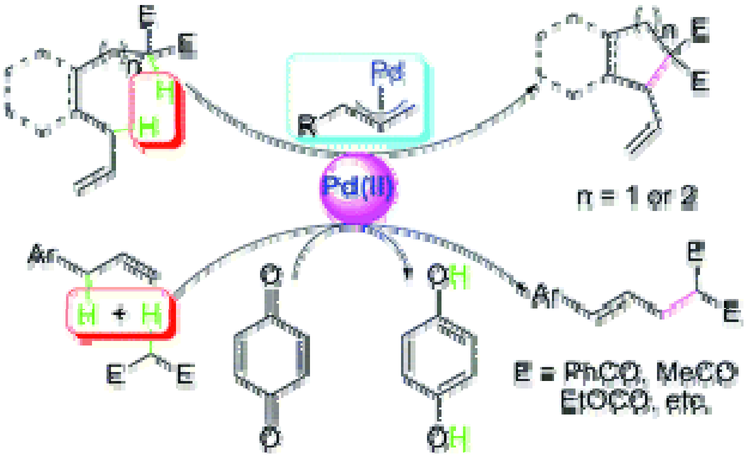
Intra/Intermolecular Direct Allylic Alkylation via Pd(II)-Catalyzed Allylic C-H Activation



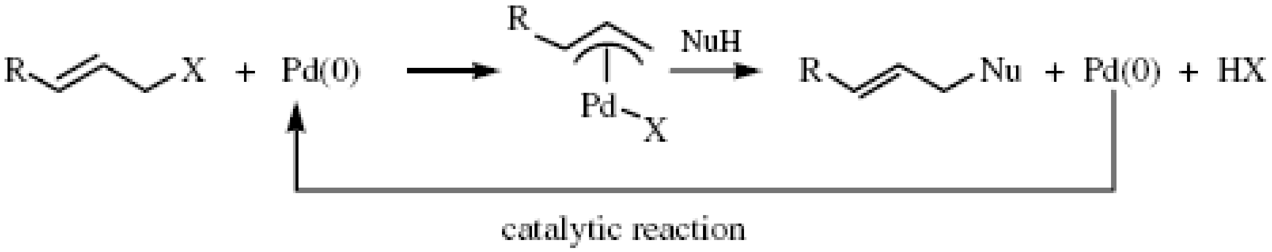
Song Lin, Chun-Xiao Song, Gui-Xin Cai, Wen-Hua Wang, and Zhang-Jie Shi*

JACS* 2008 *ASAP

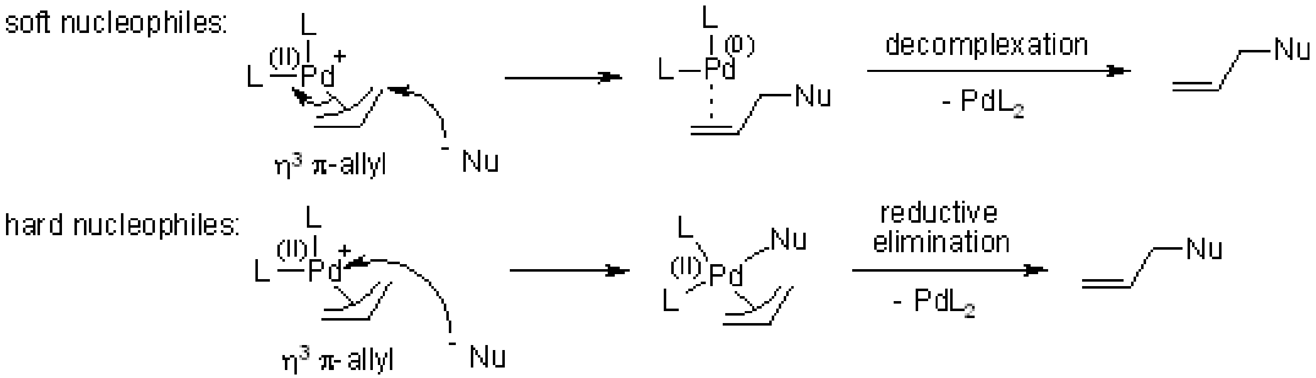
Li Zhang

Current literature
September 27th 2008

Tsuji–Trost Reaction



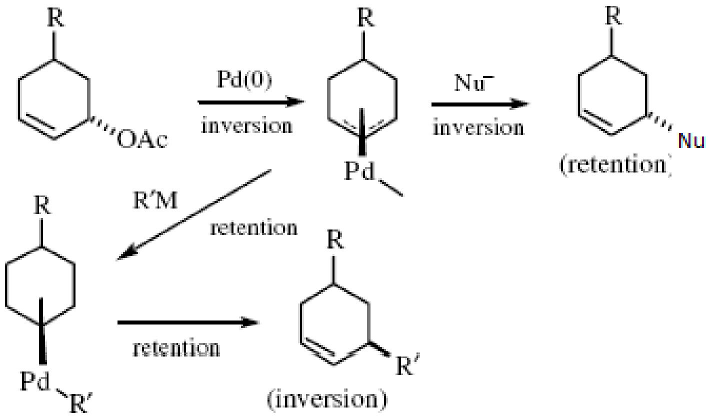
Depending on the strength of the nucleophile, the reaction can take two different pathways



- Soft nucleophiles, such as those derived from conjugate acids with a pKa < 25, normally add directly to the allyl moiety
- Hard nucleophiles, defined as those derived from conjugate acids whose p*Ka > 25,* first attack the metal center, followed by reductive elimination to give the allylation product

