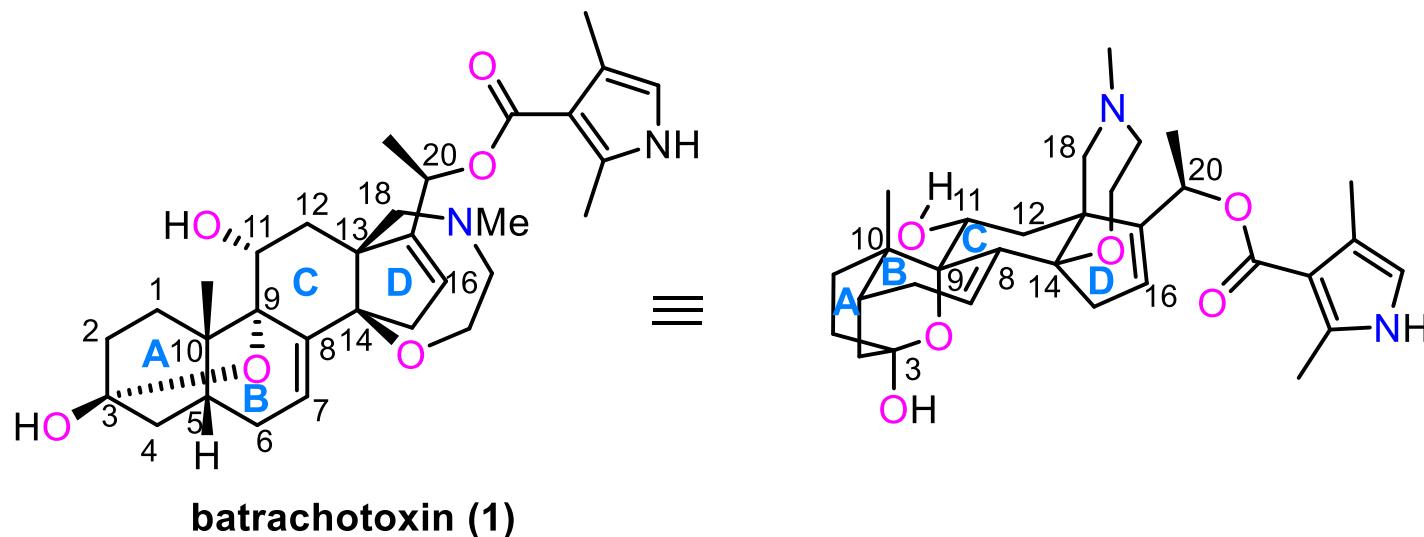




Total Synthesis of (–)-Batrachotoxin Enabled by a Pd/Ag-Promoted Suzuki–Miyaura Coupling Reaction

Yuuki Watanabe, Hisahiro Morozumi, Hiroyuki Mutoh, Koichi Hagiwara, and Masayuki Inoue*



Character: 8 stereocenters

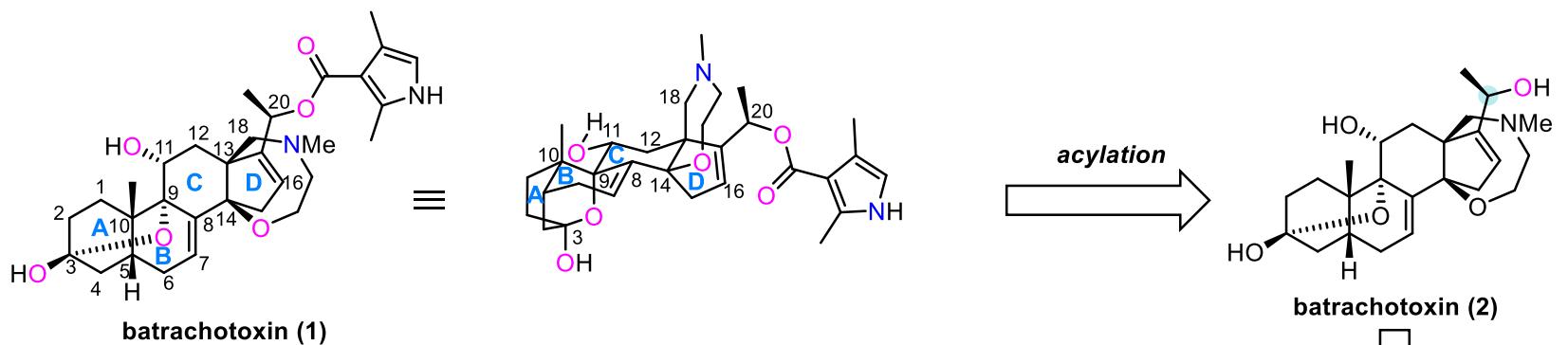
6/6/6/5 membered carbocycle

U shape with 2 double bond

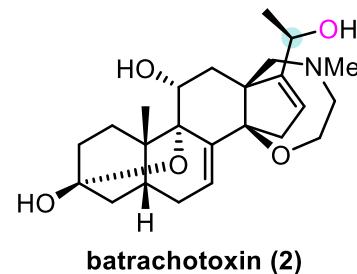
A six-membered C3-hemiacetal across the AB-ring

A seven-membered oxazepane on the CD-ring

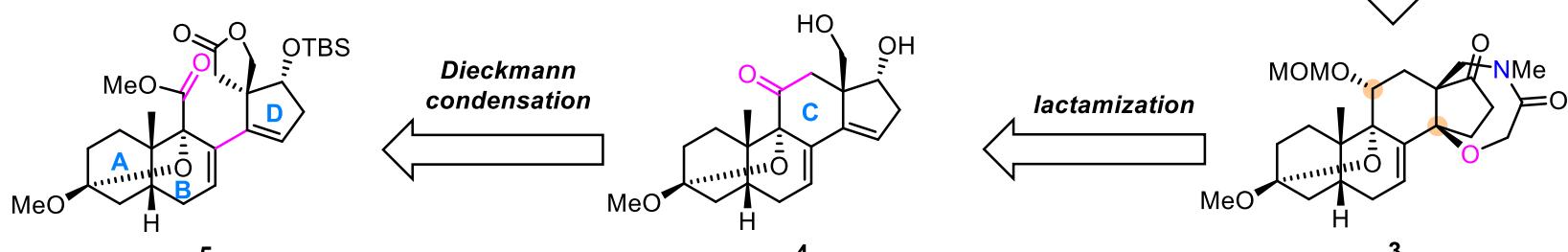
A dimethylpyrrolecarboxy group at the D-ring carbon chain.



