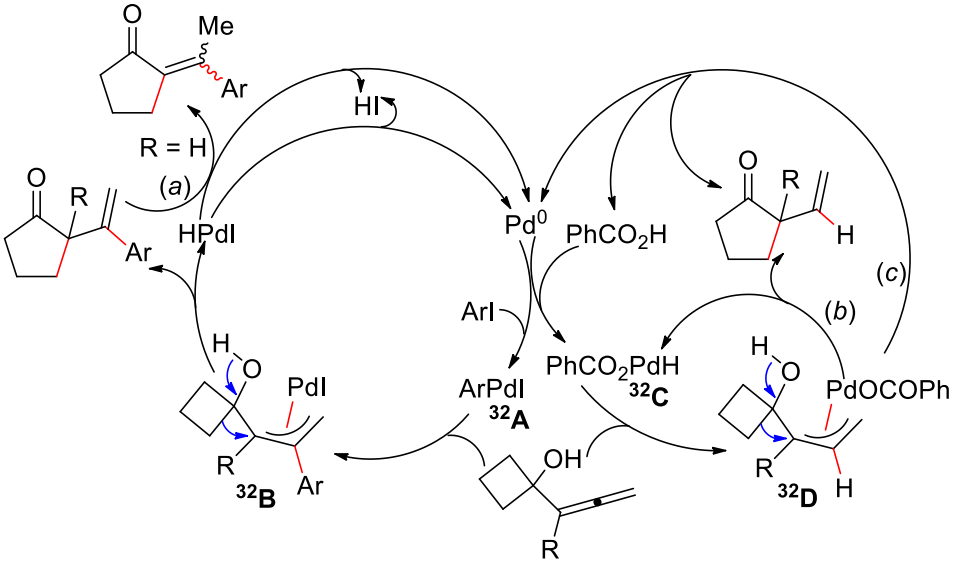
Pd^0-catalyzed cross-coupling of allenylcyclobutanols **42** with aryl iodides provided the cyclopentanones shown in Eqs 111[83] and 112[107,108] via the η^3-allylpalladium intermediate **^{32}B** formed from addition of arylpalladium^{II} complex **^{32}A** to the allene unit (Scheme 32). Rearrangement of **^{32}B** affords the unconjugated ketone. When R = H, the latter could isomerize into the conjugated ketone via the addition/elimination sequence of HPdI (path *a*), but the ratio of the isomers versus the reaction time of **42a** (Eq. 111) seems to reject such a pathway. Use of phenyl triflate instead of phenyl iodide depleted the yield (Eq. 111).



X = I, 12 h:	25%	8%	
X = I, 20 h:	40%	0%	36%
X = OTf, 6 h:	17%	10%	



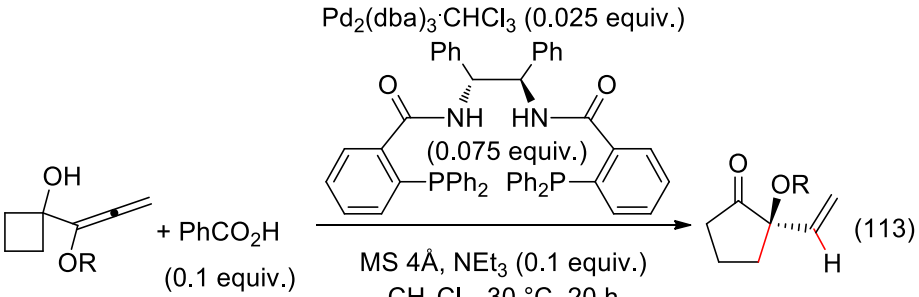
42b, R^1 = Me, R^2 = Ph, R^3 = H; 1.5 h: 72%
42c, R^1 = Ph, R^2 = Ph, R^3 = H; 3 h: 20%
42d, R^1 = Ph, R^2 = $(CH_2)_3OTBDPS$, R^3 = Me; 23 h: 79%



Scheme 32

b) hydropalladation

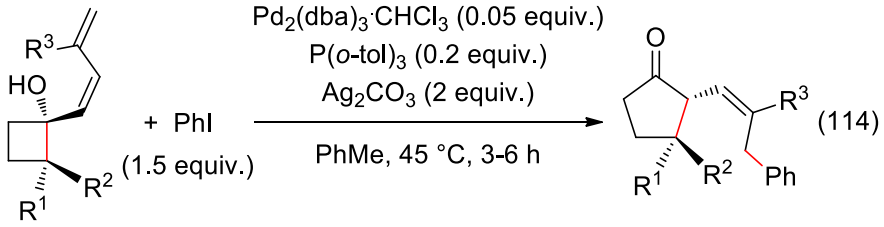
Prompted by their knowledge on the Pd^0-catalyzed enantioselective addition to allenes,[109] Trost and Xie studied the hydropalladation of **42e-h** using Trost's ligands and $PhCO_2H$ to form the required HPd species ^{32}**C** (Scheme 32, Eq. 113).[110,111] The η^3-allylpalladium complex ^{32}**D** obtained from addition of ^{32}**C** to the substrate leads to the product with regeneration of either ^{32}**C** (path *b*) or both the catalyst and $PhCO_2H$ (path *c*). The authors have shown their "chiral catalysts can control the stereochemistry of both the π-allylpalladium intermediate and the corresponding migration bond".[111]