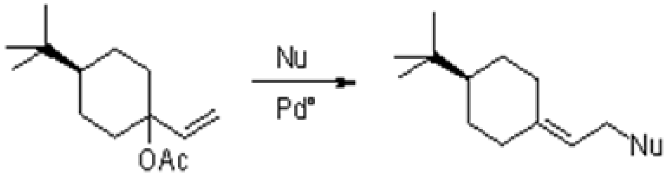
Chem. Rev. **1996**, *96*, 395-422

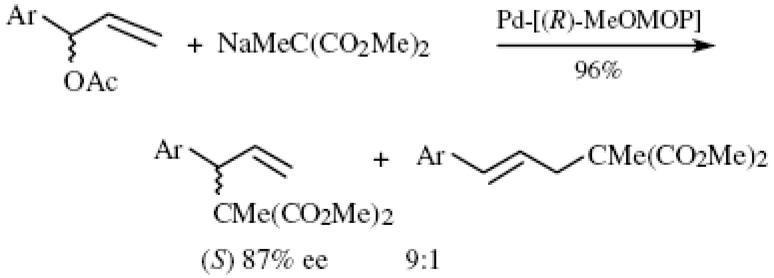
Stereochemistry of Palladium-Catalyzed Allylation



- ❖ For the soft carbon nucleophiles, overall retention is observed
- ❖ For hard carbon nucleophiles, overall inversion is observed

Regioselectivity of Palladium-Catalyzed Allylation



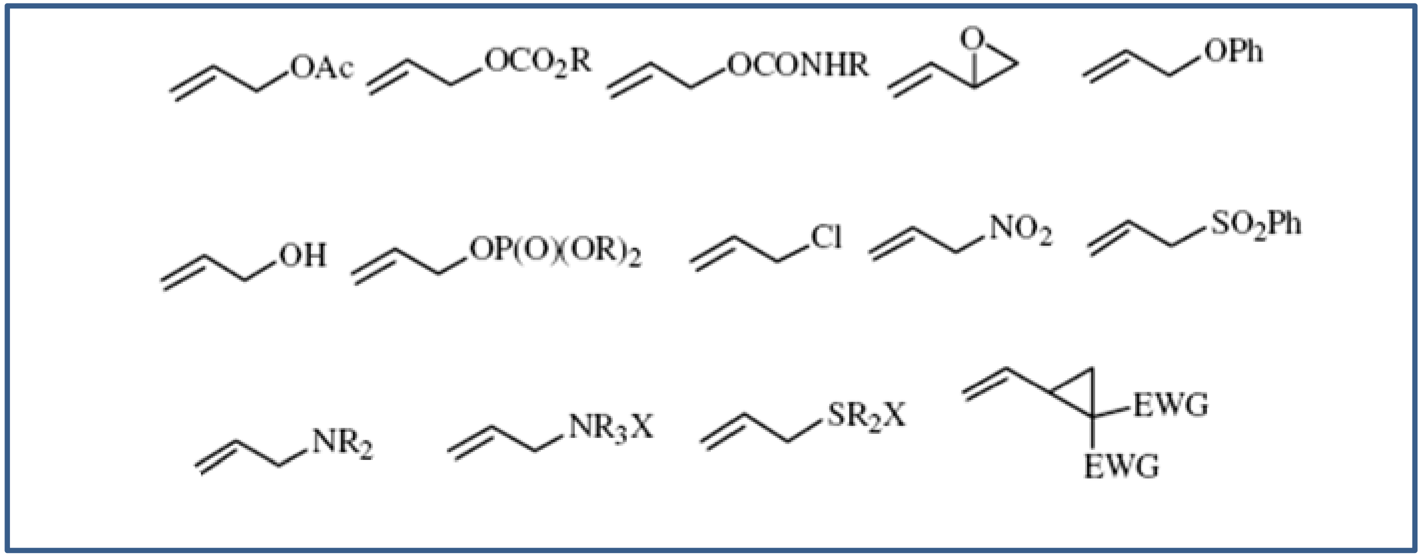


- ❖ Nonsymmetric allyl substrates normally undergo substitution at the least hindered allylic position
- ❖ But in some cases the regioselectivity depends on ligands and leaving groups