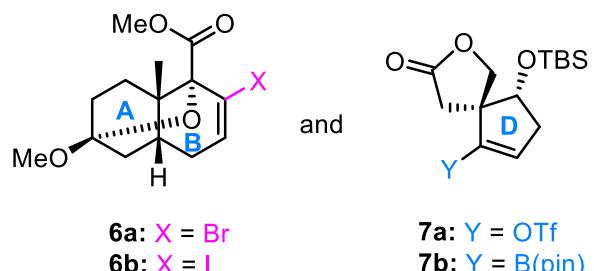
acylation



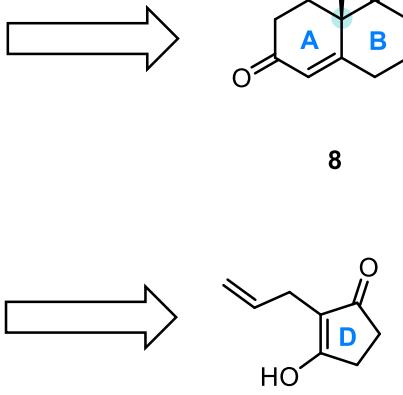
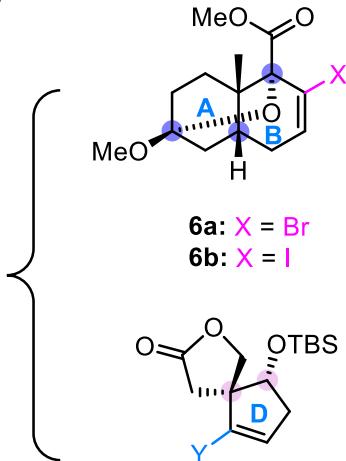
Stille coupling reaction

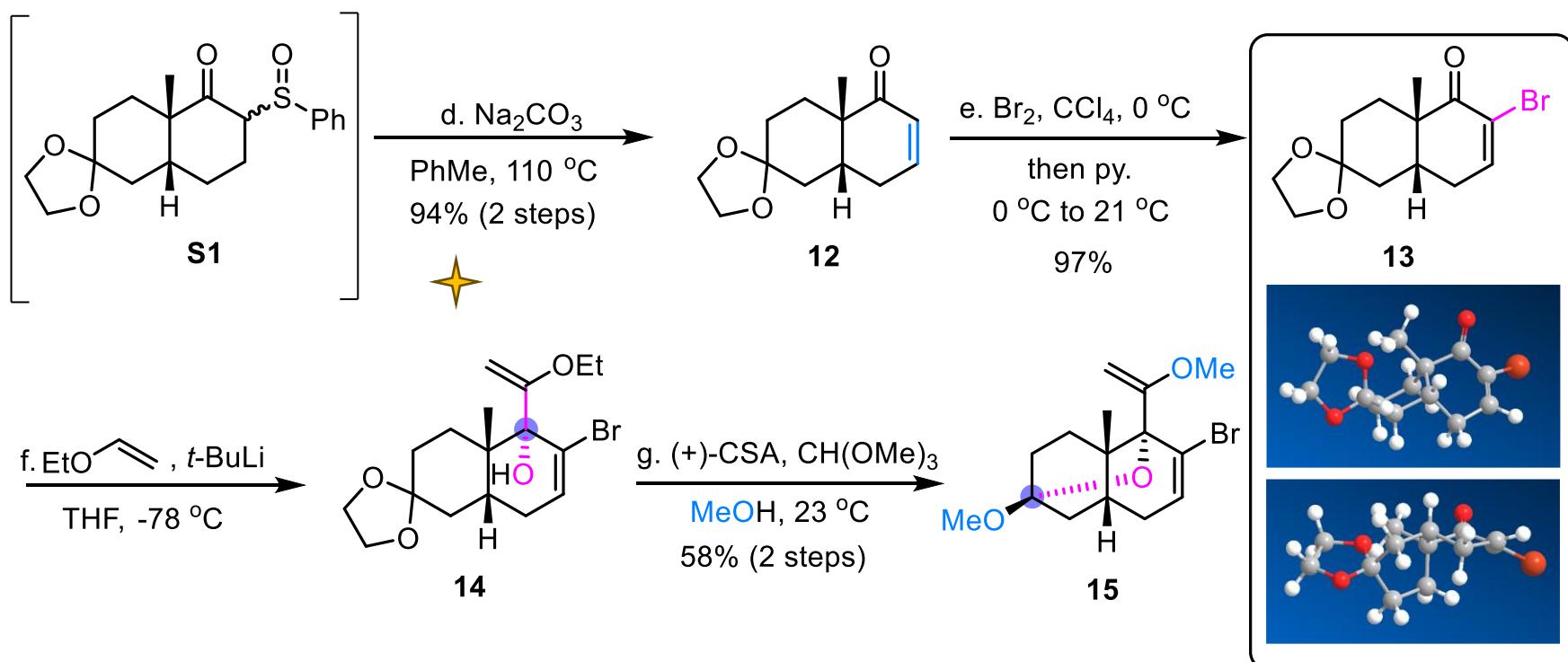
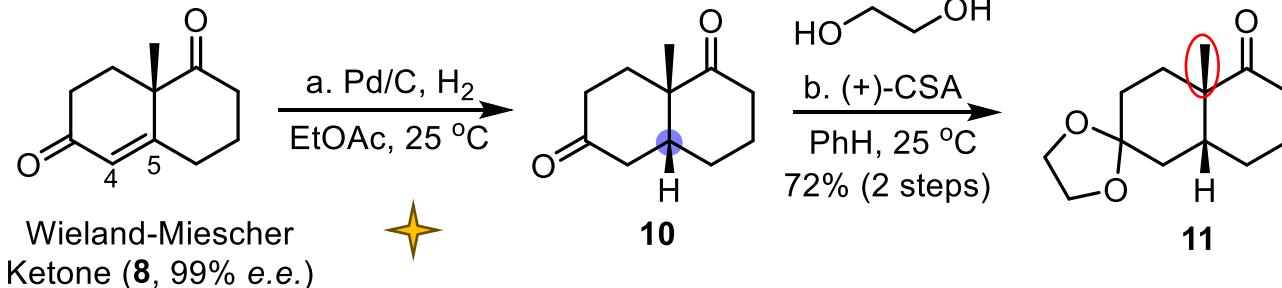
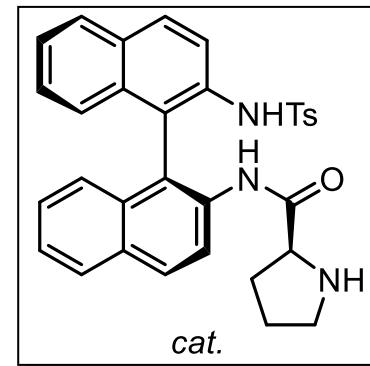
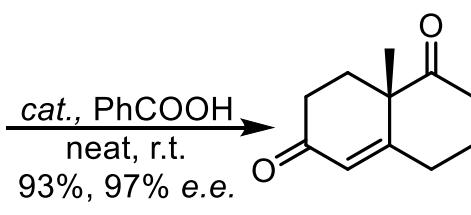
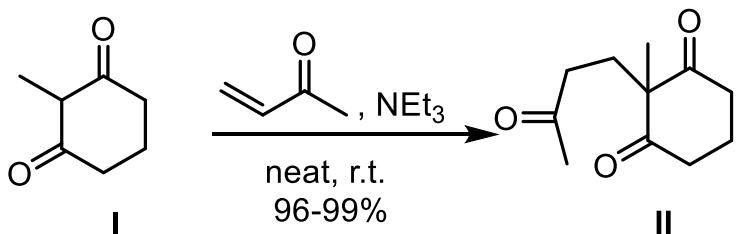