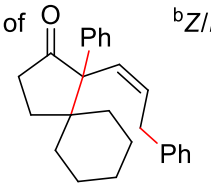
42e, R = Bn: 96%, 92% ee
42f, R = $(CH_2)_{10}Me$: 100%, 86% ee
42g, R = $(CH_2)_2CH{=}CH_2$: 78%, 87% ee
42h, R = $(CH_2)_2C{\equiv}CMe$: 88%, 84% ee

3.3.4. 1-(1,3-Butadienyl)cyclobutanols

The reaction of (*Z*)-1-(1,3-butadienyl)cyclobutanols **43** with aryl iodides, using the $Pd_2(dba)_3{\cdot}CHCl_3/P(o\text{-tol})_3$ catalytic system with Ag_2CO_3 as the base in toluene at 45 °C, selectively led to (*Z*)-2-(3-aryl-1-propenyl)cyclopentanones (Eq. 114).[112] Heck reaction of the terminal double bond would occur leading to a η^3-allylpalladium intermediate, which evolves as depicted in Scheme 32. The expected reaction being not observed from the (*E*)-isomer of **43a**, Yoshida and co-workers suggest that coordination of the hydroxy group to PhPdI controls the Heck reaction.



43a, R^1-R^2 = $(CH_2)_5$, R^3 = H: 83%[a]
43b, R^1 = R^2 = *n*-pentyl, R^3 = H: 89%
43c, R^1 = Me, R^2 = CH_2OSiPh_2t-Bu, R^3 = H: 53%
43d, R^1-R^2 = $(CH_2)_5$, R^3 = Me: 82%[b]

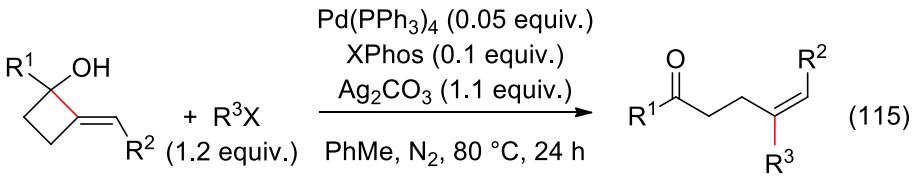
[a]Plus 15% of 

[b]*Z*/*E* mixture (5.3:1).

The diarylation product due to a subsequent reaction may also be obtained, especially with **43a** as the starting material (Eq. 114); its amount increased with the reaction temperature.

3.3.5. 2-Alkylidenecyclobutanols

Recently, the team of Cao and Xu disclosed the synthesis of γ,δ-unsaturated ketones from the reaction of organic halides with 2-alkylidenecyclobutanols **44** using $Pd(PPh_3)_4$/Xphos as the catalyst and Ag_2CO_3 as the base in toluene (Eq. 115).[113] This ring-opening/coupling transformation, which is very sensitive to the nature of both the base and the solvent, would occur via the oxidative addition of R^3X to the Pd^0 complex (Scheme 33). The Ag_2CO_3-mediated reaction of the resulting (hetero)aryl/benzyl/alkynyl palladium species with the cyclobutanol leads to alkoxypalladium intermediate ^{33}**A**, which undergoes selective cleavage of the more substituted $C(sp^2)$-$C(sp^3)$ bond to afford ^{33}**B**. Subsequent reductive elimination liberates the product and the catalyst.



44a, R^1 = Me, R^2 = Ph: R^3X = PhBr (93%), *p*-$MeOC_6H_4Br$ (78%), *p*-ClC_6H_4Br (60%), *p*-AcC_6H_4Br (63%), 2-thienylBr (68%), 1-naphthylCH_2Cl (76%), $PhCH_2Cl$ (70%[a]), *o*-$FC_6H_3CH_2Cl$ (51%)

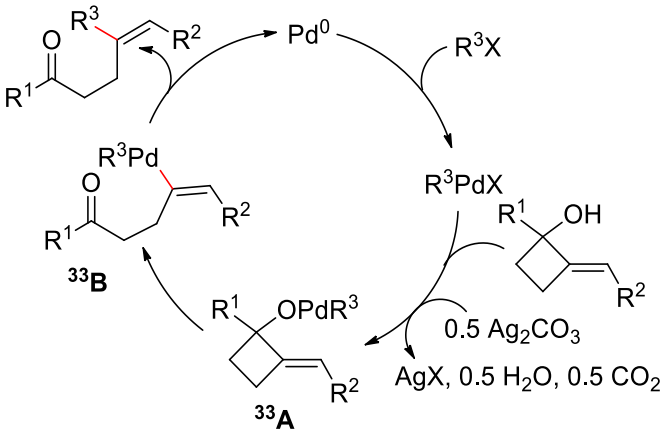
44b, R^1 = H_2C=CMe, R^2 = Cy: R^3X = PhBr (83%)

44c, R^1 = Me, R^2 = 3-furyl: R^3X = PhBr (57%)

44d, R^1 = Me, R^2 = CH=CHPh: R^3X = PhBr (63%)

44e, R^1 = R^2 = Ph: R^3X = PhBr (90%), 5-indolylBr (63%), TIPS—≡—Br (82%)

[a]$Pd_2(dba)_3$ (0.025 equiv.) as the catalyst.

