2009/07/18
Furutachi Makoto (M2)

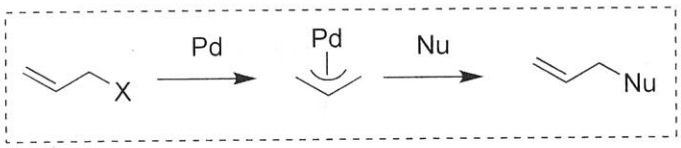
Allylic C-H Functionalization via π-Allyl Pd
--- In case of Prof. Dr. M. C. White ---

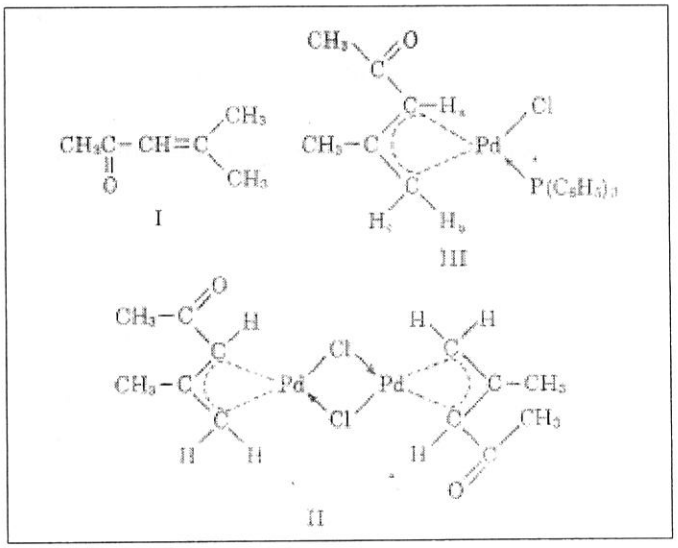
contents

1. Introduction

α-carbonyl alkylation

allylic alkylation

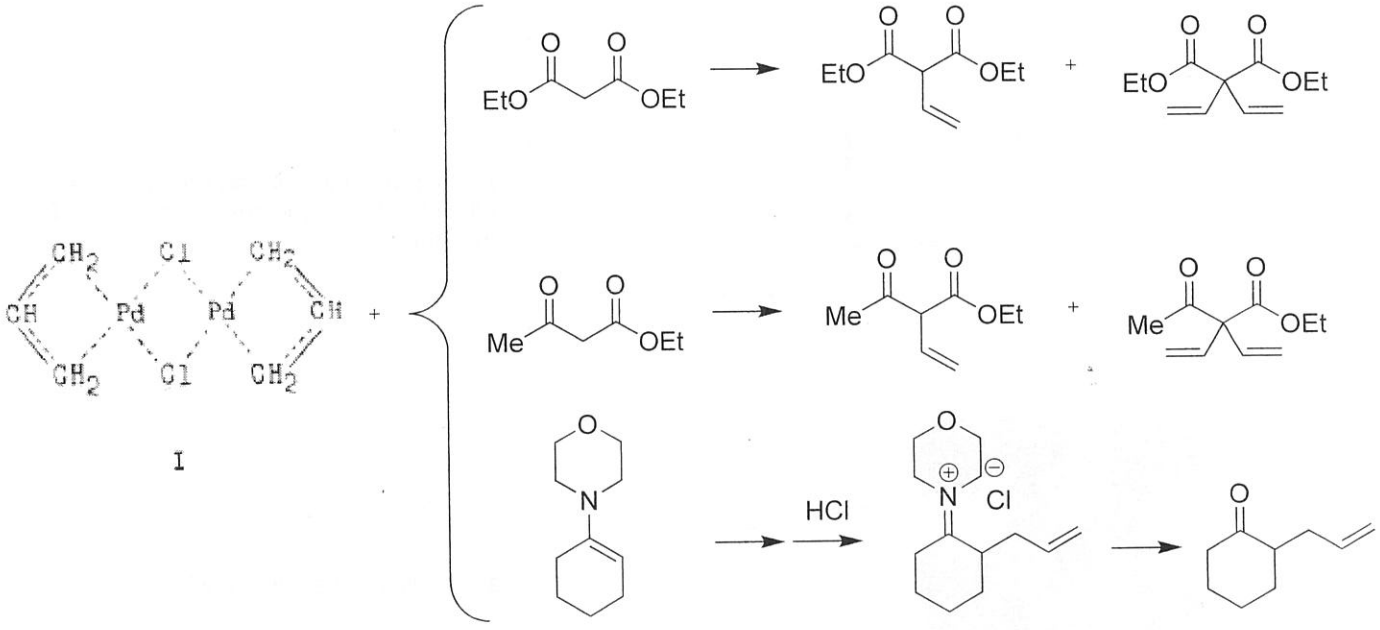




G. W. Parshall et al. *Inorg . Chem.* **1962**, *1*, 896-900.

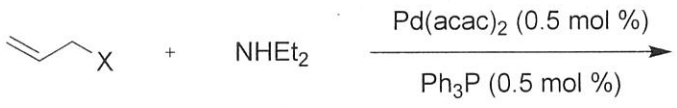
π-allylPd --- Tsuji-Trost reaction ---

Tsuji et al.
Tetrahedron Lett. **1965**, *49*, 4387-4388.



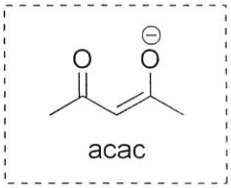
- SM= I → stoichiometric reaction
- it was established that the carbanions could attack the carbon atom of the palladium complex giving allyl derivatives

Manyik et al.
Tetrahedron Lett. **1970**, *43*, 3821-3824.



X = OH or OAc

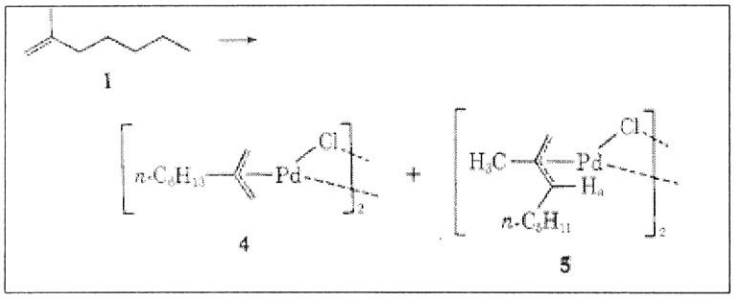
95%



- catalytic reaction

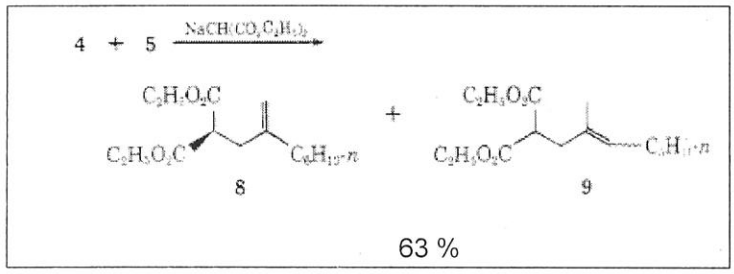
Trost et al.
J. Am. Chem. Soc. **1973**, *95*, 292-294.

Initial alkylation experiments were performed with the isomeric mixture of 4 and 5



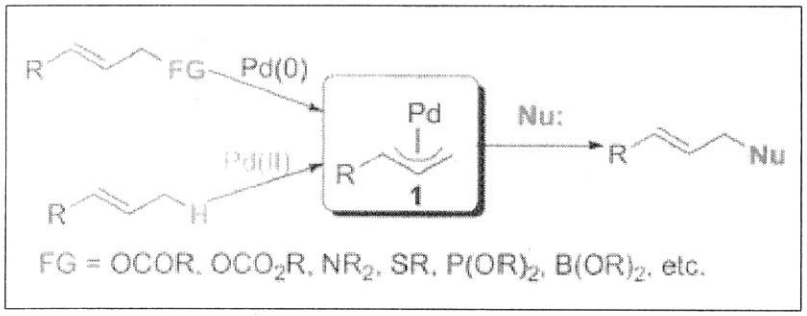
- treatment of this mixture with malonate anion led to no reaction

However



- addition of at least 4 equiv of triphenylphosphine allowed reaction to proceed in minutes at room temperature

- stoichiometric reaction



- many trials have already been made to eliminate the allylic substituents(FG) for this chemistry

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"streamlining the synthesis"

2. Allylic C-H Oxidation

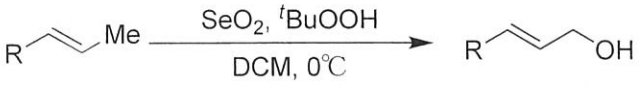
2-1. Catalytic Method for the Regioselective Synthesis of Allylic Acetates

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

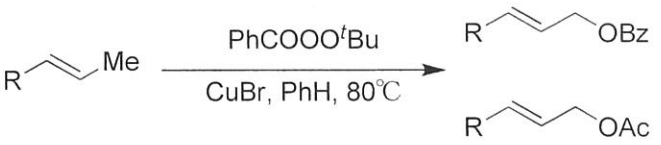
2-1-1. Outline

related works

Sharpless et al.
J. Am. Chem. Soc. **1977**, *99*, 5526-5528.



Andrus et al.
Tetrahedron **2002**, *58*, 845-866.

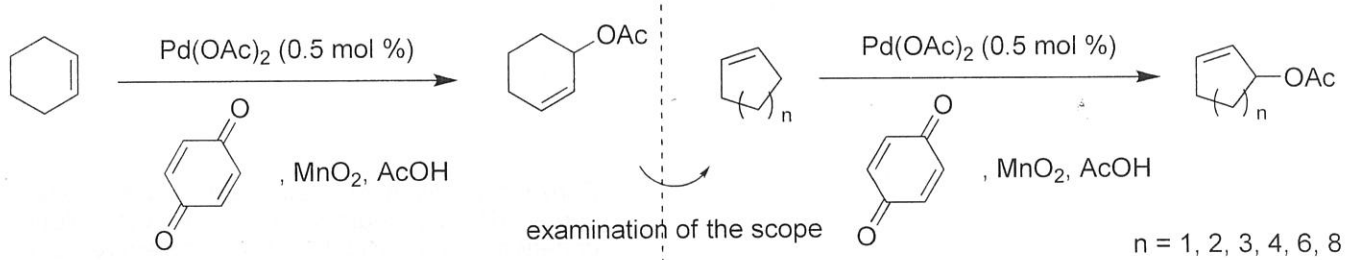


- these are limited by low conversions and/or lack of substrate generality due to poor functional group tolerance

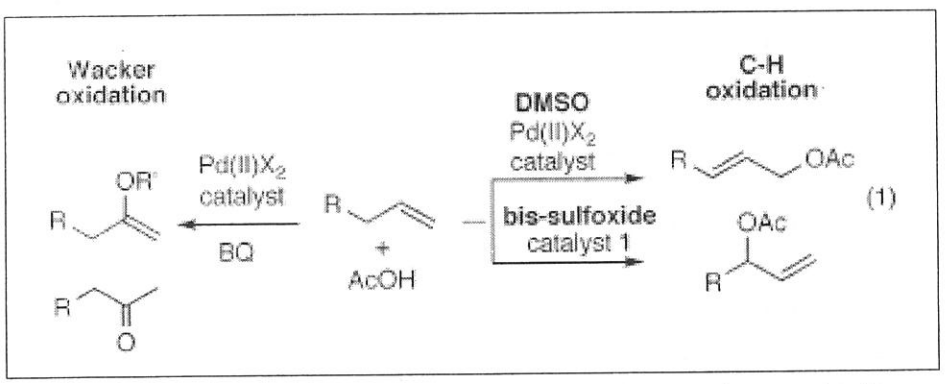
an of this reaction and also
on the results of an exploratory study of its m

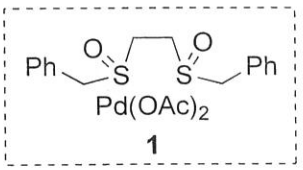
Heumann et al.
Angew. Chem. Int. Ed. **1984**, *23*, 453-454.