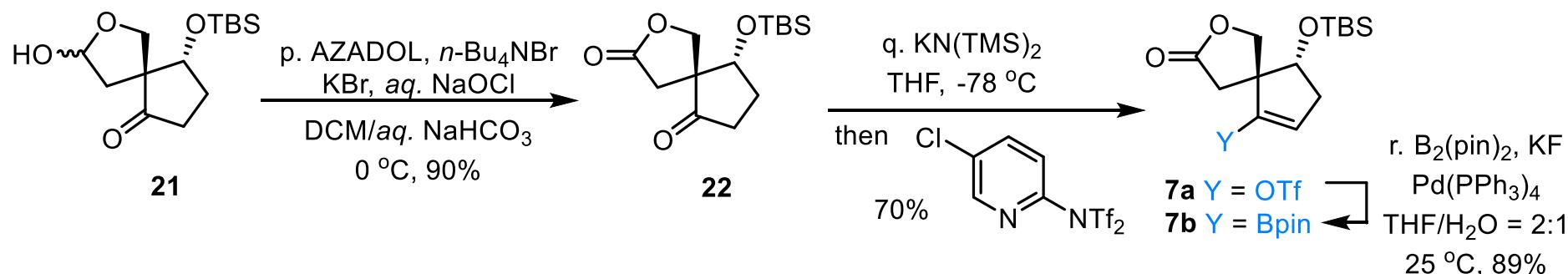
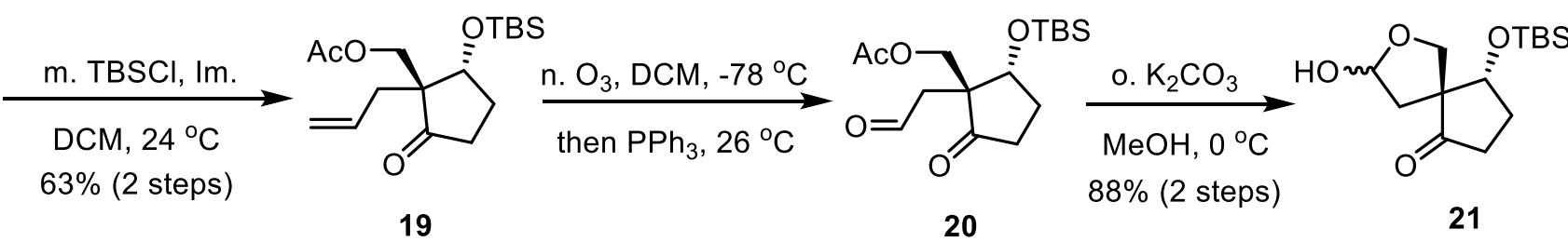
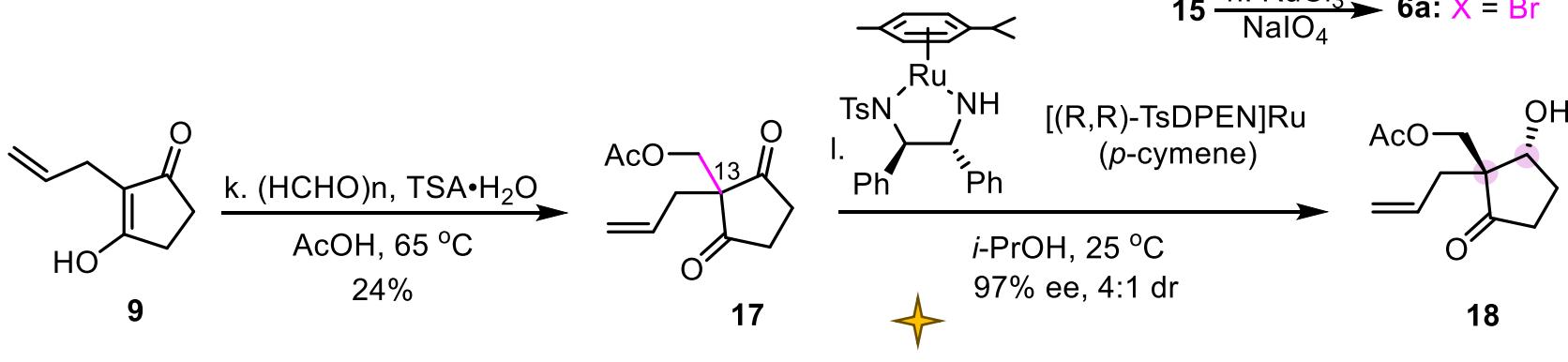
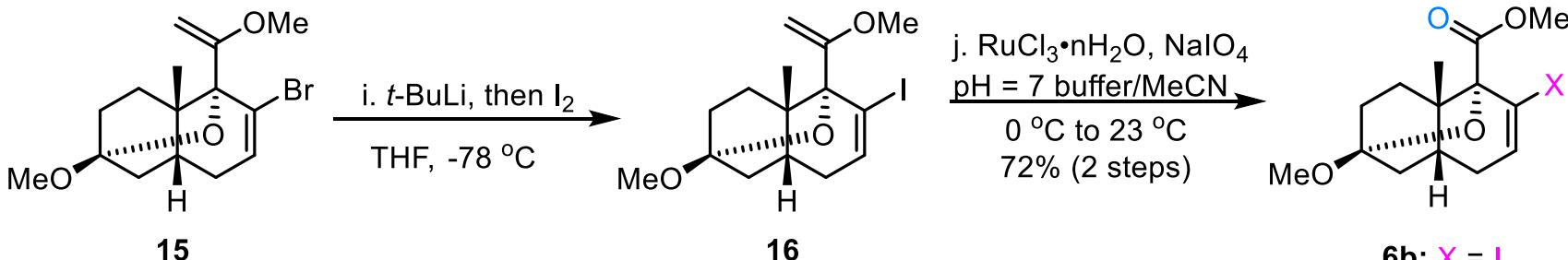
Pd/Ag-Promoted Suzuki-Miyaura cross-coupling reaction