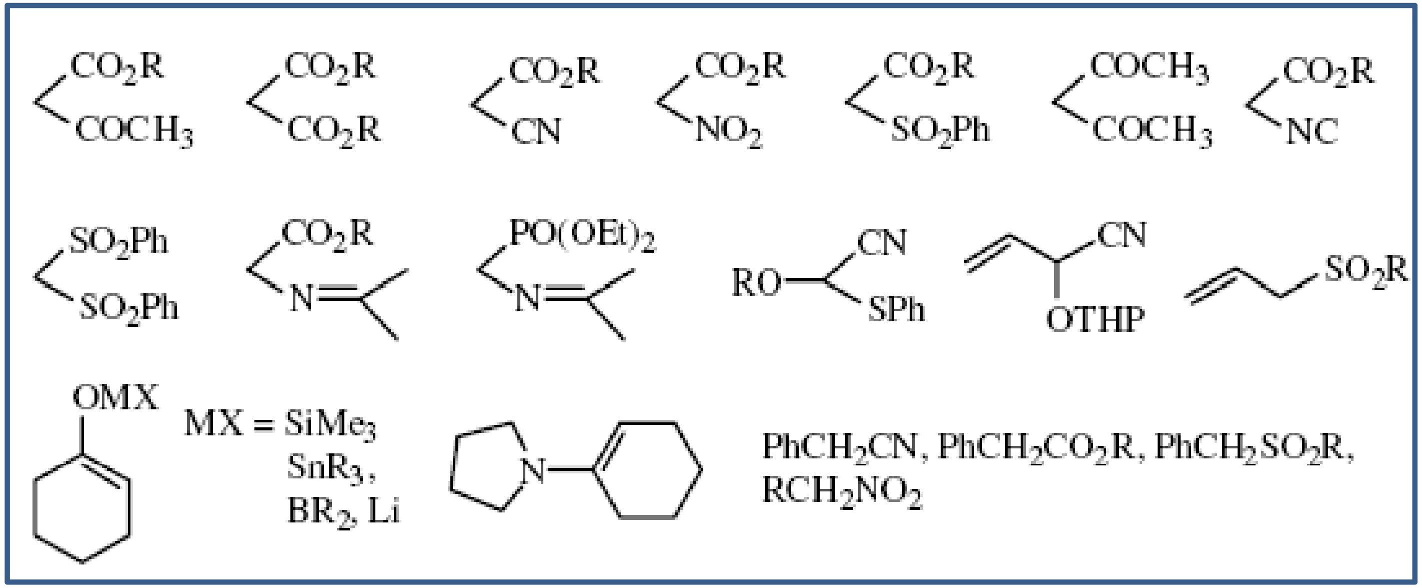
Chem. Commun., **1997**, 561 - 562

Handbook of Organopalladium Chemistry for Organic Synthesis;
Wiley-Interscience 2002

Allylic leaving groups

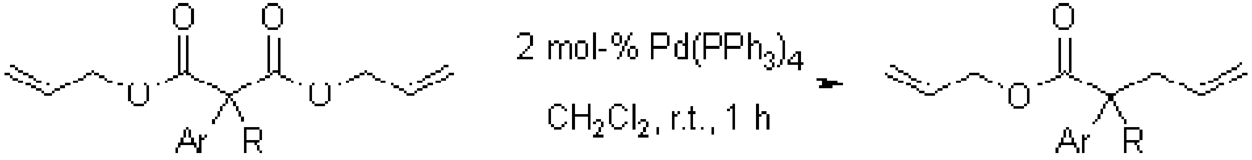


Range of Soft Carbon Nucleophiles



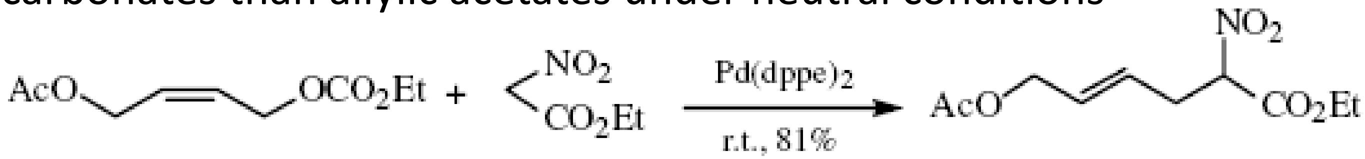
Some Examples of Tsuji–Trost Reaction

Easy Access to Esters with a Benzylic Quaternary Carbon Center from Diallyl Malonates by Palladium-Catalyzed Decarboxylative Allylation



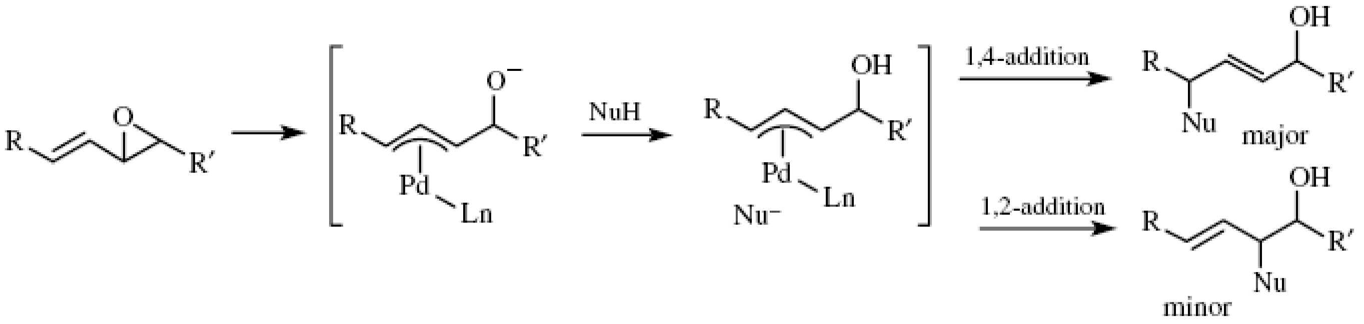
J. Org. Chem., **2007**, *72*, 1534-1537

The chemoselective reaction clearly shows the higher reactivity of allylic carbonates than allylic acetates under neutral conditions



Tetrahedron Lett., **1984***, 25, 3579*

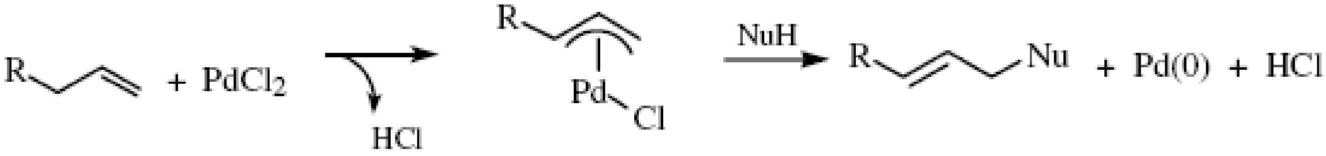
For vinyl epoxides, mainly the 1,4-adduct is formed regioselectively rather than the 1.2-adduct under neutral conditions