Heumann et al.
J. Org. Chem. **1990**, *55*, 975-984.



- available for transforming internal olefins into regioisomeric mixtures of allylic acetates





- DMSO→linear = L
- bis-sulfoxide→branched = B

- for reasons that are not clear, under these same conditions monosubstituted olefins predominantly undergo Wacker oxidation (Markovnikov oxypalladation/ β-hydride elimination) to yield mixtures of vinyl acetates and methyl ketone

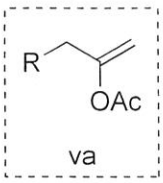
2-1-2. Optimization

Table S3. Solvent screen (solvent:AcOH, 1:1) with 10 mol% $Pd(OAc)_2$, BQ (2 eq), 40°C.

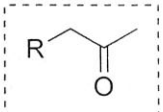
entry	solvent	% yield (GC), 48h L	B	va	mk
1	AcOH	3%	4%	18%	12%
2	DMSO	40%	2%	3%	4%
3	DMF	3%	<1%	3%	<1%
4	dioxane	<1%	2%	20%	6%
5	CH_3CN	8%	5%	2%	2%
6	THF	<1%	1%	13%	3%
7	Et_2O	<1%	1%	14%	5%
8	DME	<1%	2%	16%	6%
9	CH_2Cl_2	<1%	2%	10%	3%
10	Benzene	<1%	1%	10%	2%
11	Toluene	2%	2%	10%	2%

Table S4. Solvent screen (solvent:AcOH, 1:1) with 10 mol% catalyst 1, BQ (2 eq), 40°C.

entry	solvent	% yield (GC), 48h L	B	va	mk
1	AcOH	17%	59%	<1%	<1%
2	DMSO	12%	7%	<1%	<1%
3	DMF	13%	50%	<1%	<1%
4	CH_3CN	6%	3%	2%	<1%
5	dioxane	9%	61%	<1%	<1%
6	THF	7%	53%	<1%	<1%
7	Et_2O	8%	54%	<1%	<1%
8	DME	8%	57%	<1%	<1%
9	CH_2Cl_2	9%	68%	<1%	<1%
10	Benzene	8%	63%	<1%	<1%
11	Toluene	9%	59%	<1%	<1%



va

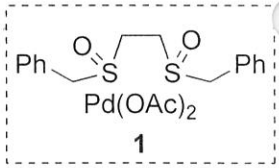


mk

II

Wacker products

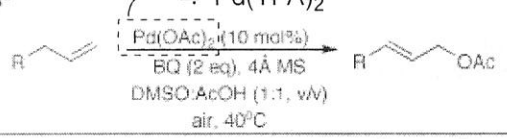
in the absence of DMSO, Wacker products are favored

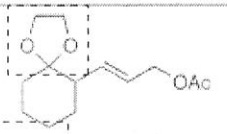
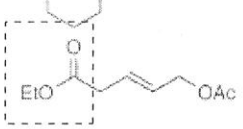
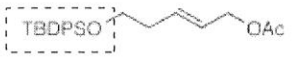
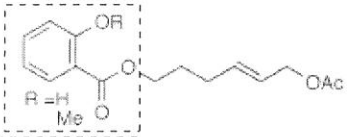
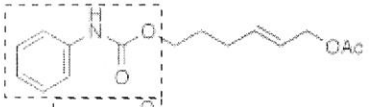
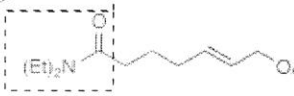
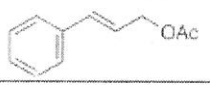


1

2-1-3. Substrate scope

Table 2. Allylic Oxidation of Terminal Olefins to (*E*)-Allylic Acetates[a]



entry	major product	linear: branched[c]	*E*:*Z*[d]	yield[e]
1		>99:1	>20:1	50% (72h)
2[b]		>20:1[d]	13:1	54% (48h)
3		24:1	12:1	52% (48h)
4[b]		31:1	11:1	50% (72h)
5[b]		31:1	11:1	57% (48h)
6		14:1	11:1	61% (72h)
7		17:1	13:1	56% (72h)
8		13:1	12:1	64% (72h)
9		23:1	12:1	62% (48h)
10		>99:1	13:1	65% (48h)

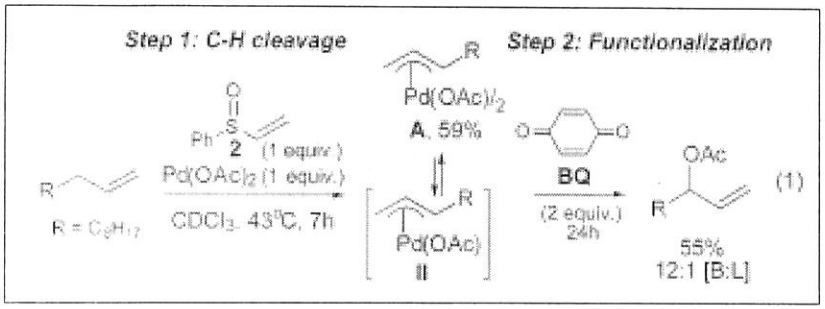
[a] All data reported ([L:B], [*E*:*Z*] ratios, yields) based on an average of two runs. Minor peaks consistent with diene byproducts were detected by ^{1}H NMR analysis of the crude. [b] 10 mol % of $Pd(TFA)_2$. [c] Ratio based on GC analysis of crude. Not corrected for small response factor variations. [d] Ratio based on 1H NMR analysis of crude. [e] Isolated yields after chromatography from reactions carried out on a 1.0 mmol scale (0.17 M).

- Benzyl and silyl ether-, ketal-, ester-, carbamate-, and amide-functionalized monosubstituted, olefins underwent direct oxidation with excellent regio- and stereoselectivities to generate the corresponding linear (*E*)-allylicacetates in preparatively useful yields

2-2. Serial Ligand Catalysis: A Highly Selective Allylic C-H Oxidation

J. Am. Chem. Soc. **2005**, *127*, 6970-6971.

2-2-1. Outline

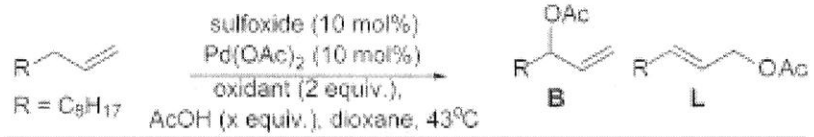


- different steps within the cycle place different demands on the catalyst

- reaction proceeds via a mechanism in which two different ligands are responsible for promoting different steps in the catalytic cycle

2-2-2. Optimization

Table 1



	entry	sulfoxide		AcOH (equiv.)	oxidant	% yield GC[a], 48h, B	[B:L]
control	1	none		52	BQ	3%	3:1
	2	1		52	BQ	73%	11:1
	3	2	a.	52	BQ	66%	12:1
			b.	**4**	**BQ**	**64%**	**31:1**
			c.	4[b]	BQ	60%	31:1
			d.	4	$Cu(OAc)_2$	1%	1:1
			e.	4	BQ(Me)[c]	59%	32:1
			f.	4	$BQ(Me)_2$[d]	15%	21:1
			g.	4	DQ[e]	1%	1:1
			h.[f]	4	BQ	58%	9:1
control	4	3		52	BQ	3%	2:1
	5	4		52	BQ	4%	3:1

[a] Average of 2−3 runs. Yields are corrected for response factor variations. [b] Complex A (10 mol % based on Pd), 72 h. [c] Methyl-1,4-benzoquinone. [d] 2,6-Dimethyl-benzoquinone. [e] Duroquinone. [f] 1 equiv of Pd(OAc)2/**2**, 24 h.

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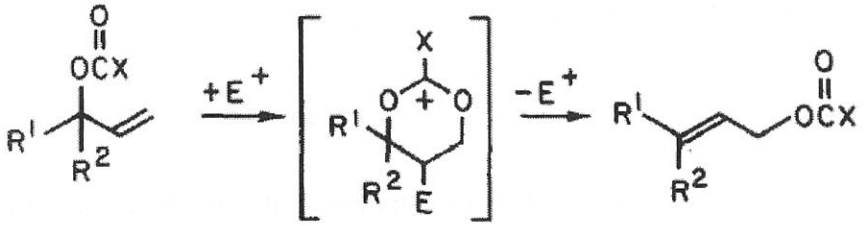
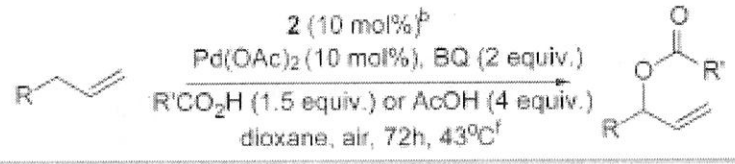
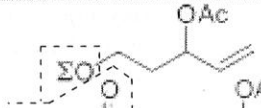
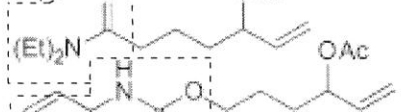
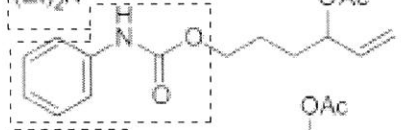
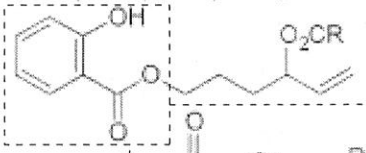
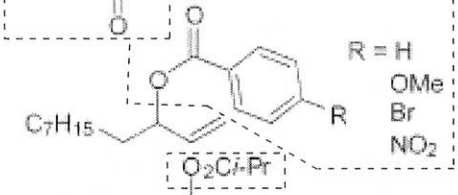
a cyclization-induced rearrangement pathway — Overman et al. *Tetrahedron Lett.* **1979**, *4*, 321-324.