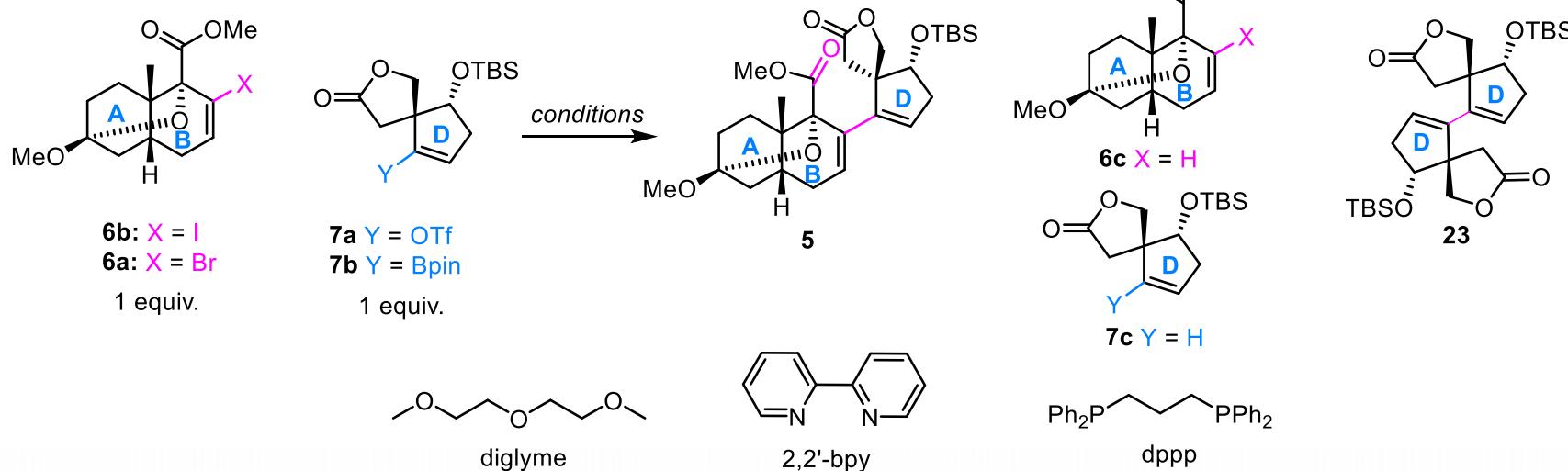


7a: Y = OTf
7b: Y = B(pin)