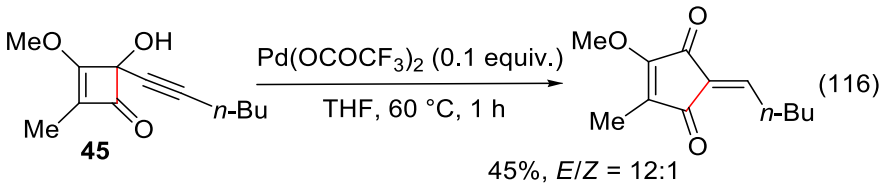


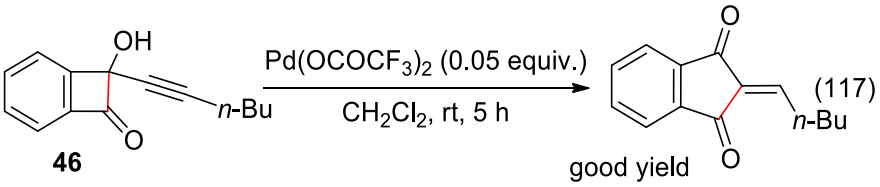
Scheme 33

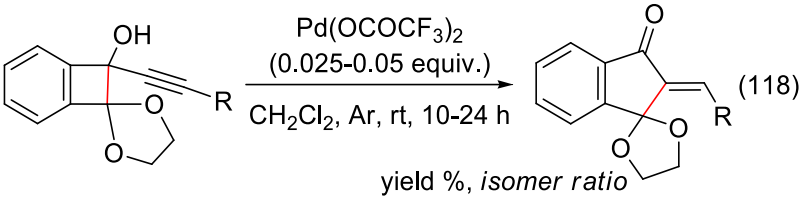
4. Cyclobutenols

4.1. Intramolecular reactions

At the end of the eighties, Liebeskind and co-workers reported the synthesis of (*E*)-4-methoxy-5-methyl-2-pentylidenecyclopent-4-ene-1,3-dione (Eq. 116)[114,115] and 3-oxo-2-pentylideneindanone (Eq. 117)[114-116] from the $Pd(OCOCF_3)_2$-catalysed ring expansion of 1-alkynyl-1-hydroxycyclobutenones **45** and **46**, respectively. The dione obtained from **46** suffering rapid decomposition during purification, the reactions were then carried out from ketals **47** which afford stable ring expanding products (Eq. 118).[114-116] The proposed mechanism (Scheme 34) involves the η^2-alkynylpalladium complex **[34]A** which undergoes ring expansion leading to η^1-vinylpalladium intermediate **[34]B** and CF_3CO_2H. Protonation of **[34]B** with CF_3CO_2H provides the product and regenerates the catalyst.