2-2-3. Substrate scope

Table 3 [a]



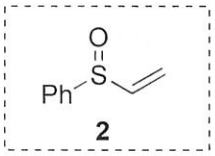
entry	major product	isolated yield	branched:linear [c]
1	 Σ = TBDPS	72%	16:1
2	Bn	59%	18:1
3 [e]		56%	18:1
4		64%	26:1
5		56%	>20:1 [d]
6		57%	19:1 [d]
7	 R = CH_3	64%	22:1
8	*p*-BrPh	65%	>20:1 [d]
9	 R = H	71% [g]	37:1
10	OMe	70%	41:1
11	Br	74% [g]	46:1
12	NO_2	83% [g]	>20:1 [d]
13		64% [g]	32:1

[a] Data based on an average of 3–4 runs. [b] **2** and $Pd(OAc)_2$ must be mixed neat. [c] Ratio based on GC analysis of crude. [d] Ratio based on ^1H NMR analysis of crude. [e] 20 mol % **2**. [f] Temperatures below 40 °C (e.g., 38 °C) result in decreased yields. [g] 48 h.

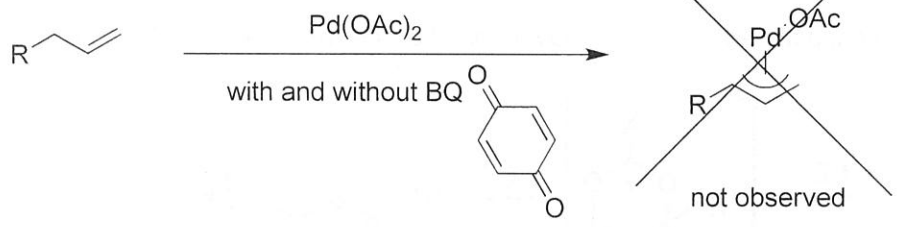
2-2-4. Mechanistic study

Step 1

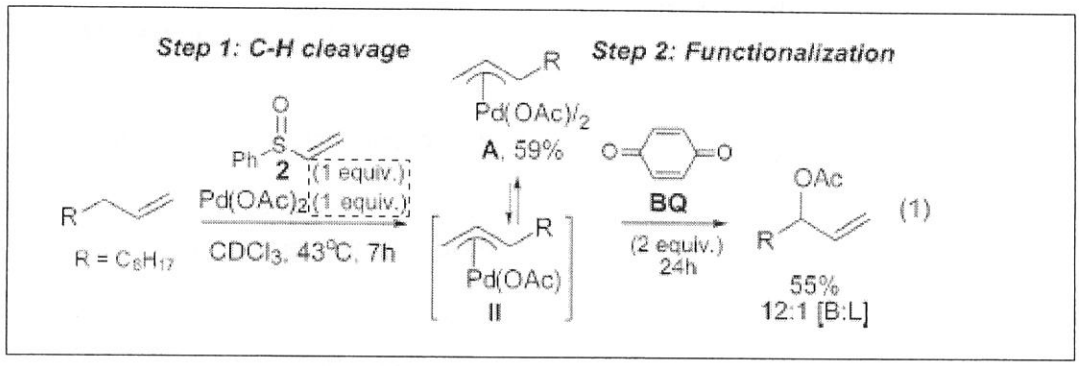
in the absence of **2**



2



- In the absence of **2**, with and without BQ, formation of π-allylPd was not observed



- When stoichiometric mixtures of 1-undecene (C_7H_{15}), $Pd(OAc)_2$, and **2** (Ph, S, O) were heated and monitored by ^1H NMR, dimeric π-allylpalladium acetate complex **A** was observed in ca. 59% yield

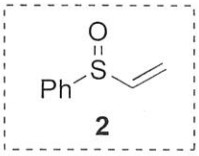
- When BQ was then added to this reaction mixture, formation of allylic acetate product was observed with yields and regioselectivities similar to those observed for the stoichiometric reaction run in the presence of BQ

- In the absence of **2**, with and without BQ, formation of complex **A** was not observed

→ These data are consistent with **2,** and not BQ, acting as a ligand to effect Pd-mediated allylic C-H cleavage to likely form a monomeric π-allylpalladium intermediate

Step 2

Table 2[a]

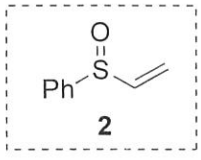


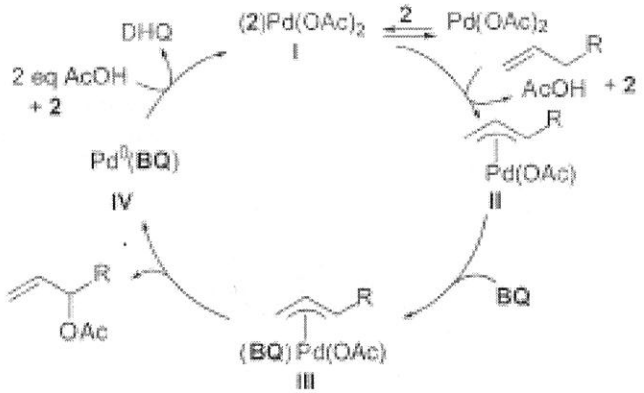
entry	conditions	GC yield, B $t = 6$ h	[B:L]
1	AcOH (40 equiv)	<1%	–
2	**2** (1 equiv)	<1%	–
3	BQ (20 equiv)	58%	32:1
4	**2** (1 equiv) BQ (20 equiv)	62%	34:1
5	PPh_3 (20 equiv)	42%	1:1[b]
6	dppe[c] (10 equiv)	44%	1:1[d]

[a] Average of 3 runs. [b] L, 46%. [c] 1,2-Bis(diphenylphosphino)ethane. [d] L, 47%.

- These data are consistent with BQ, and not vinyl sulfoxide **2**, acting as a ligand to effect functionalization from a monomeric Pd-d-allyl intermediate

Scheme 1. Serial Ligand Catalysis

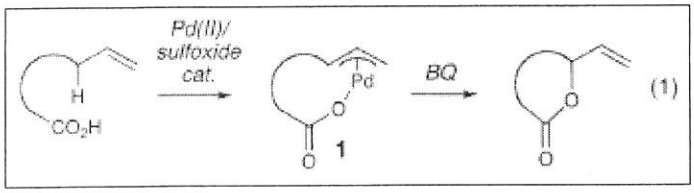




2-3. Macrolactonization via Hydrocarbon Oxidation

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

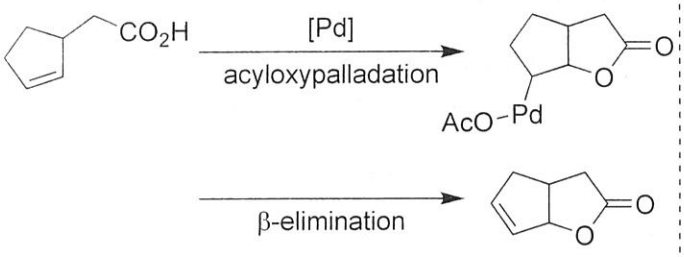
2-3-1. Outline



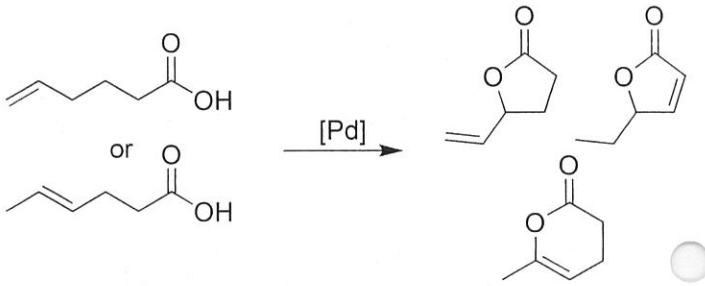
- macrocyclic lactones are important structural units
- macrolactonizations under these conditions (Pd^{II}/base) have not been demonstrated

related works

Catalytic Pd(II)
Larock et al. *J. Org. Chem.* **1993**, *58*, 5298-5300.

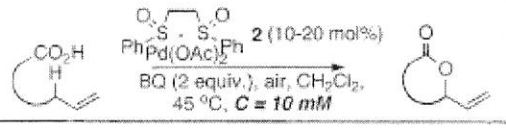


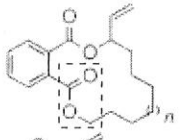
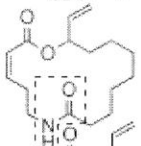
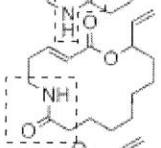
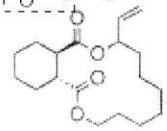
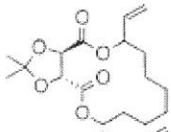
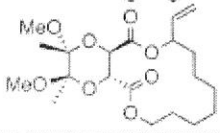
Stoichiometric Pd(II)
Annby et al. *Tetrahedron Lett.* **1993**, *34*, 8545-8548.



2-3-2. Optimization & Substrate scope

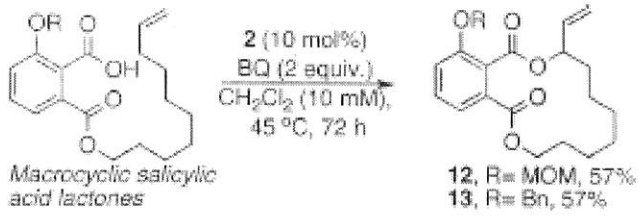
Table 1.



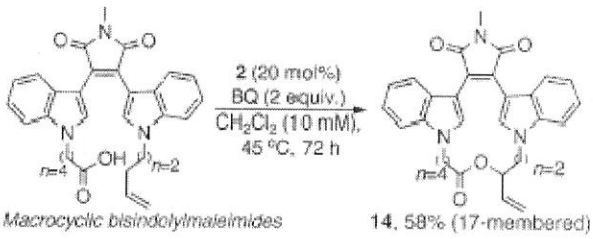
entry	macrolactone product	ring size	isolated yield[a]
1a		14	3,61%[b]
1b		1g scale	->62%[c]
2		15	4,52%
3		16	5,60%
4		17	6,53%
5		16	7,52%[d] 98:2 (*Z*:*E*)[e]
6		16	8,63%[d] 99:1 (*E*:*Z*)[e]
7		14	9,60% 1.4:1 (d.r.)[f]
8		14	10,54%[d,g] 1:1 (d.r.)[f]
9		14	11,60%[h] 1.4:1 (d.r.)[f]

[a] Average yields of pure branched isomer for two runs at 0.2 mmol, 72 h. Up to 18% starting material observed (Supporting Information). Some head-to-tail dimerization byproducts have been observed. [b] Higher diultions result in lower macrolide yields. [c] 1 g (3.3 mmol). [d] 20 mol % **2**; 10 mol % **2** gave 17−22% lower yields (Supporting Information). [e] Ratio by GC. [f] Ratio by ^{1}H NMR. [g] C = 20 mM. [h] 15 mol % **2**.