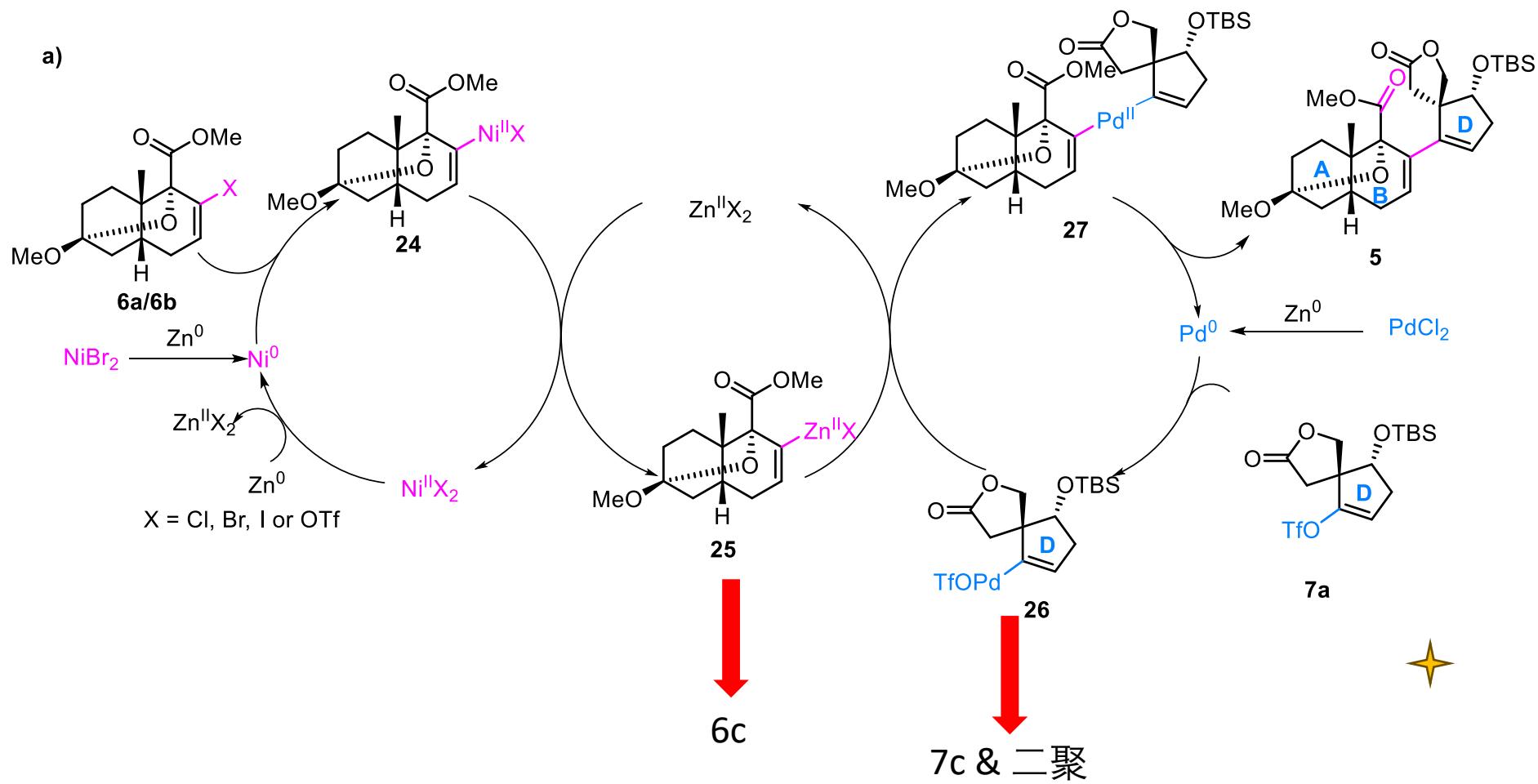




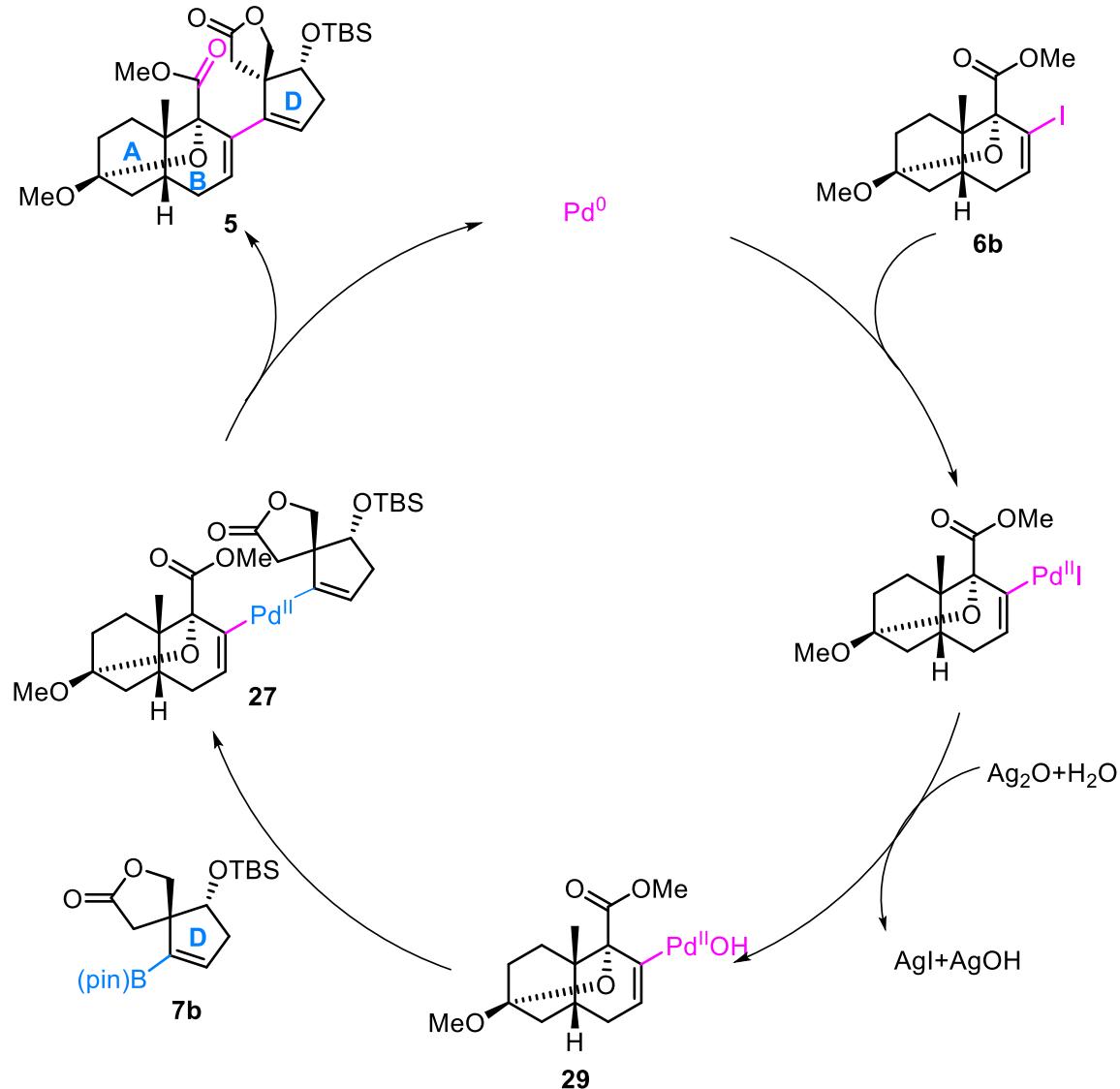
Entry	Substrate		Conditions	Yield [%]					
	6 (<i>X</i>)	7 (<i>Y</i>)		5	6c (<i>H</i>)	7c (<i>H</i>)	23	6a/6b	7a/7b
1 ^[a,b]	6a (<i>Br</i>)	7a (<i>OTf</i>)	$\text{NiBr}_2 \cdot \text{diglyme}$ (2 eq), $2,2'\text{-bpy}$ (2 eq) PdCl_2 (2 eq), dppp (2 eq) Zn (5 eq), DMF (0.2 M), 80°C	19 ^[c]	25 ^[d]	22 ^[d]	14 ^[d]	0	0
2 ^[a,e]	6b (<i>I</i>)	7a (<i>OTf</i>)	$\text{NiBr}_2 \cdot \text{diglyme}$ (2 eq), $2,2'\text{-bpy}$ (2 eq) PdCl_2 (2 eq), dppp (2 eq) Zn (5 eq), DMF (0.2 M), 80°C	18 ^[c]	26 ^[d]	23 ^[d]	15 ^[d]	0	0