J. Am. Chem. SOC. **1981**,*103*, 5969-5972

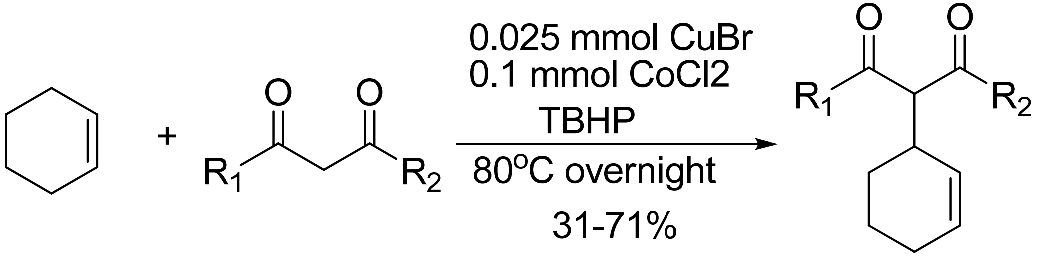
Allylic alkylation proceeded via C-H activation

The double bond was as a direct activating group for introduction of alkyl residues
The reaction is stoichiometric with Pd(II)



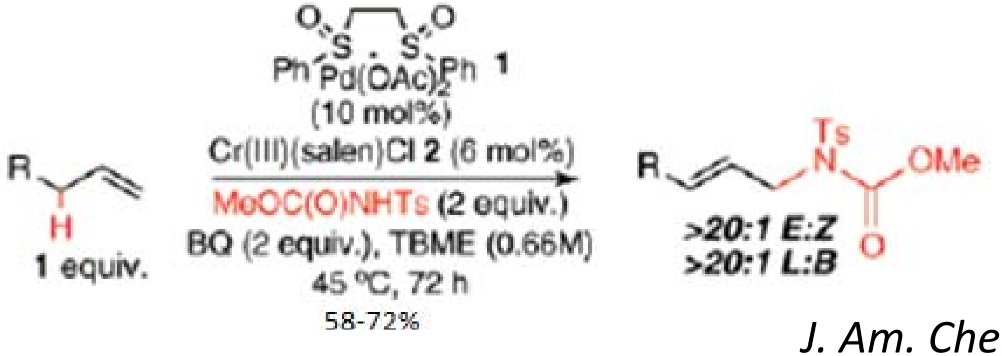
J. Am. Chem. Soc. **1973**, *95*, 292-294

Catalytic Allylic Alkylation via the Cross-Dehydrogenative-Coupling Reaction between Allylic sp3 C-H and Methylenic sp3 C-H Bonds

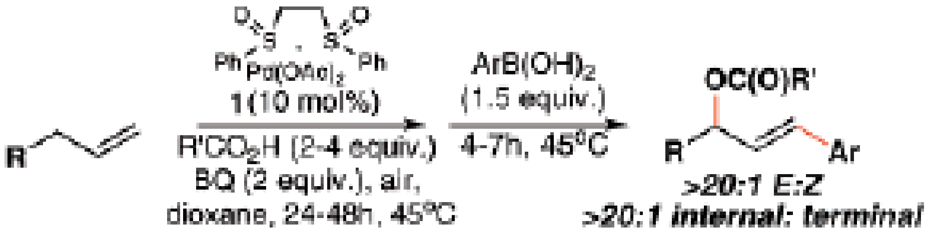


J. Am. Chem. Soc. **2006**, *128, 56-57*

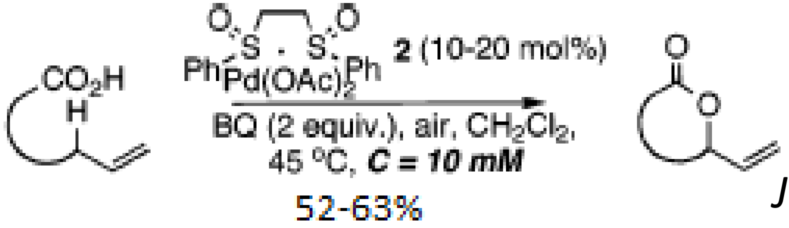
Allylic C-O/N formation via Pd(II)-catalyzed C-H activation



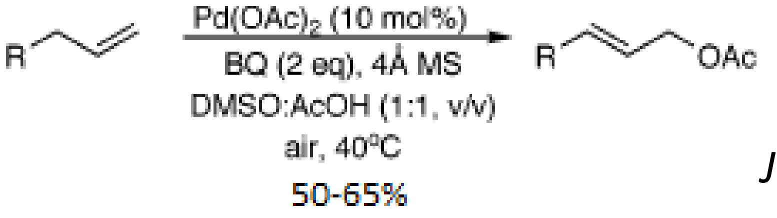
J. Am. Chem. Soc. **2008**, *130*, 3316-3318



J. Am. Chem. Soc. **2006**, *128*, 15076-15077

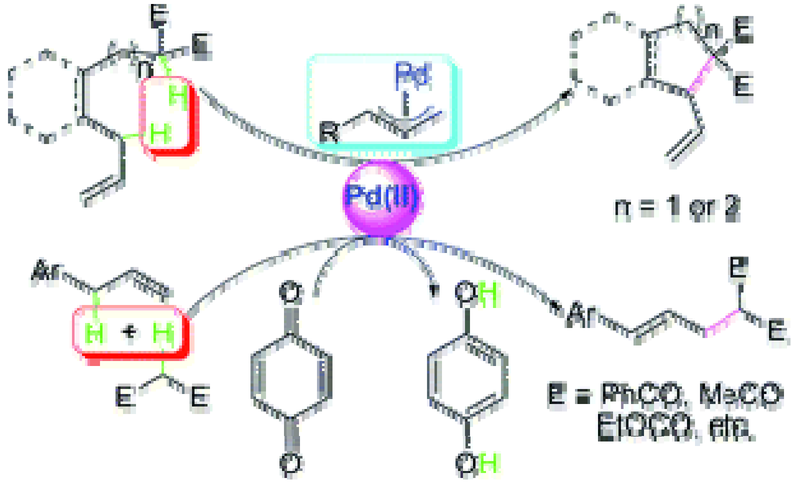


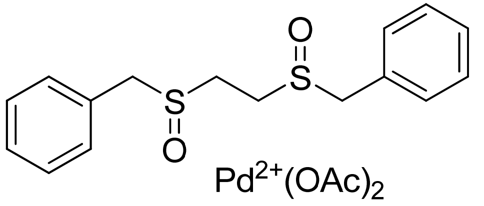
J. Am. Chem. Soc. **2006**, *128*, 9032-9033