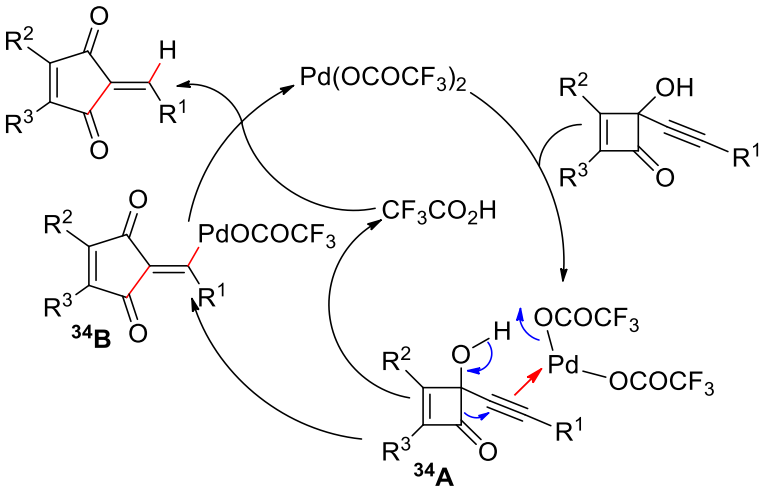






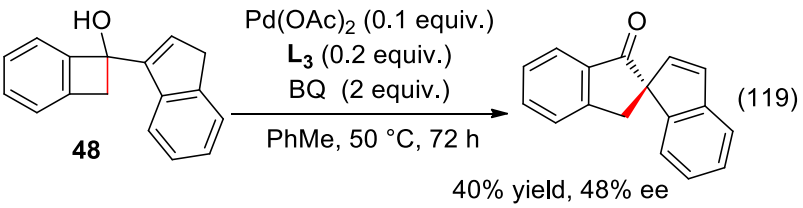
yield %, *isomer ratio*

47a, R = *n*-Bu:	91, *36:1*
47b, R = Cy:	75, *>25:1*
47c, R = $SiMe_3$:	56, *20:1*
47d, R = Ph:	89, *20:1*
47e, R = CH_2OMe:	84, *>25:1*
47f, R = CH(OTBDMS)Me:	66, *18:1*

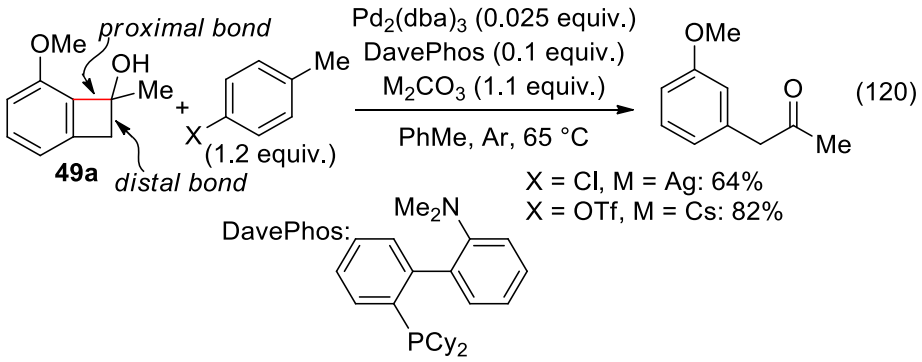


Scheme 34

The $Pd(OAc)_2$/BQ/**L_3** association used for the enantioselective ring expansion of indenyl propanols **27** (Eq. 71) mediated a similar transformation of indenyl benzocyclobutenol **48** (Eq. 119).[70]

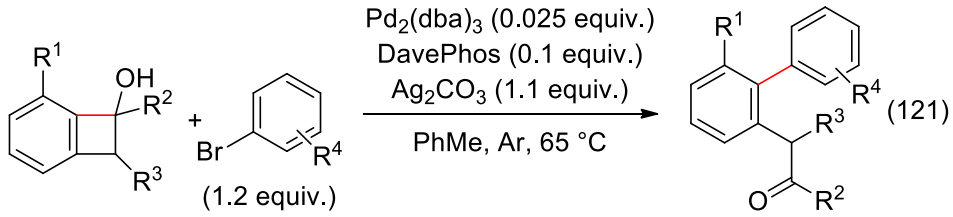


While the $Pd_2(dba)_3$/DavePhos catalyzed reaction of *p*-bromotoluene with benzocyclobutenol **49a** afforded the cross-coupling product (see below Subchapter 4.2.; DavePhos = 2-dicyclohexylphosphino-2′-(*N*,*N*-dimethylamino)biphenyl), that of *p*-chlorotoluene or *p*-tosyltoluene under the same experimental conditions led to the undesired ring-opened product in 64-82% yield (Eq. 120).[117] In contrast to the ring expansion of Eq. 119, this reaction implies the cleavage of the proximal bond. This led us to suspect that the C=C bond of the indenyl group of **48** is involved in the transition state in a manner similar to that depicted from **27** in Scheme 24.



4.2. Intermolecular reactions of the cyclobutenol core

In contrast to chloro- and tosylaryls (see above Eq. 120), bromoaryls underwent cross-coupling with benzocyclobutenols **49** under $Pd_2(dba)_3$/DavePhos catalysis in PhMe containing Ag_2CO_3 or Cs_2CO_3 (Eq. 121).[117] The selectivity was very sensitive to the reaction conditions, a mixture of the cross-coupling and ring-opened products being isolated using $Pd_2(dba)_3/PPh_3/K_2CO_3$ in THF (Eq. 121). Mixture of the two compounds was also isolated using *p*-iodotoluene under the optimum conditions. The cross-coupling product would be attained via alkoxyarylpalladium complex ^{35}**A** which undergoes selective cleavage of the proximal C-C bond to afford ^{35}**B** (Scheme 35). Subsequent reductive elimination leads to the product. According to Orellana's team,[117] cleavage of the proximal bong rather than the distal bond would be due to the relative bond strengths of Pd−C(sp^2) and Pd−C(sp^3) bonds.[118]



49a, R^1 = OMe, R^2 = Me, R^3 = H: R^4 = *p*-Me (94%[a, b]), *p*-CO_2Me (69%), *p*-F (>90%), *p*-CN (89%), *p*-OMe (>90%), *o*-Me (>90%), *o*-OMe (86%)