3 ^[a,b]	6a (<i>Br</i>)	7b (<i>B(pin)</i>)	$\text{Pd}(\text{PPh}_3)_4$ (30 mol%), KF (6 eq) $\text{THF}/\text{H}_2\text{O}$ (2/1), 23°C	0.2 ^[d]	0	3 ^[d]	0	81 ^[c]	32 ^[d]
4 ^[a]	6b (<i>I</i>)	7b (<i>B(pin)</i>)	$\text{Pd}(\text{PPh}_3)_4$ (30 mol%), KF (6 eq) $\text{THF}/\text{H}_2\text{O}$ (2/1), 23°C	4 ^[c]	0	3 ^[d]	0	93 ^[d]	41 ^[d]
5 ^[a,b]	6a (<i>Br</i>)	7b (<i>B(pin)</i>)	$\text{Pd}(\text{PPh}_3)_4$ (30 mol%), Ag_2O (1.5 eq) $\text{THF}/\text{H}_2\text{O}$ (2/1), 27°C	11 ^[c]	0	0	48 ^[c]	81 ^[c]	0
6 ^[f]	6b (<i>I</i>)	7b (<i>B(pin)</i>)	$\text{Pd}(\text{PPh}_3)_4$ (30 mol%), Ag_2O (1.5 eq) $\text{THF}/\text{H}_2\text{O}$ (2/1), 27°C	70 ^[c]	0	0	18 ^[c]	21 ^[c]	0