- in addition to aryl acids, vinylic and alkyl acids are competent nucleophiles (entries 5-9)
- both (*Z*)- and (*E*)-α,β- unsaturated acids undergo cyclization using this allylic C-H oxidation method to furnish 16-membered macrolides **7** and **8** in good yields with no olefin isomerization (entries 5 and 6)
- chiral, alkyl acids effectively cyclize and do not appear to significantly influence diastereoselectivity (entries 7-9)
- the mildness of this method is illustrated by macrolactonization of alkenyl acids with densely oxygenated acetonide and acetal moieties (entries 8 and 9, respectively)

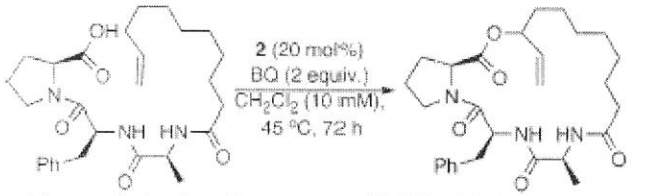


Macrocyclic salicylic acid lactones



Macrocyclic bisindolylmaleimides

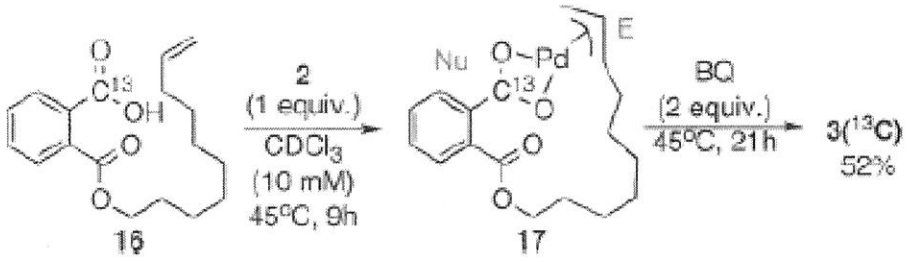
14, 58% (17-membered)

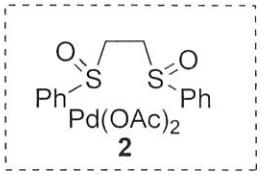


Macrocyclic depsipeptides

15, 61%, 3:1 d.r. (19-membered)

2-3-3. Mechanic study





- when stoichiometric mixtures of ^{13}C-labeled alkenoic acid 16 and bis-sulfoxide/$Pd(OAc)_2$ complex **2** were heated and monitored by ^{1}H NMR spectroscopy, peaks consistent with a d-allylPd complex **17** were observed

- simultaneous monitoring of the C-H cleavage step by ^{13}C NMR spectroscopy showed a Pd-bound carboxylate suggestive of intermediate **17**

- evidence for the monomeric nature of **17** was obtained via ESI-HRMS

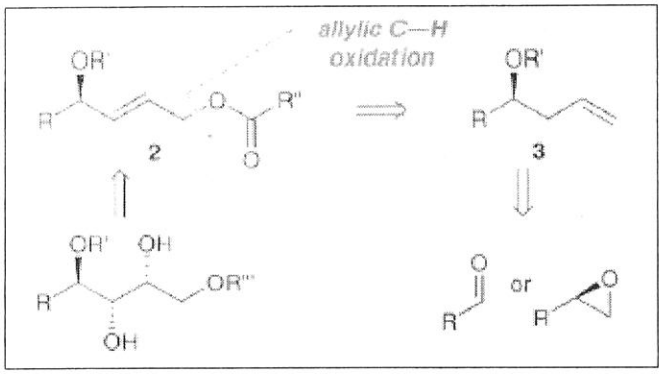
- addition of BQ to **17** results in formation of macrolide **3** in 52% yield (62% catalytic reaction)

- significantly, in the absence of BQ, reductive elimination is not observed

- macrolactonization proceeds via a serial ligand catalysis mechanism and provide evidence in support of BQ promoted inner-sphere C-O bond formation from a templated π-allylPd carboxylate intermediate

Angew. Chem. Int. Ed. **2006**, *45*, 8217 –8220.

2-4-1. Outline



- **2** may be synthesized directly from protected chiral homoallylic alcohols such as **3** through the DMSO/Pd(II)-promoted allylic oxidation

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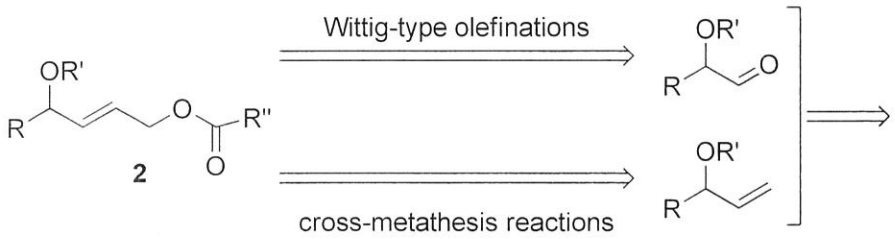
syntheses of **2** based on Wittig-type olefinations or cross-metathesis reactions



- difficult in accessing enantioenriched α-hydroxyaldehyde and α-hydroxy olefin starting materials

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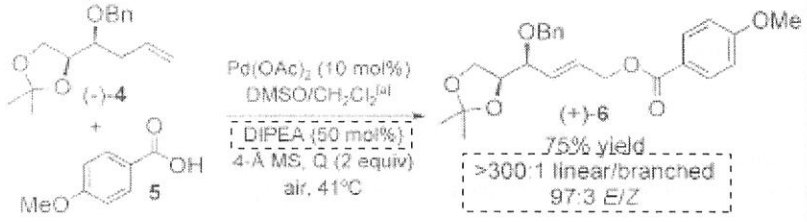
2-4-2. Optimization

Table 1: Investigation into the linear allylic oxidation reaction to form the hexose precursor **6**.

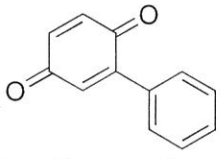


Entry	$DMSO/CH_2Cl_2$ Molarity [M]	Quinone (Q)	Acid **5** (equiv)	Yield [%][c]
1	0.33	BQ	15	23[d]
2	0.33	BQ	15	45
3	0.33	PhBQ	15	55
4	0.6	PhBQ	10	66
5	1.0	PhBQ	5	67
6[b]	2.0	PhBQ	3	75
7[b]	2.0	PhBQ	3	71[e]
8	2.0	PhBQ	3	63[f]
9	3.0	PhBQ	1.5	50

[a] $DMSO/CH_2Cl_2$ (3.2:1). [b] Linear to branched allylic ester and *E*/*Z* ratios were determined by HPLC for the material obtained from entries 6 and 7 on comparison with branched or acetonide-free *E* and *Z* standard compounds: linear/branched > 300:1, *E*/*Z* = 30:1 and 36:1 (for entries 6 and 7, respectively). [c] Yield of isolated product from the reactions carried out on a 1 mmol scale (**4**, 262 mg). Yields and selectivities represent an average of at least 2 runs. [d] With no DIPEA added. [e] $[Pd(CH_3CN)_4](BF_4)_2$ (10 mol%), 13% of **4** was recovered. [f] $Pd(OAc)_2$ (5 mol%). Bn = benzyl, DIPEA = *N*,*N*-diisopropylethylamine, MS = molecular sieves.

- the addition of DIPEA, a noncoordinating base additive, effected a significant increase in yield (entry 2) although the exact role of the base is currently unclear, they hypothesize that it increases concentrations of the benzoate anion

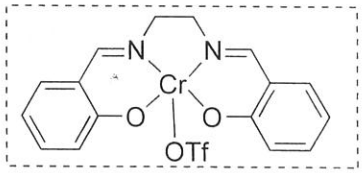
- the yield was also increased on switching oxidants from benzoquinone (BQ) to phenylbenzoquinone (entry 3)

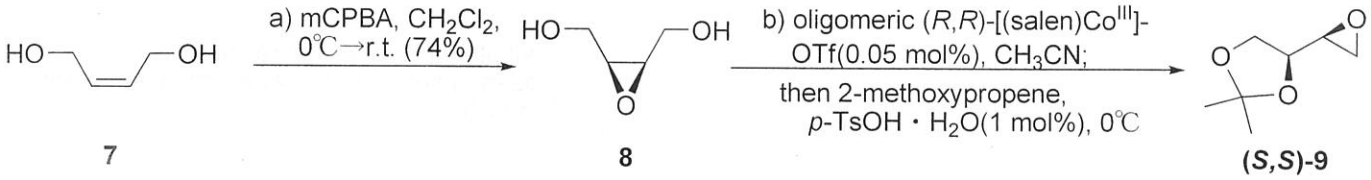


phenylbenzoquinone

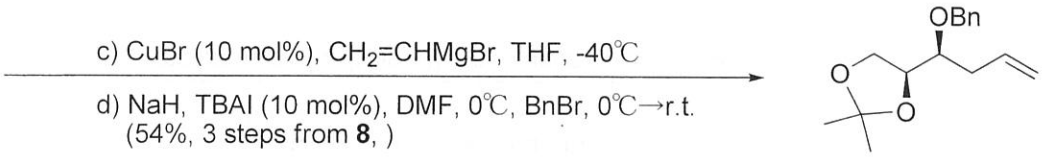
- on increasing the reaction concentration to 2.0M, they achieved further increases in yields, and were able to use fewer equivalents of carboxylic acid (entry 6)