J. Am. Chem. Soc. **2004**, 126, 1346-1347

Title paper: Intra/Intermolecular Direct Allylic Alkylation via Pd(II)-Catalyzed Allylic C-H Activation

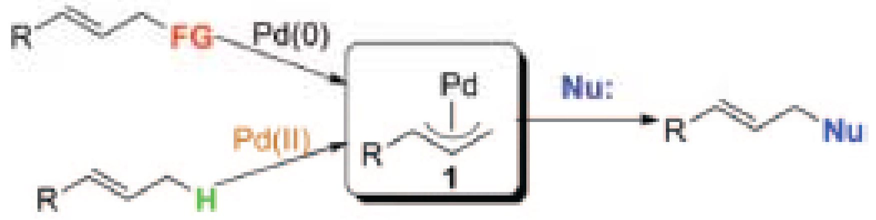




1,2-bis(benzylsulfinyl)-ethane
palladium acetate

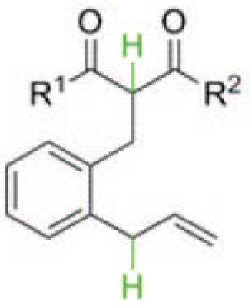
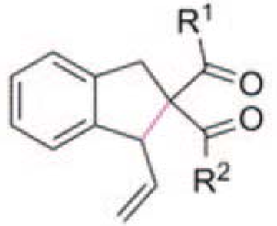
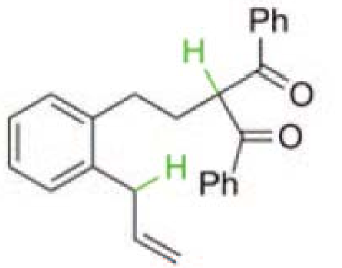
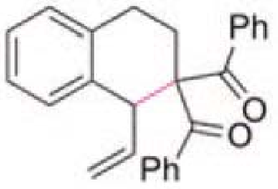
BQ: benzoquinone

Traditional Tsuji–Trost Alkylation and Paper Proposed Allylic C-H Alkylation



FG = OCOR, OCO$_2$R, NR$_2$, SR, P(OR)$_2$, B(OR)$_2$, etc.

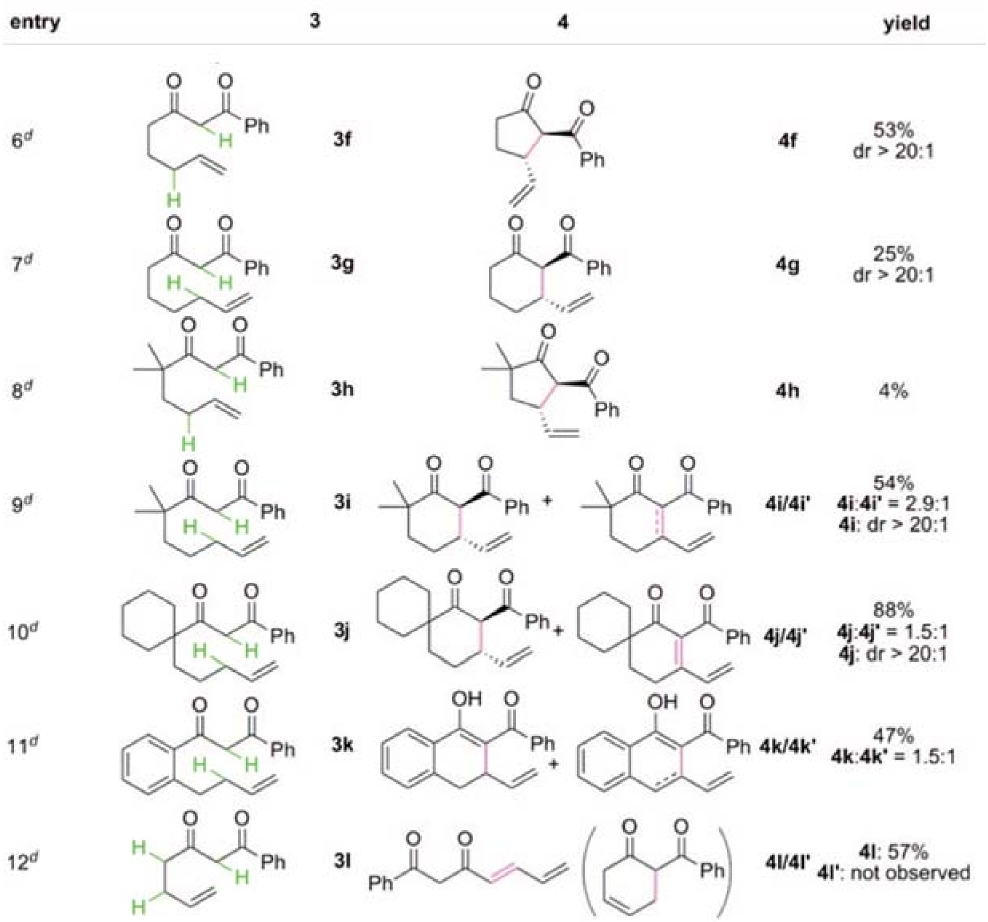
Intramolecular Direct Allylic Alkylation *via* Palladium-Catalyzed sp3 C-H Activation

entry	3			4		yield
1[b]		R^1 = Ph, R^2 = Ph	**3a**		**4a**	65%
2[b]		R^1 = Me, R^2 = Me	**3b**		**4b**	44%
3[b]		R^1 = Me, R^2 = OEt	**3c**		**4c**	63% *cis:trans* = 2.4:1
4[b]		R^1 = Ph, R^2 = Me	**3d**		**4d**	56% *cis:trans* = 1.1:1
5[c]			**3e**		**4e**	48%

b With 10 mol% of 2.
c With 20 mol% of 2.