49b, R^1 = OMe, R^2 = Cy, R^3 = H: R^4 = *p*-Me (>90%)

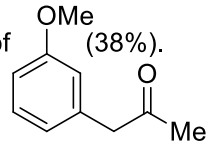
49c, R^1 = H, R^2 = 4-anisyl, R^3 = H: R^4 = *p*-CF_3 (81%), *p*-NO_2 (79%)

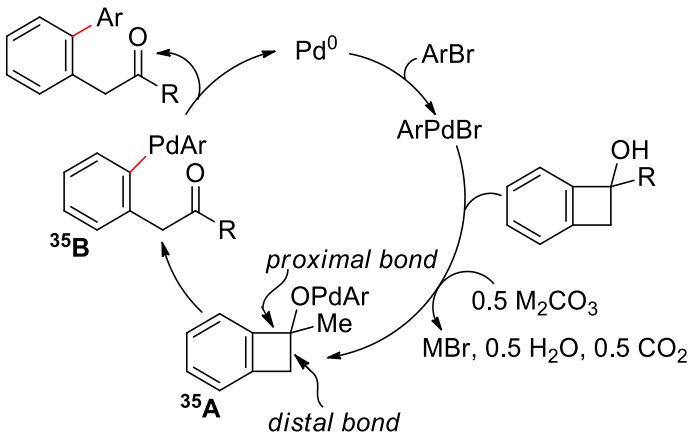
49d, R^1 = H, R^2 = *i*-Pr, R^3 = H: R^4 = *p*-$O(CH_2)_2Cl$ (60%)

49e, R^1 = H, R^2-R^3 = $(CH_2)_4$: R^4 = *p*-Me (70%)

49f, R^1 = H, R^2-R^3 = $(CH_2)_5$; R^4 = *p*-OMe (56%), *p*-CO_2Me (85%)

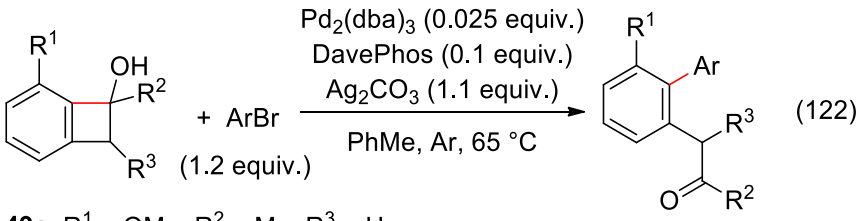
[a]Similar yield with $CsCO_3$ instead of Ag_2CO_3.

[b]42% using $Pd_2(dba)_3/PPh_3/K_2CO_3$ in THF and formation of  (38%).

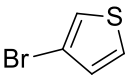
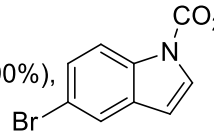


Scheme 35

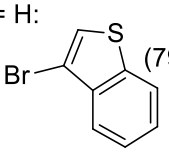
The $Pd_2(dba)_3$/DavePhos/Ag_2CO_3 procedure was also efficient for the cleavage/cross-coupling of **49** with heteroaryl bromides (Eq. 122), and the domino reaction with *ortho*-functionalized aryl bromides leading to tricyclic compounds (Eqs 123 to 125).[117]

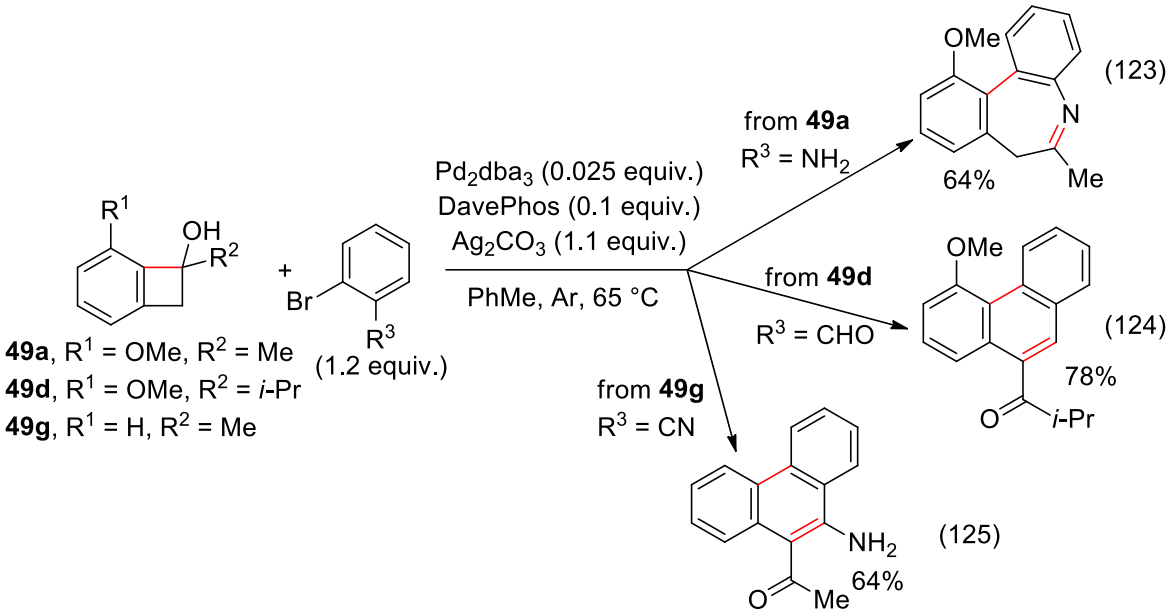


49a, R^1 = OMe, R^2 = Me, R^3 = H:

ArBr =  (>90%),  (>90%)

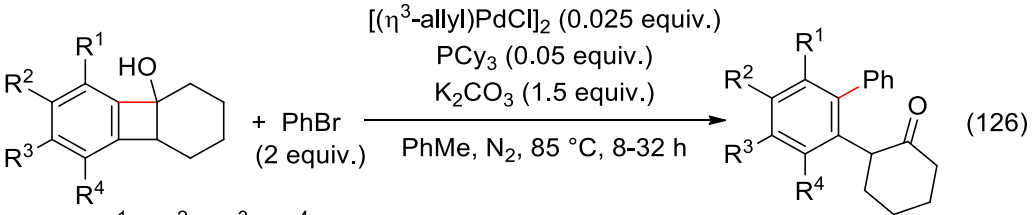
49c, R^1 = H, R^2 = 4-anisyl, R^3 = H:

ArBr =  (79%)

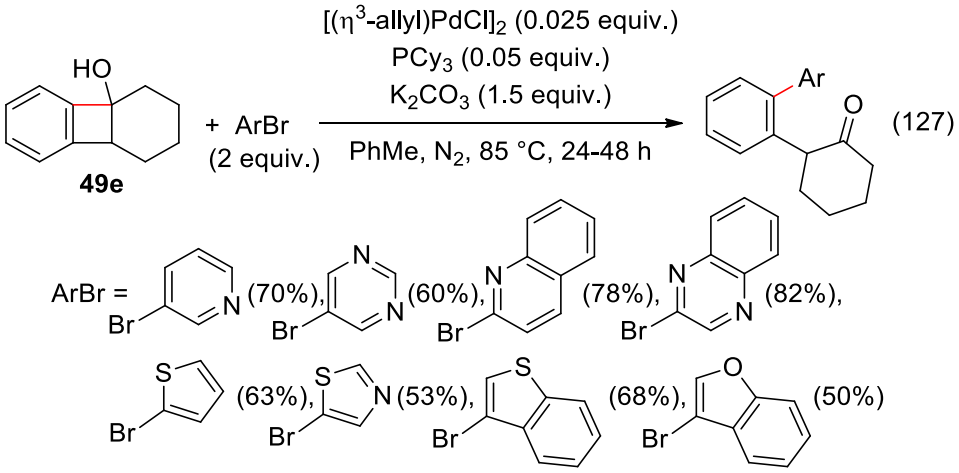


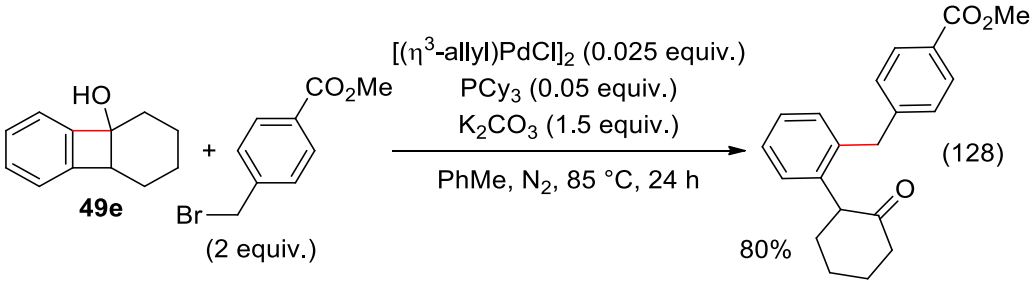
49a, R^1 = OMe, R^2 = Me
49d, R^1 = OMe, R^2 = *i*-Pr
49g, R^1 = H, R^2 = Me

Given the costly ligand and the stoichiometric amount of Ag_2CO_3 of the above procedure, Zhu and Mao looked for less expensive experimental conditions.[119] Screening of different reaction parameters led them to obtain valuable results for the cross-coupling of **49** with various aryl and heteroaryl bromides using $[(\eta^3\text{-allyl})PdCl]_2$ associated to PCy_3 as the catalytic system and K_2CO_3 as the base in PhMe at 85°C (Eqs 126 and 127). Interestingly, these conditions allowed cross-coupling with a benzylic bromide (Eq. 128).