2-4-3. Total synthesis of differentially protected l-galactose (-)-**11**

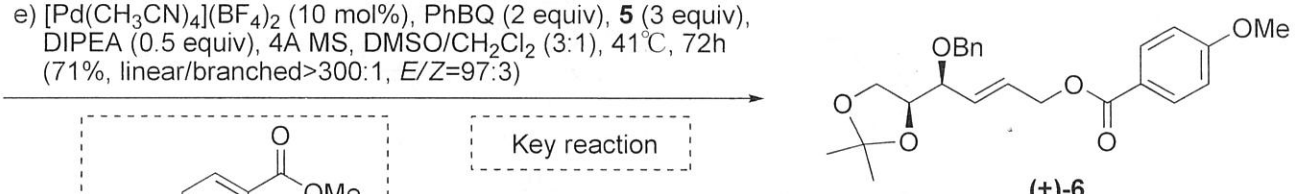




7 **8** **(*S*,*S*)-9**

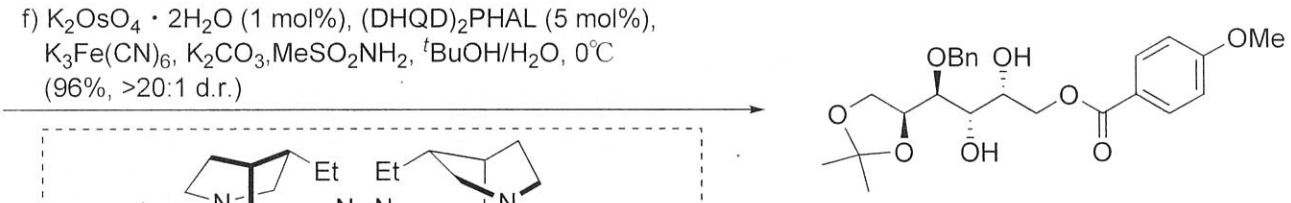


(-)-4
99% ee



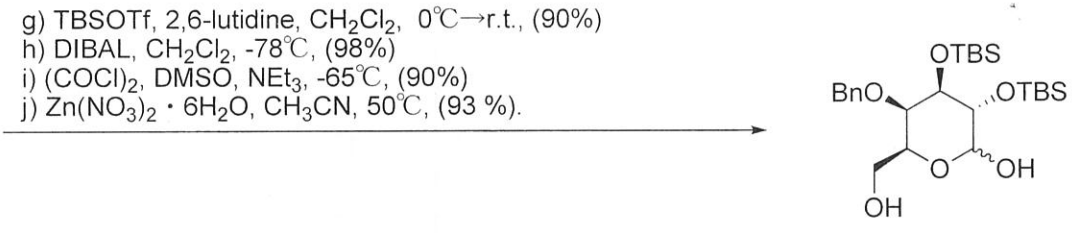
5

(+)-6



$(DHQD)_2PHAL$

(-)-10



(-)-11

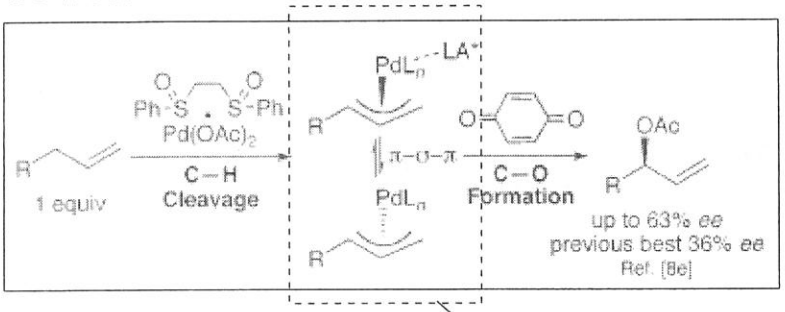
- proceeded in a total of 10 linear steps with 20% overall yield from the commercially available **7**

- previously reported
(for example: 11 steps, 18% overall yield, and 9 steps, 16% overall yield)

2-5. A Chiral Lewis Acid Strategy for Enantioselective Allylic C-H Oxidation

Angew. Chem. Int. Ed. **2008**, *47*, 6448 –6451.

2-5-1. Outline

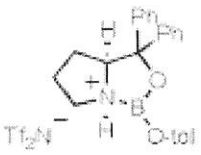


- All attempts to use chiral sulfoxides have been unsuccessful in effecting asymmetric induction

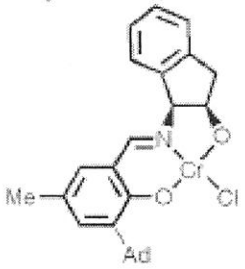
π-σ-π isomerization of the [(π-allyl)Pd] intermediate

2-5-2. Optimization

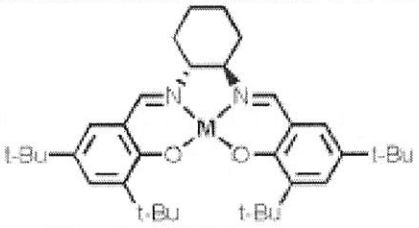
Table S1. Extended Analysis of Lewis Acid Mediated Enantioselective C-H Bond Oxidation



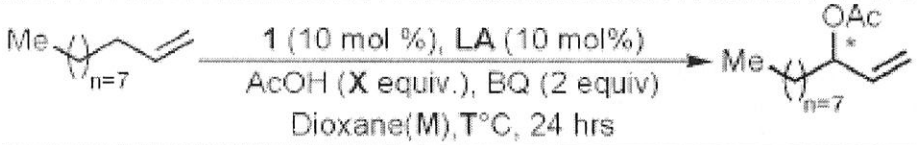
A



B = monomeric
C = dimeric



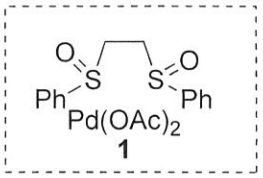
M		
Co(III)OAc	D	
Cr(III)Cl	2	
Cr(III)F	3	
Cr(III)OAc	4	



Entry	LA	M	X	T	% Yield[a]	B:L	ee[b]
1	-	0.33	4	45	71	>30:1	0
2	A	0.33	4	45	27	28:1	0
3	B	0.33	4	45	7	8:1	0
4	C	0.33	4	45	41	6:1	0
5	D	0.33	4	45	6	>30:1	0
6[c]	D	2	1.1	rt	1	1.9:1	4
7[d]	D	2	1.1	rt	4	2.8:1	14
8	2	0.33	4	45	7	1.2:1	32
9	2	0.33	1.1	45	10	1.2:1	32
10	2	2	1.1	rt	35	1.1:1	32
11[d]	2	2	1.1	rt	41	1.4:1	32
12	3	0.33	4	45	74	9.3:1	9
13	3	0.33	1.1	45	59	7.9:1	15
14	3	2	1.1	rt	86	4.6:1	54
15[d]	3	2	1.1	rt	93	5.1:1	57
16	4	0.33	4	45	11	3.2:1	8
17	4	0.33	1.1	45	8	2.0:1	14
18	4	2	1.1	rt	50	1.5:1	29
19[d]	4	2	1.1	rt	71	2.0:1	31

control (entries 16–19)

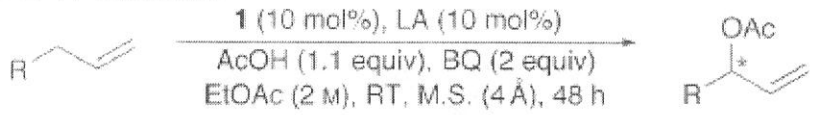
[a]GC yield, average of at least two runs [b]Determined by Chiral GC [c] TBME, 1.1 equiv. DIPEA [d]EtOAc solvent, 4A MS bead added(~30 mg), 48 hrs.

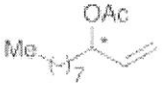
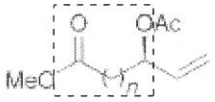
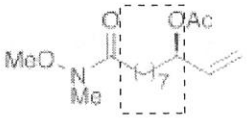
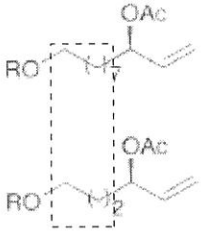
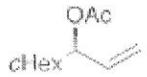


- introduction of chiral phosphine ligands, are not compatible with electrophilic, oxidative C-H activation conditions

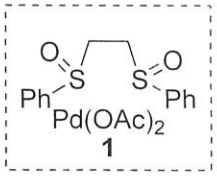
- Lewis acid co-catalysts have been demonstrated

Table 2: Preliminary investigation of the scope of the enantioselective allylic C–H oxidation.



Entry	Product		Yield [%][a] (brsm)[b]	B:L	*ee* [%][c]
1			92	5.3:1	59
2[d]			92	5.3:1	–59
3	$n=7$		89	4.8:1	57
4	$n=2$		69 (73)	4.6:1	50
5			81 (88)	4.4:1	54
6	R=TBDPS		84 (90)	4.4:1	63
7	R=H		83	4.4:1	50
8	R=THP		91	3.6:1	49
9	R=Bn		90	4.3:1	45
10[e]			78 (83)	1.5:1	62

[a] Yields of isolated allylic oxidation products (1.0 mmol substrate) are an average of at least three experiments. [b] Yield is based on recovered starting material. [c] The *ee* values were determined by GC analysis on a chiral stationary phase. (see the Supporting Information). [d] The (*S*,*S*)-**3** catalyst was used. [e] 72 h. Bn = benzyl, *c*Hex = cyclohexyl, TBDPS = *tert*-butyldiphenylsilyl, THP = tetrahydropyranyl.

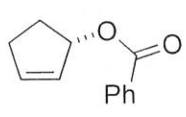


- the functional-group tolerance of this system matched that of the original bis(sulfoxide)/Pd^{II} methodology, with tolerance for esters, amides, a wide variety of protected alcohols, and even a free alcohol (entries 3-9)

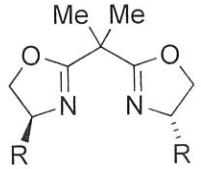
- these results represent the highest enantioselectivity observed for the allylic C-H oxidation of terminal olefins

related works

Pfaltz et al. *Tetrahedron Lett.* **1995**, *36*, 1831-1834.