- ❖ Polysubstituted indane and 1,2,3,4-tetrahydronaphthalene with quaternary carbons were easily obtained in good efficiencies (4a-e)
- ❖ Prochiral substrate gave two diastereoisomers (4c and 4d)

Intramolecular Direct Allylic Alkylation *via* Palladium-Catalyzed sp3 C-H Activation



entry	3	4	yield
6[d]	3f	4f	53% dr > 20:1
7[d]	3g	4g	25% dr > 20:1
8[d]	3h	4h	4%
9[d]	3i	4i/4i'	54% 4i:4i' = 2.9:1 4i: dr > 20:1
10[d]	3j	4j/4j'	88% 4j:4j' = 1.5:1 4j: dr > 20:1
11[d]	3k	4k/4k'	47% 4k:4k' = 1.5:1
12[d]	3l	4l/4l'	4l: 57% 4l': not observed

d With 15 mol% of ***2***

❖ For the aliphatic allylic substrates, high diastereoselectivities, only trans adducts were detected

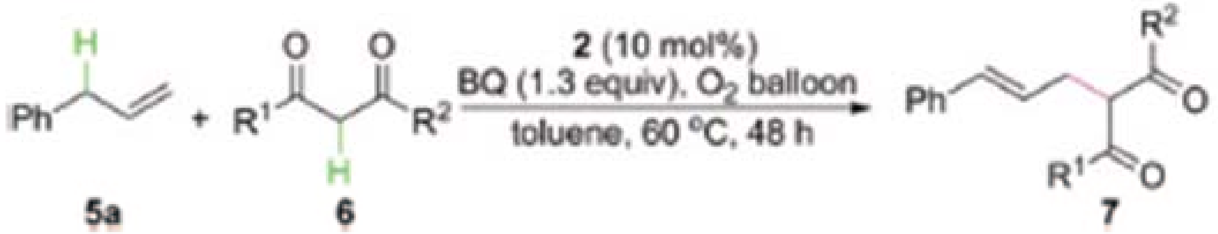
❖ Without the γ-substituents of the dione, a five-membered ring was more efficiently formed than a six-membered one (4f vs 4g)

❖ When steric hindrance was at the γ-position, five-membered ring was hardly constructed (4h vs 4i,j)

❖ For 4i′-k′, the coupling products were partially dehydrogenated to form highly conjugated compounds

❖ Only 4l was isolated, which may be generated via allylic C-H activation followed by β–H elimination

Intermolecular Direct Allylic Alkylation with Different Nucleophiles



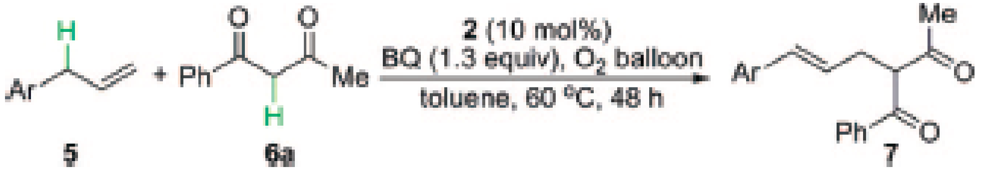
entry	R¹	R²	7	yield (%)[b]
1	Ph	Me	7aa	82
2	Ph	Ph	7ab	69
3	Et	Et	7ac	64
4	Me	Me	7ad	55
5	Me	Oet	7ae	25
6[c]	Oet	Oet	7af	<5

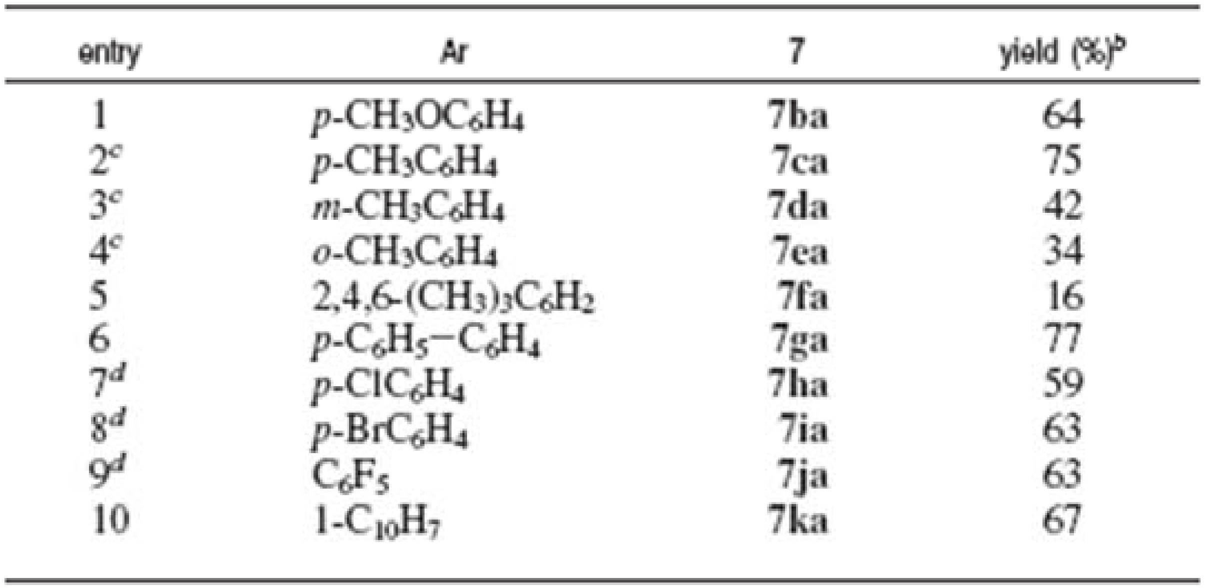
- These intermolecular transformations had dominant terminal regioselectivities