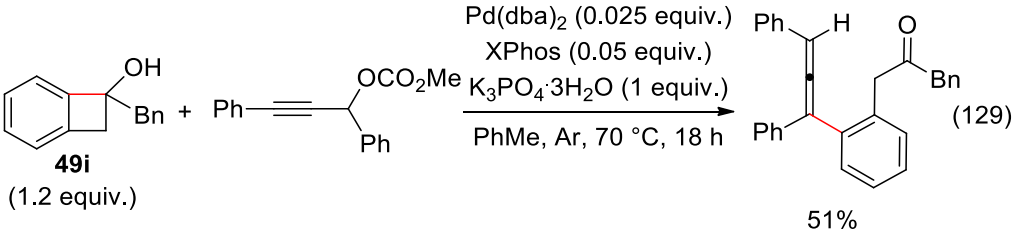


49e, R^1 = R^2 = R^3 = R^4 = H: 92%
49h, R^1-R^2 = $(CH{=}CH)_2$, R^3 = R^4 = H: 80%
49h, R^1-R^2 = R^3-R^4 = $(CH{=}CH)_2$: 74%

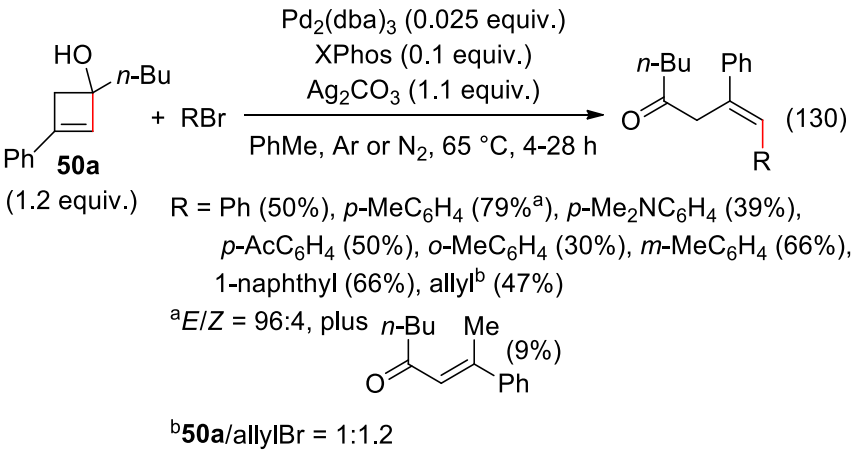




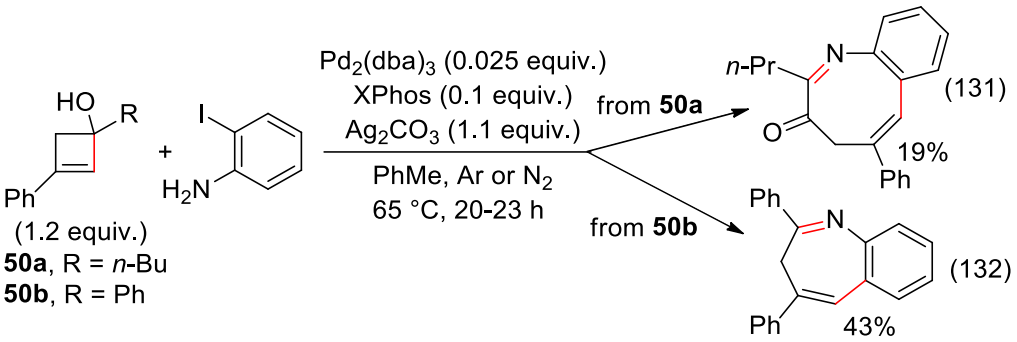
Cross-coupling of **49i** with 1,3-diphenylprop-2-yn-1-yl methyl carbonate (Eq. 129) was carried out by Ma and co-workers under the experimental conditions used for that of *tert*-cyclobutanols (Eq. 103).[100] Intermediates similar to those of Scheme 10 are involved.