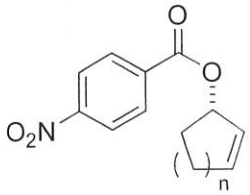


internal olefin
up to 89% ee

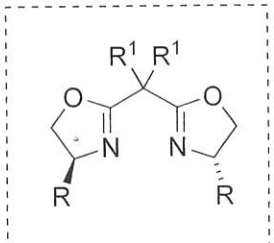


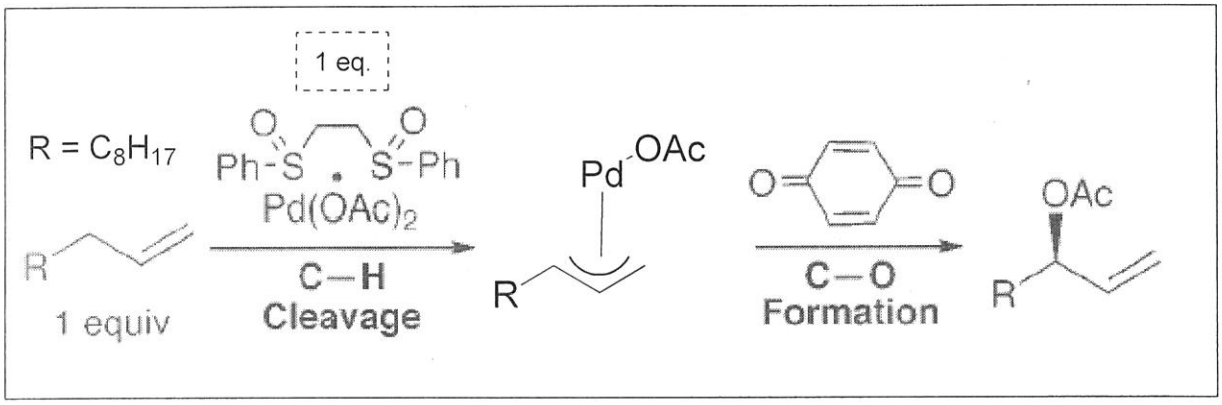
R = ^{i}Pr, ^{t}Bu, Ph

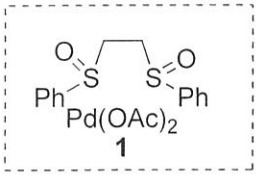
Andrus et al. *J. Am. Chem. Soc.* **2002**, *124*, 8806-8807.



internal olefin
up to 99% ee

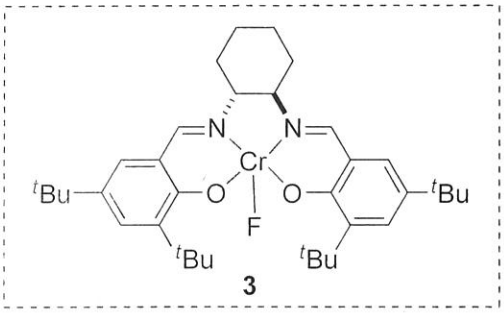






1

- studies with stoichiometric amounts of undecene and bis(sulfoxide)/$Pd(OAc)_2$ catalyst **1** indicate that the rate of C-H cleavage to form the π-allyl palladium acetate dimer is unaffected by **3**
- functionalization in the absence of BQ does not occur
- sterically hindered 2,6-dimethylbenzoquinone gave only a trace amount of product in the catalytic reaction

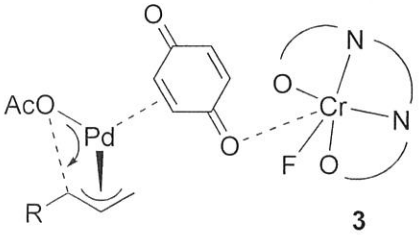


3

undecene 

three mechanistic scenarios

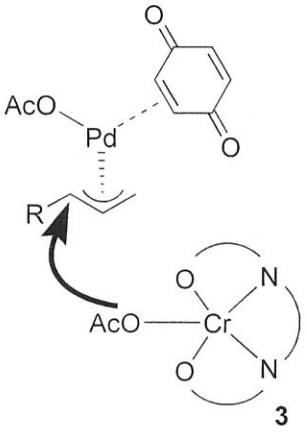
scenario 1



3

reductive elimination of acetate by a [L*Cr(BQ)]-activated π-allyl palladium complex

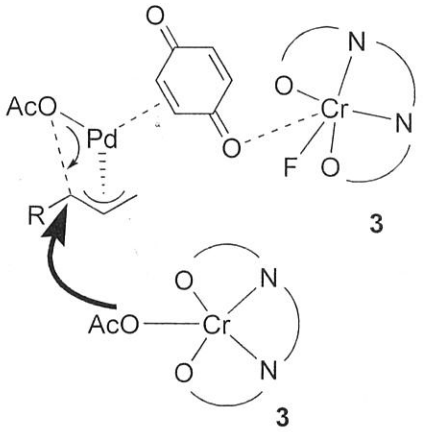
scenario 2



3

delivery of an acetate group from [L*Cr(OAc)] to [(π-allyl)Pd(BQ)L] complex

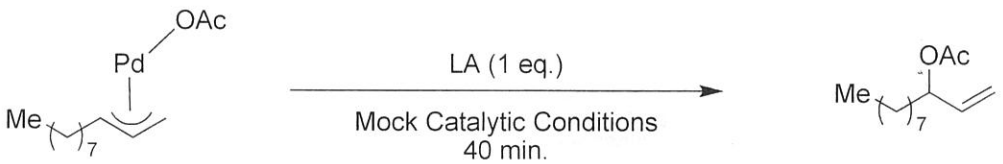
scenario 3



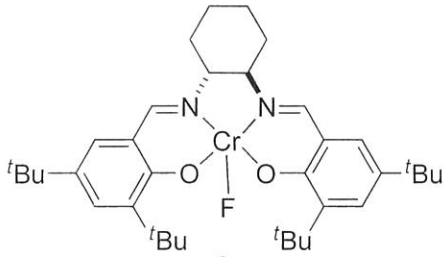
3

delivery of an acetate group from [L*Cr(OAc)] to an activated L*Cr(BQ)–Pd(π-allyl)

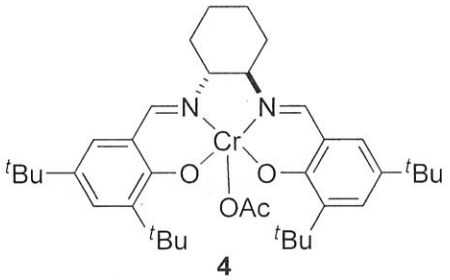
dual activation



LA



3



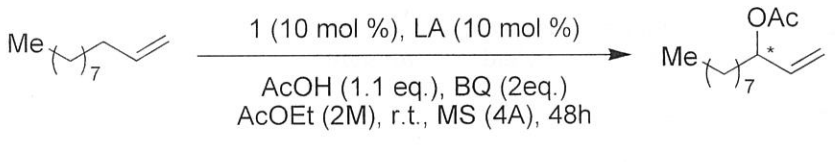
4

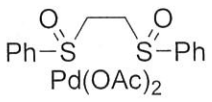
10-fold

Entry	LA	k_{rel}	Yield [%]	B:L	ee [%]
1	–	1.0	20	>20:1	–
2	(*R*,*R*)-**3**	9.7	85	5.2:1	55
3	(*R*,*R*)-**3**	–	0	–	–
4	(*R*,*R*)-**4**	3.8	41	2.2:1	29

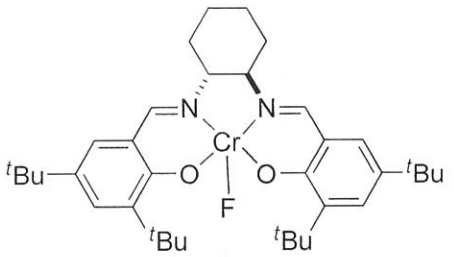
no BQ added

diminished

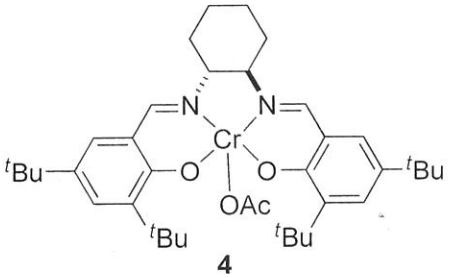




1



3



4

y. : 93%
B:L: 5.1:1
ee : 57% ee

diminished

y. : 71%
B:L: 2:1
ee : 31% ee

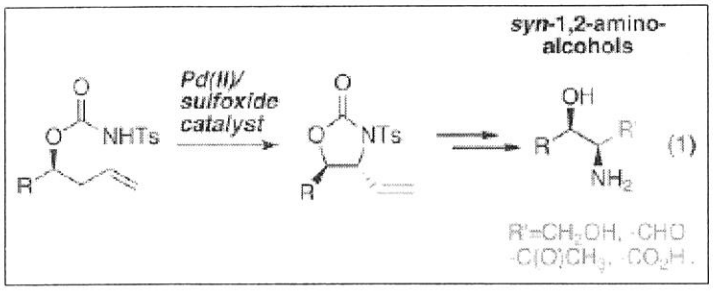
- these results are inconsistent with asymmetric induction arising exclusively through the delivery of an acetate group by **4**, while they are most consistent with a **3**-BQ-promoted functionalization (scenario 1). However, at this time we cannot rule out a dual activation mechanism in which 4 delivers the acetate nucleophile to a [(π-allyl)Pd(BQ)-**3**] electrophilic intermediate

3. Allylic C-H Amination

3-1. syn-1,2-Amino Alcohols via Diastereoselective Allylic C-H Amination

J. Am. Chem. Soc. **2006**, *129*, 7274-7276.

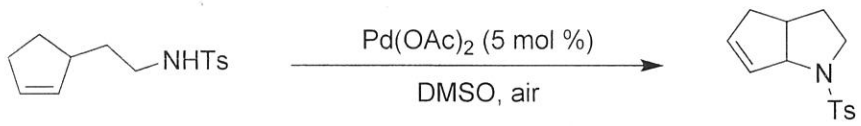
3-1-1. Outline



- syn-1,2-Amino alcohols are prevalent motifs in a diverse range of important small molecules
- Pd(II)-promoted allylic C-H amination processes are rare

related wokk

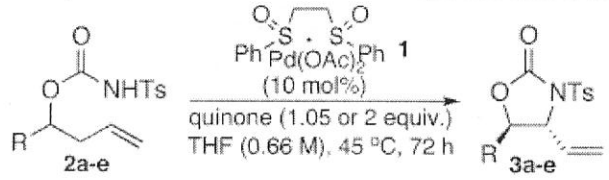
Larock et al. *J. Org. Chem.* **1996**, *61*, 3584-3585.

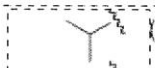
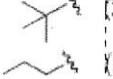
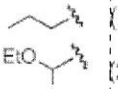
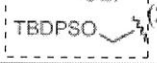


86%

3-1-2. Optimization & Substrate scope

Table 1. Allylic C–H Amination Reaction Optimization and Scope

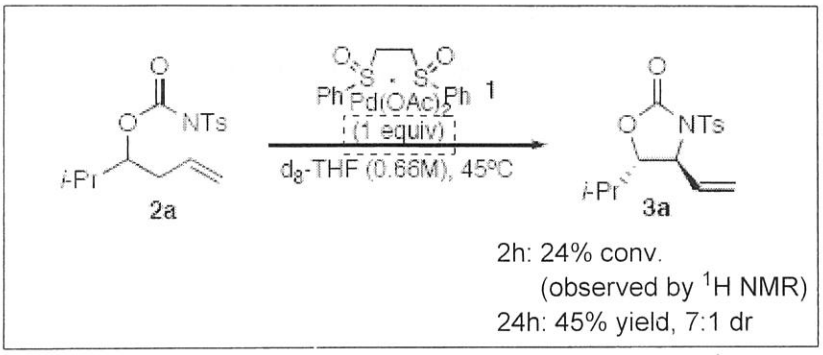


entry	R	quinone (equiv.)	isolated yield[a]	dr[b] (*anti:syn*)
1	*i*-Pr (**2a**)	BQ (2)[c]	37%	7:1
2	*i*-Pr	BQ (2)[c,d]	3%[e]	--
3	*i*-Pr	BQ (2)	50%	7:1
4	*i*-Pr	PhBQ (2)	66%	6:1
5	*i*-Pr	PhBQ (1.05)	72%	6:1
6	 (**2a**)	PhBQ (1.05)[f]	76%	6:1
7	 (**2b**)	PhBQ (1.05)[f]	8%	18:1
8	 (**2c**)	PhBQ (1.05)[f]	86%	1.6:1
9	(**2d**)	PhBQ (1.05)[f]	84%	7:1
10	 (**2e**)	PhBQ (1.05)[f]	84%	1.8:1[e]

[a] Average of two runs at 0.3 mmol. [b] Determined by GC analysis of the crude reaction mixture. [c] Reaction run at 0.33 M. [d] Reaction run using 10 mol % $Pd(OAc)_2$ (no sulfoxide ligand). [e] Determined by NMR analysis of the crude reaction mixture. [f] Reaction run using 5 mol % additional bis-sulfoxide ligand.