- Highly regio- and stereo-selective, no branched or cis-product

- Unlike the corresponding intramolecular reaction, ethyl acetoacetate (6e) gave poor yield because of its relatively lower nucleophilicity

Intermolecular Direct Allylic Alkylation with Different Allylarenes

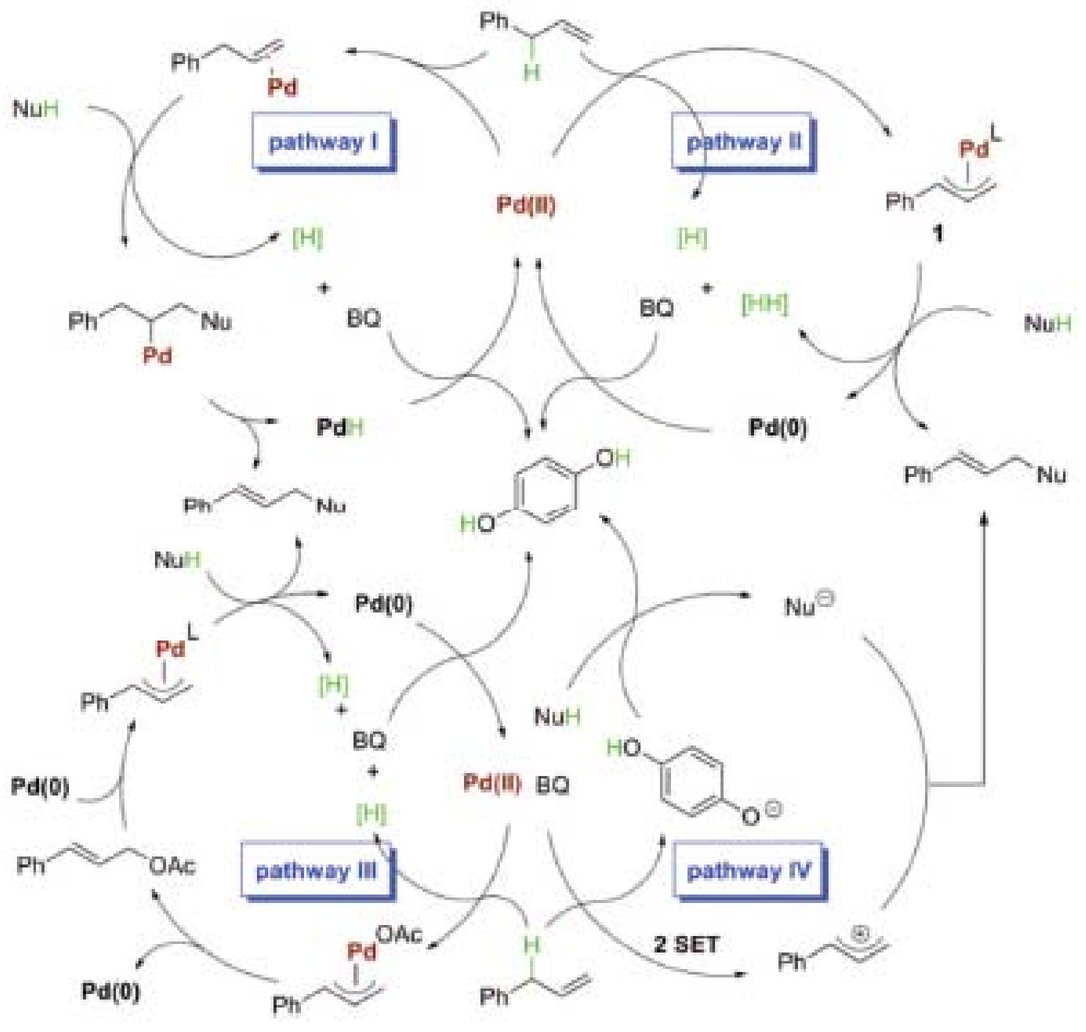




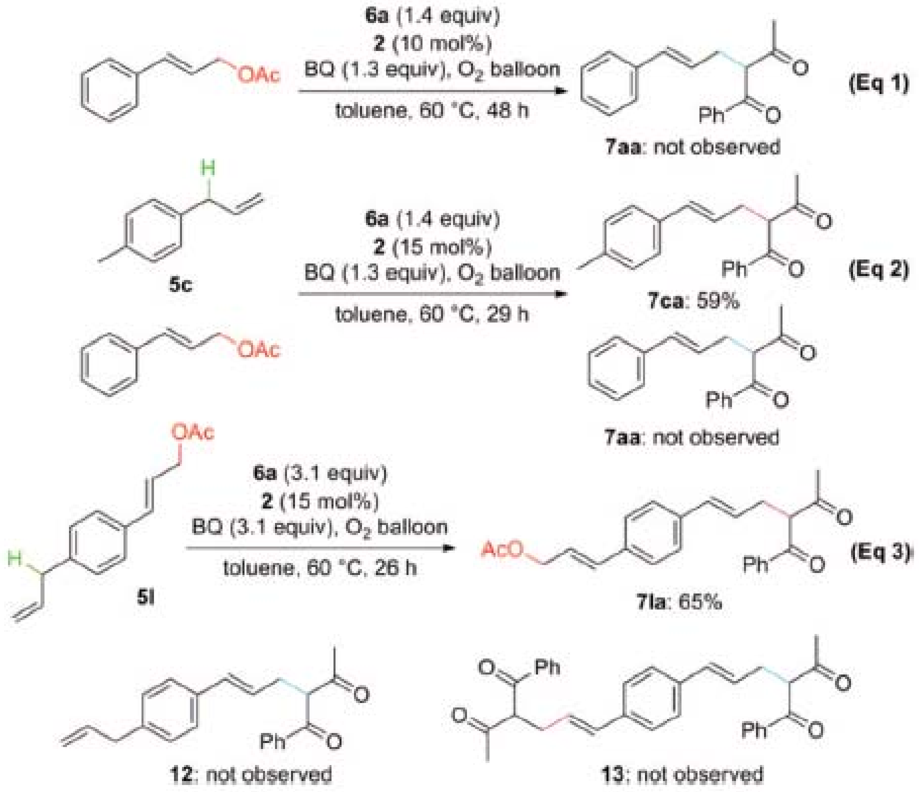
entry	Ar	7	yield (%)[b]
1	p-$CH_3OC_6H_4$	7ba	64
2[c]	p-$CH_3C_6H_4$	7ca	75
3[c]	m-$CH_3C_6H_4$	7da	42
4[c]	o-$CH_3C_6H_4$	7ea	34
5	2,4,6-$(CH_3)_3C_6H_2$	7fa	16
6	p-$C_6H_5-C_6H_4$	7ga	77
7[d]	p-ClC_6H_4	7ha	59
8[d]	p-BrC_6H_4	7ia	63
9[d]	C_6F_5	7ja	63
10	1-$C_{10}H_7$	7ka	67

- ❖ Steric hindrance obviously influenced the efficiency (Entry 5)
- ❖ Ortho- and meta-methyl allyl benzenes were not as reactive as para-substituted substrate (entries 3-4 vs entry 2)
- ❖ Substrates with electron-withdrawing groups had lower reactivities, and relatively high catalyst loading was required to reach higher yields (Entry 7-9)
- ❖ Simple olefins such as n-dodecene led to the formation of ketones through Wacker process, instead of the alkylation product in the same reaction condition

Proposed Mechanisms for Direct Allylic Alkylation



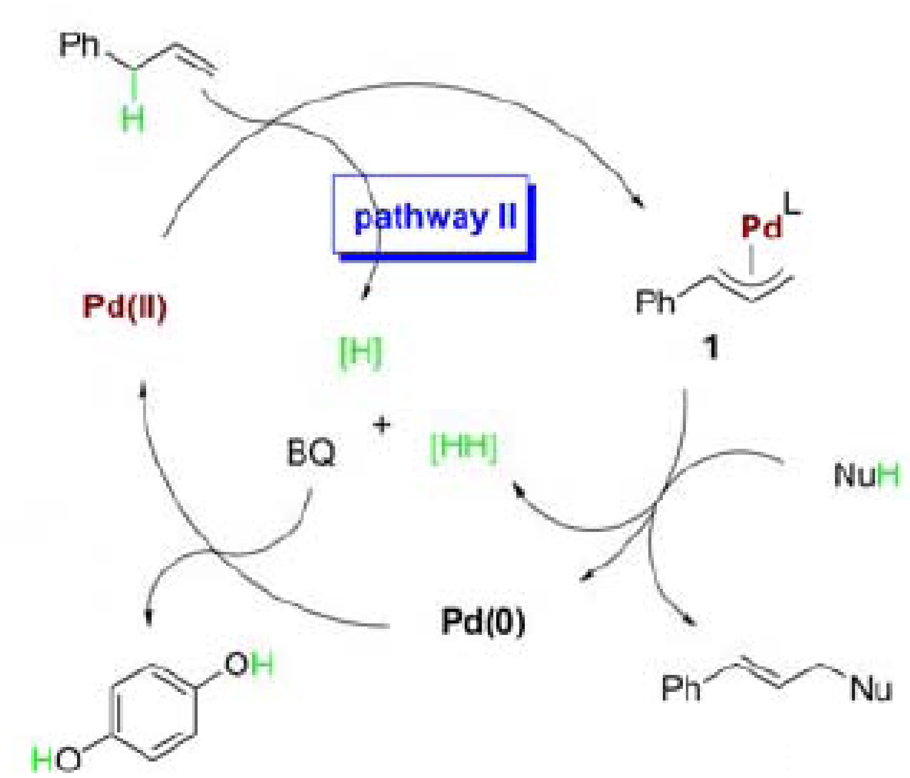
The transformation was not mediated by allyl acetate as shown in pathway III



❖ The traditional allylic alkylation originating from cinnamyl acetate under the described condition failed to produce 7aa

❖ Inter/intramolecular studies with both allyl acetate and bare allyl groups as the competitive reacting partners exhibited a highly selective alkylation from the allylic C-H bond, leaving the C-OAc bond untouched

Author hypothesized a reasonable mechanism for this direct allylic alkylation



π-Allylpalladium species 1 was assumed as the key intermediate formed via an electrophilic allylic C-H bond cleavage by Pd(II) catalyst. Nucleophilic attack occurred subsequently to afford the final product. Pd(0) was reoxidized by BQ to carry out the catalytic cycle

Summary

- A novel method toward direct intra/intermolecular allylic alkylation between allylic sp3 C-H bond and methylenic sp3 C-H bond via Pd(II)-catalysis was reported
- No base was required for both inter/intramolecular reactions
- The quinone was shown to play a vital role as a proton acceptor as well as the oxidant
- This methodology not only broadened the application of traditional Tsuji-Trost alkylation, but also offered an opportunity to study its stereoselectivity with chiral ligands