[a] 20–40 mg scale. [b] **6a** ($\text{C11}-\text{OMe}$) was used as a mixture with **6a'** ($\text{C11}-\text{OEt}$) [**6a** ($\text{C11}-\text{OMe}$):**6a'** ($\text{C11}-\text{OEt}$) = 8:1]. [c] Yield of the isolated product. [d] Yield calculated from ^1H NMR data. [e] **6b** ($\text{C11}-\text{OMe}$) was used as a mixture with **6b'** [**6b** ($\text{C11}-\text{OMe}$):**6b'** ($\text{C11}-\text{OEt}$) = 8:1]. [f] 480 mg scale. $2,2'\text{-bpy}$ = $2,2'\text{-bipyridine}$, dppp = 1,3-bis(diphenylphosphino)propane.

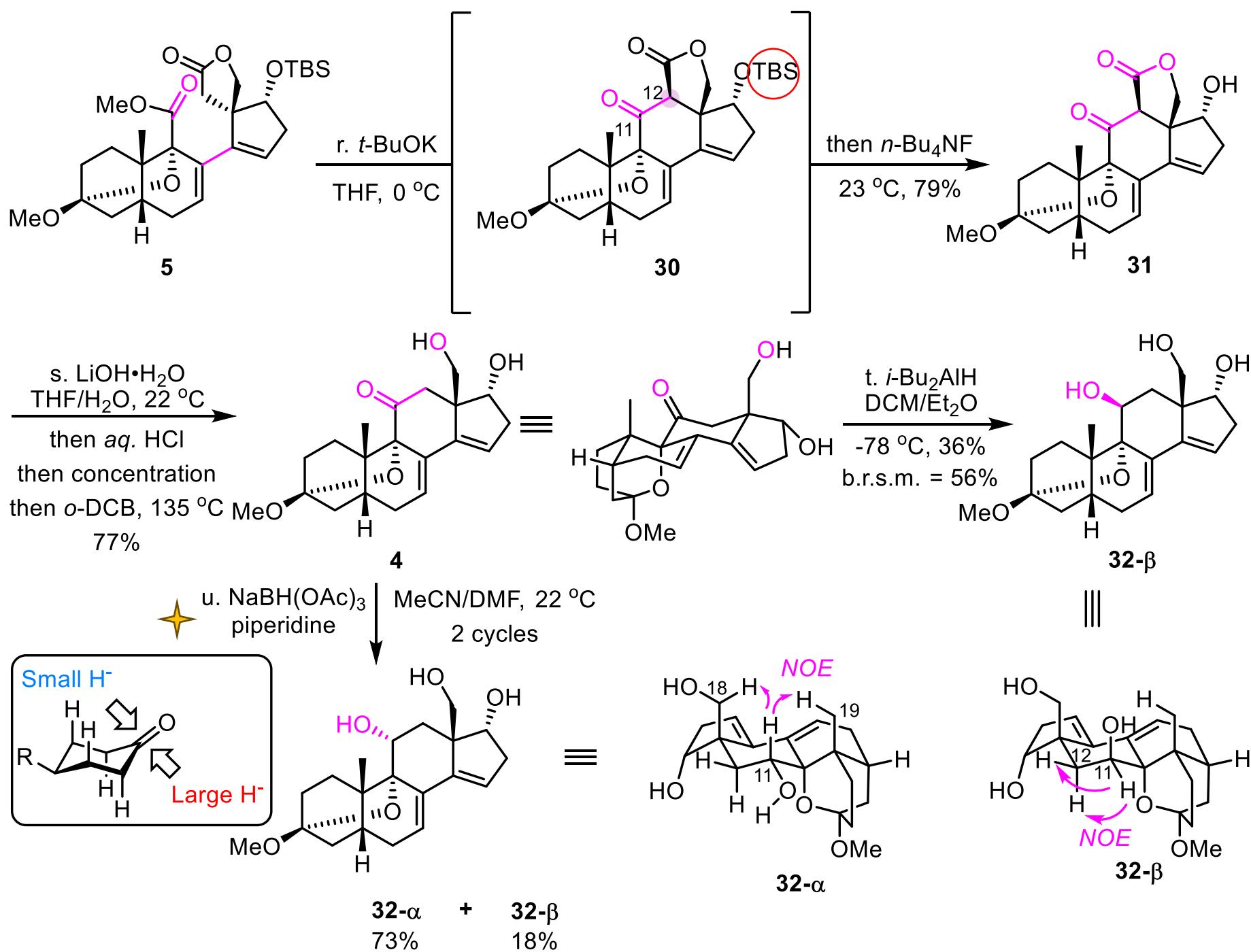
a)