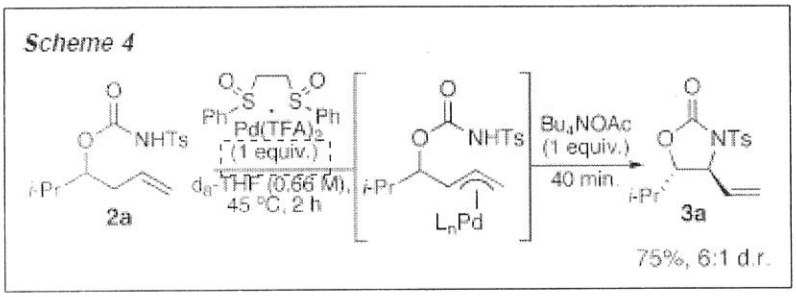
3-1-3. Mechanistic study

Stoichiometric study



2h: 24% conv.
(observed by ^{1}H NMR)
24h: 45% yield, 7:1 dr

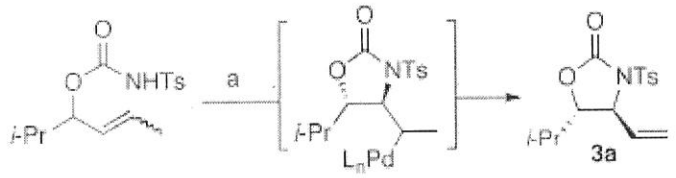
- note that yield for the catalytic reaction is 72% yield [6:1 dr] (table 1, entry 5)



- a key to this catalytic amination reactivity is the ability to use catalytic quantities of acetate base that can be regenerated via quinone-mediated Pd(0) oxidation
- The use of stoichiometric base significantly attenuates this reactivity, most likely by interfering with the electrophilic C-H cleavage step of the catalytic cycle

An alternative mechanism

Table 2. Testing for a Possible Aminopalladation Mechanism



entry	olefin isomer	isolated yield 3a	5 h dr[b] (anti/syn)	72 h dr[b] (anti/syn)
1	*E* isomer (17)	20%	9:1	8:1
2	*Z* isomer (18)	9%	13:1	11:1
3	α-olefin (2a)	72%	6:1	6:1

[a] Reaction run using 1 (10 mol %), PhBQ (1.05 equiv), THF (0.66 M), 45 °C, 72 h. [b] GC.

{ via (1) aminopalladation (2) β-elimination

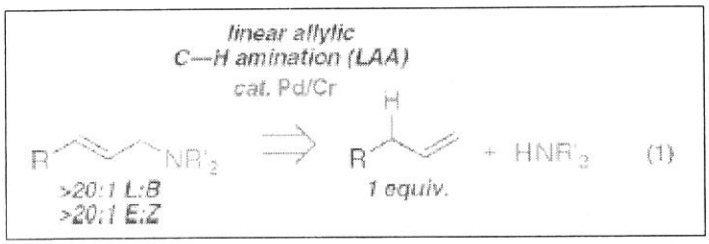
via π-allylPd

- this data strongly supports a mechanism for allylic C-H amination involving Pd(II)/bis-sulfoxide promoted allylic C-H cleavage to form a π-allylPd intermediate followed by acetatemediated functionalization

3-2. Catalytic Intermolecular Linear Allylic C-H Amination via Heterobimetallic Catalysis

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

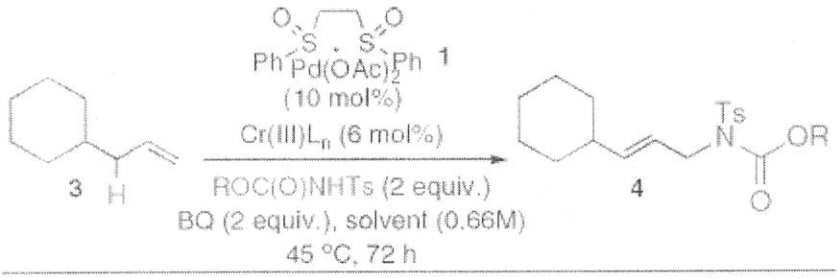
3-2-1. Outline



- Linear Allylic C-H Amination

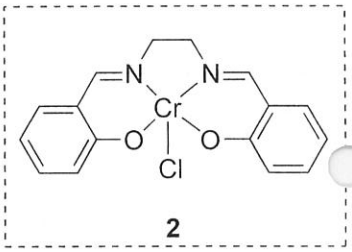
3-2-2. Optimization

Table 1. Development of the Intermolecular LAA Reaction

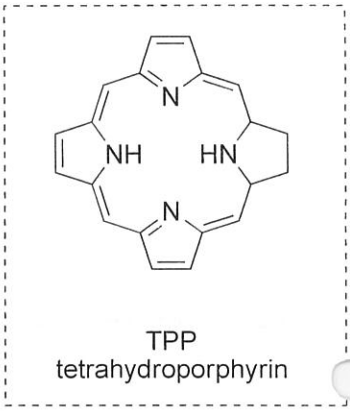


	entry	$Pd(II)L_n$	R	$Cr(III)L_n$	isolated yield[a]	L:B[b]	*E*:*Z*[b]
control	1[c]	1	Me	----	----	----	----
control	2[c]	----	Me	(salen)Cr(III)Cl **2**	----	----	----
	3[c]	1	Me	**2**	43%	>100:1	65:1
control	4[c]	$Pd(OAc)_2$	Me	**2**	17%	----	----
control	5[c]	1	Me	$CrCl_3 \cdot 3THF$	----	----	----
control	6[c]	1	Me	(TPP)Cr(III)Cl	25%	>100:1	71:1
	7[d]	1	Me	(salen)Cr(III)Cl **2**[e]	53%	>100:1	57:1
	8[d]	1	Me	(salen)Al(III)Cl	21%	>100:1	76:1
	9[d]	1	Me	(salen)Co(III)OAc	17%	>100:1	91:1
	10[d]	1	Me	(salen)Mn(III)Cl	44%	>100:1	78:1
	11[d]	1	Bn	**2**	65%	>20:1[f]	>20:1[f]
	12[d]	1	*t*-Bu	**2**	40%	>20:1[f]	>20:1[f]
	13[d]	1	Fm	**2**	40%	>20:1[f]	>20:1[f]

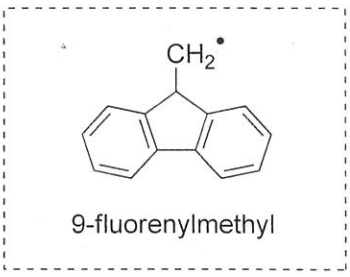
[a]Average of 2 runs at 0.3 mmol. [b] Determined by GC analysis of the crude reaction mixture (unless otherwise stated). [c] THF (0.66M). [d] TBME (0.66M). [e]Other metal complexes gave 2% or less GC yield: Ni(II)(TPP), Fe(III)(TPP)Cl, Ru(II)(TPP), Cu(II)(TPP), Co(II)(*p*-MeO-TPP) Fe(III)PthCl, Mn(III)PthCl, Si(IV)$PthCl_2$ (TPP = tetraphenylporphyrin, Pth = phthalocyanine). [f]Determined by ^1H NMR analysis of the crude reaction mixture.



2



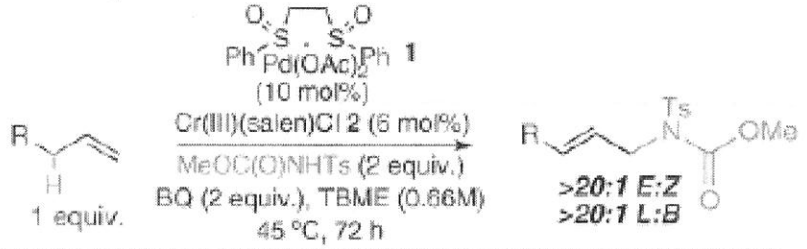
TPP
tetrahydroporphyrin

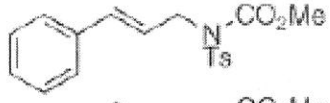
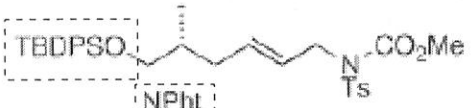
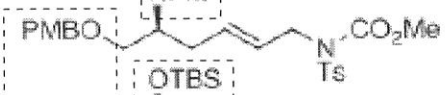


9-fluorenylmethyl

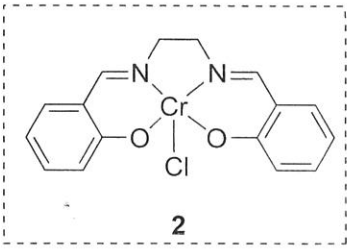
3-2-3. Substrate scope

Table 2. Scope of the Intermolecular LAA Reaction



entry	allylic amine product	isolated yield[a]
1		**5** 58%
2		**6** 72%
3		**7** 59%[b]
4		(+)-**8** 57%
5		(+)-**9** 65%
6		*n* = 0 (+)-**10** 52%
7		*n* = 1 (+)-**11** 65%

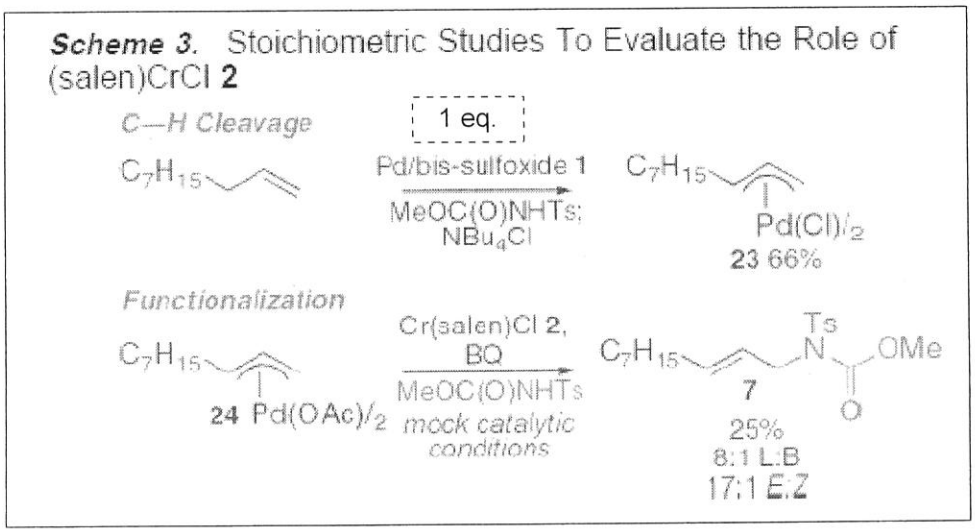
[a] Average of two runs at 0.3 mmol. Products were isolated as one regio- and olefin isomer (^{1}H NMR). [b] Mixture of 7:1 L/B and 17:1 *E*/*Z* (^{1}H NMR).