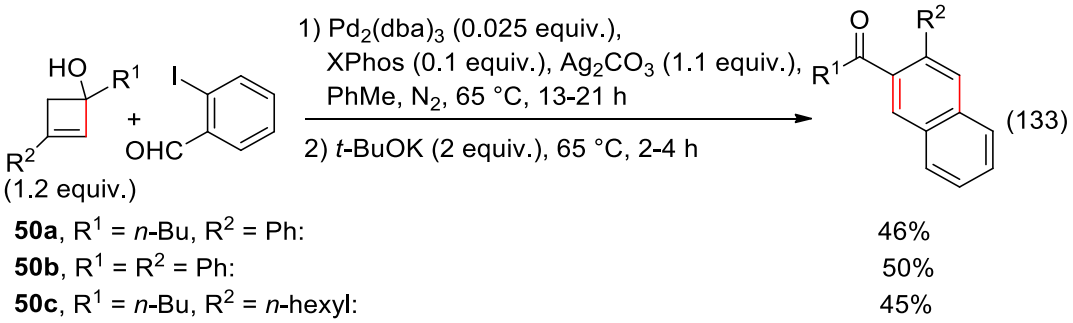


Recently, Matsuda's team disclosed the ring-opening coupling of cyclobutenol **50a** with aryl and allyl bromides.[120] The optimum results were obtained with the $Pd_2(dba)_3$/XPhos catalytic system and Ag_2CO_3 in toluene at 65°C (Eq. 130). Slight amount of 2-phenyloct-2-en-4-one due to the thermal ring opening of the substrate[121] was isolated as side-product. DavePhos as the ligand as well *t*-BuOK as the base led to lower yields. Use of *p*-iodotoluene instead of *p*-bromotoluene decreased the yield from 79% to 45%. To rationalize the selective $C(sp^2)$-$C(sp^3)$ bond cleavage leading to the cross-coupling product, the authors consider, like Orellana's team,[117] the bond strength of Pd–$C(sp^2)$ superior to that of Pd–$C(sp^3)$, but also a plausible stabilization by an interaction between Pd^{II} and the C=C bond.

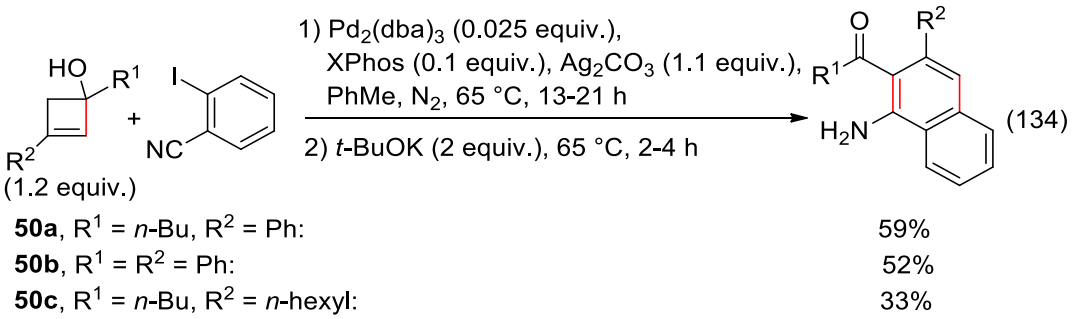


The $Pd_2(dba)_3$/XPhos/Ag_2CO_3 procedure was used for the domino reaction of *o*-iodoaniline with **50a** and **50b** leading to eight- and seven-membered imines, respectively (Eqs 131 and 132). For the cross-coupling of **50a-c** with *o*-iodobenzonitrile or *o*-iodobenzaldehyde, subsequent basic treatment was required to form the bicyclic aromatic compounds (Eqs 133 and 134).[120]





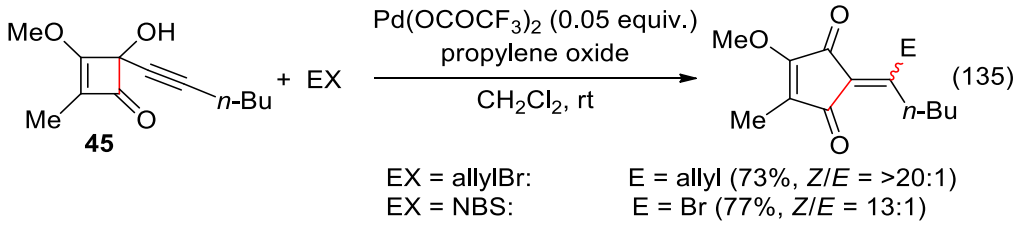
50a, R^1 = *n*-Bu, R^2 = Ph: 46%
50b, R^1 = R^2 = Ph: 50%
50c, R^1 = *n*-Bu, R^2 = *n*-hexyl: 45%



50a, R^1 = *n*-Bu, R^2 = Ph: 59%
50b, R^1 = R^2 = Ph: 52%
50c, R^1 = *n*-Bu, R^2 = *n*-hexyl: 33%

4.3. Intermolecular reactions of functionalized cyclobutenols

The formation of pentylidendione from the ring expansion of **45** (Eq. 116) requires the protonation of intermediate [34]**B** with *in situ*-produced CF_3CO_2H (Scheme 34). Quenching the acid with propylene oxide allowed Liebeskind and co-workers to trap the vinylic palladium intermediate with allyl bromide or *N*-bromosuccinimide, leading to tetrasubstituted alkylidene adducts (Eq. 135).[114,115]



5. Conclusion

As highlighted in this review, the outstanding reactivity of strained cycla(e)nols under Pd^{II}- and Pd^0-catalysis attracted considerable attention, leading to a variety of ring opening/expansion/contraction/fragmentation and cross-coupling reactions depending on the substitution and the presence of partners. Most Pd^0-catalyzed procedures required screening of ligands to obtain efficient processes. Given the accessibility of the substrates and the range of plausible coupling partners, it is likely that further useful Pd-catalyzed methods and applications in natural product synthesis will be developed.

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