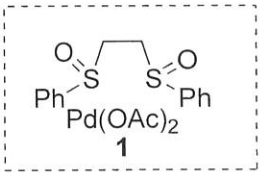


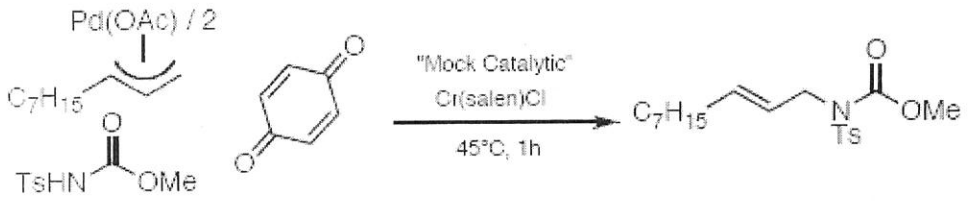
3-2-4. Mechanistic study

Stoichiometric study

Scheme 3. Stoichiometric Studies To Evaluate the Role of (salen)CrCl **2**







Conditions	Yield[a]	L/B	E/Z
no BQ, no Cr(salen)Cl	-	-	-
"Mock catalytic"	25%	8:1	17:1
no BQ	-	-	-
no Cr(salen)Cl	-	-	-

[a]Isolated yield

- no amount of the product was detected by GC analysis of the crude reaction mixture when either BQ or Cr(salen)Cl was omitted from the reaction conditions

- the Pd(II)/bis-sulfoxide catalyst promotes allylic C-H cleavage

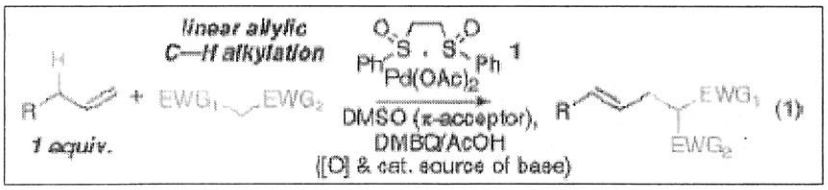
- the Cr(III)(salen) catalyst together with BQ promotes amination of the d-allylPd intermediate

4. Allylic C-H Alkylation

4-1. Catalytic Intermolecular Allylic C-H Alkylation

J. Am. Chem. Soc. **2008**, 130, 14090–14091.

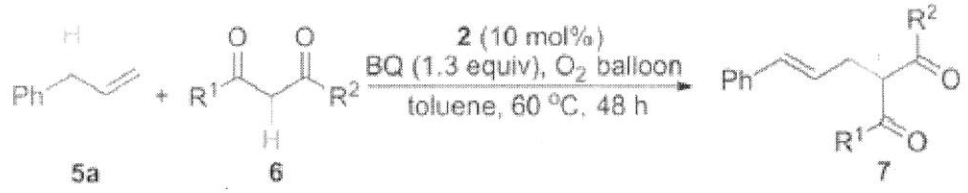
4-1-1. Outline

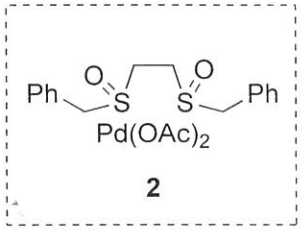


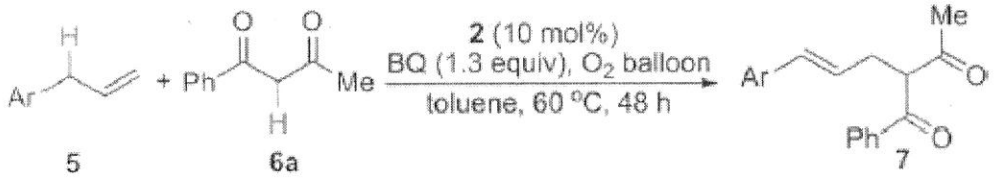
- Pd(II)-mediated electrophilic CsH cleavage and nucleophilic π-ally l Pd functionalization

Related work

Shi et al. *J. Am.Chem. Soc.* **2008**, *130*, 12901–12903.

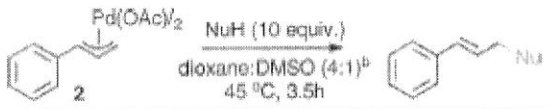






4-1-2. Optimization & Mechanistic study

Table 1. Development of the Allylic C—H Alkylation Reaction



entry	NuH	yield (L + B)[a]	L:B[a]
1	$PhO_2SCH_2CO_2Me$, 3	9%	—
2	NO_2CH_2COPh, 4	82%	8:1
3	$NO_2CH_2CO_2Me$, 5	86%	4:1
4	$NO_2CH_2SO_2Ph$, 6	89%	16:1
5	5 (no DMSO)[c]	—	—

[a] Determined by ^{1}H NMR analysis of the crude. [b] 0.033 M. [c] Dioxane (0.033 M).

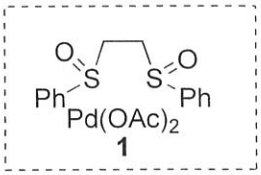
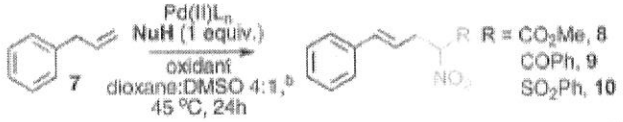


Table 2.

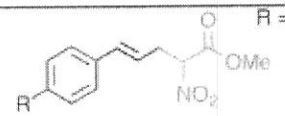
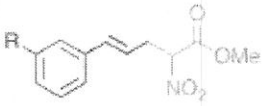
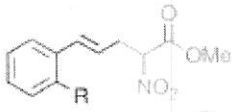
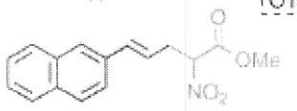
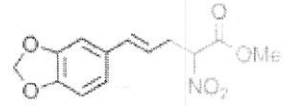
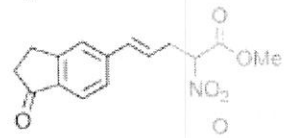
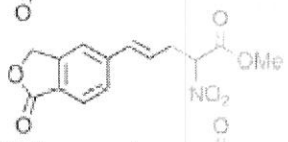
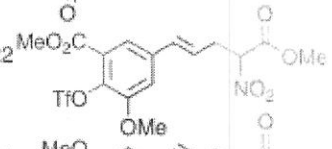
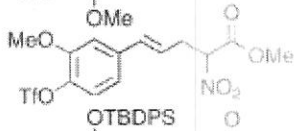
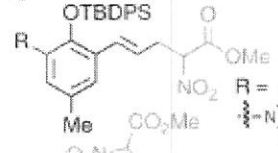
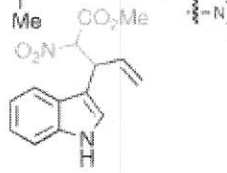


entry	$Pd(II)L_n$ (equiv)	NuH (equiv)	oxidant	yield (L + B)[a]	L:B[a]
1[c]	1 (1.0)	5 (1.0)	—	50%	5:1
2	1 (0.1)	5 (1.0)	O_2 (1 atm)	27%	4:1
3	1 (0.1)	5 (1.0)	DMBQ/AcOH[d]	72%	4:1
4	1 (0.1)	5 (1.0)	DMBQ/AcOH[d,e]	—	—
5	11 (0.1)[f]	5 (1.0)	DMBQ	4%	—
6	$Pd(OAc)_2$ (0.1)	5 (1.0)	DMBQ/AcOH[d]	63%	4:1
7	1 (0.1)	5 (3.0)	DMBQ/AcOH[d]	83%	4:1
8	1 (0.1)	4 (3.0)	DMBQ/AcOH[d]	74%	7:1
9	12 (0.1)[g]	6 (3.0)	DMBQ/AcOH[d]	71%	13:1

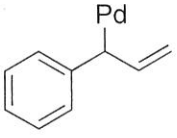
[a] ^{1}HNMR analysis of crude. [b] 0.33 M. [c] 8 h [d] DMBQ (1.5 equiv), AcOH (0.5 equiv). [e] Bu_4NOAc (1 equiv). [f] 1,2-Bis(phenylsulfinyl)-ethane/$Pd(TFA)_2$. [g] 1,2-Bis(benzylsulfinyl)ethane/$Pd(OAc)_2$.[4a]

4-1-3. Substrate scope

Table 3. Scope of the Allylic C—H Alkylation Reaction

entry	major product		L:B[b]	isolated yield L[a] *E:Z >20:1*
1		R = OMe	1.7:1	50%
2		Me	3:1	61%
3		$CH_2=CH_2$	3:1	63%
4		H	4:1	62%
5		Br	4:1	60%
6		NTsMe	4:1	63%
7		F	4:1	65%
8		CO_2Me	10:1	61%
9		C(O)Me	10:1	66%
10		CF_3	10:1	56%
11		CN	12:1	65%
12		OMe	5:1	58%
13		$N=CPh_2$	9:1	58%
14		Me	5:1	62%
15		CF_3	>20:1	59%
16		OTBS	3:1	58%
17		OTf	15:1	57%
18			4:1	65%
19			3:1	56%
20			12:1	62%
21			15:1	70%
22			7:1	63%
23			5:1	64%
24			5:1	68%
25			1:5	42% 1.2:1 d.r.

[a] Olefin (1 equiv), 5 (3 equiv), DMBQ (1.5 equiv), AcOH (0.5 equiv), 1 (10 mol%), dioxane/DMSO (4:1, 0.33 M). Average of two runs at 0.5 mmol. Products isolated as one regioisomer and olefin isomer [b] Determined by ^{1}H NMR analysis of the crude.



a Pd benzyl allyl intermediate