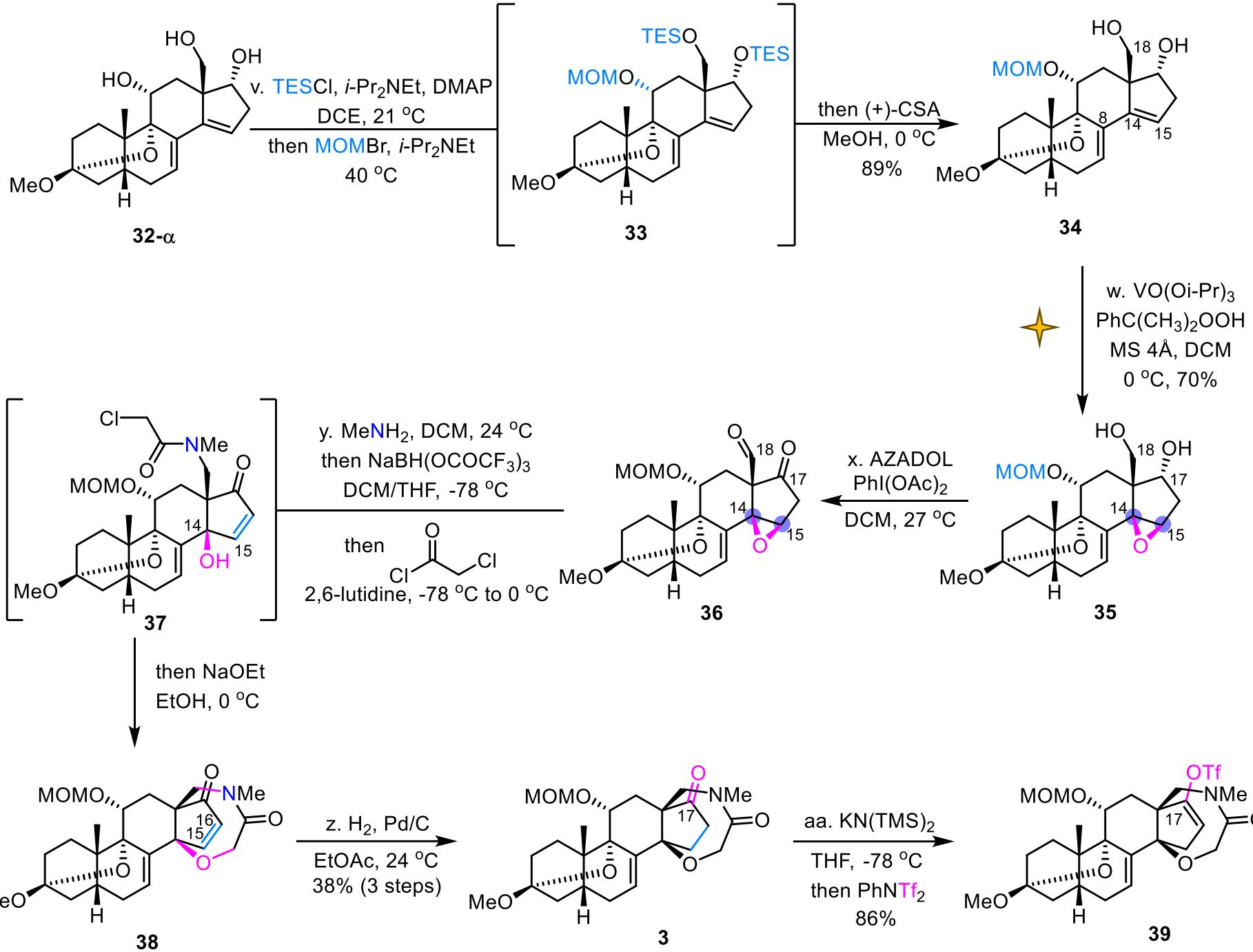


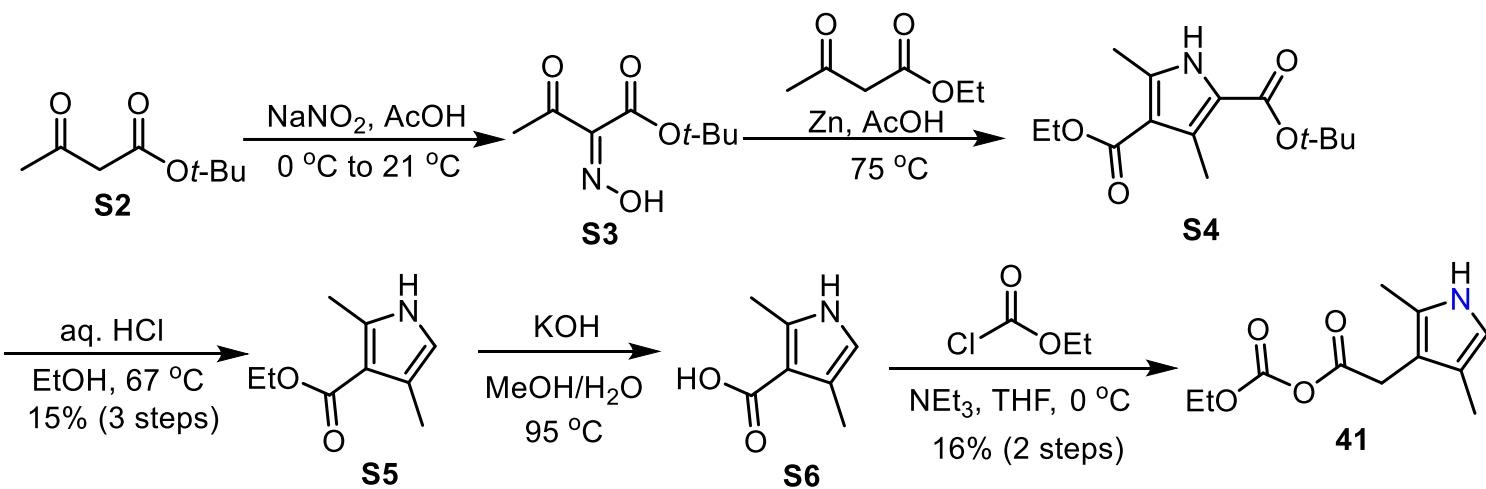
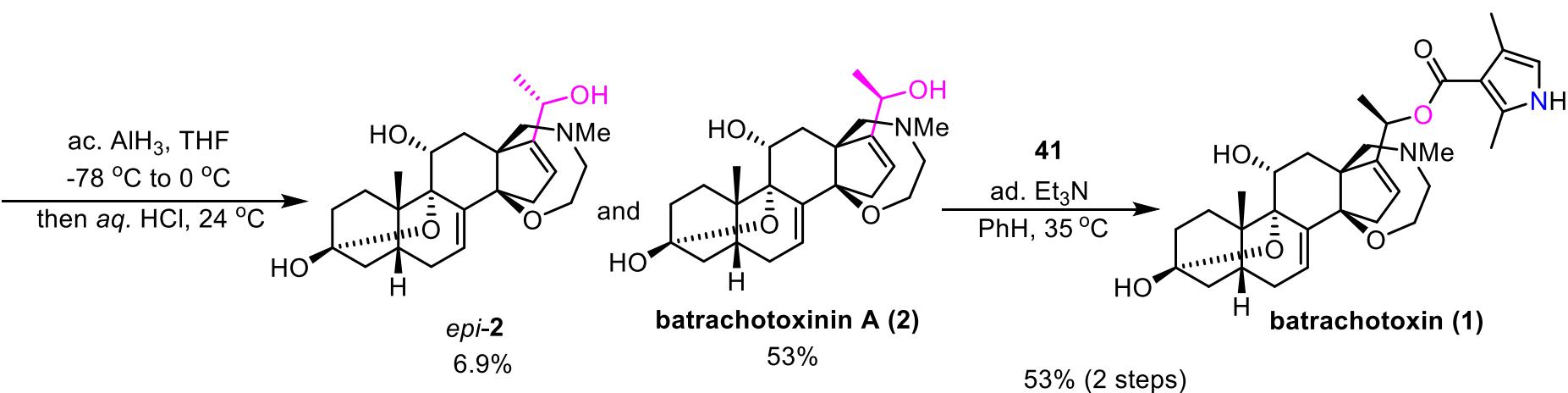
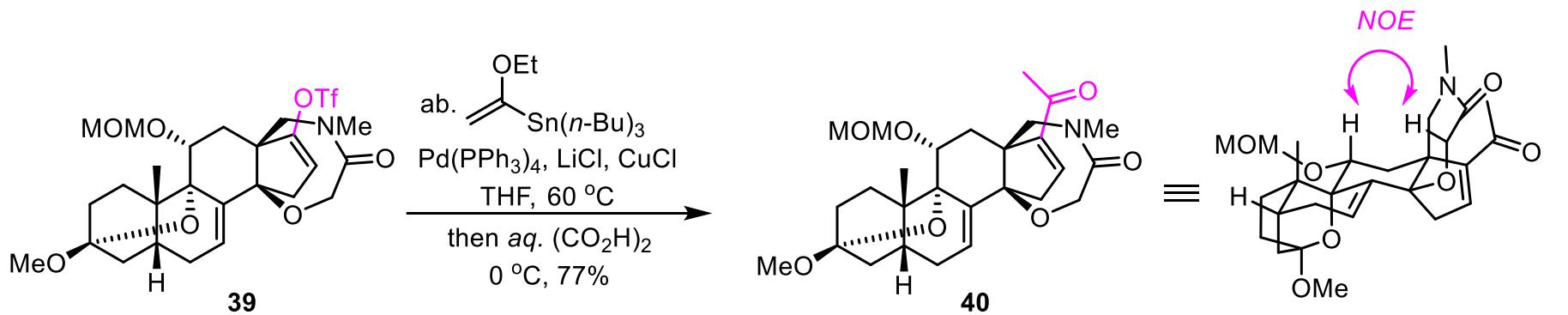
b)



Mechanistic rationale of a) the Pd/Ni-mediated Weix coupling and b) Pd/Ag-promoted Suzuki–Miyaura coupling



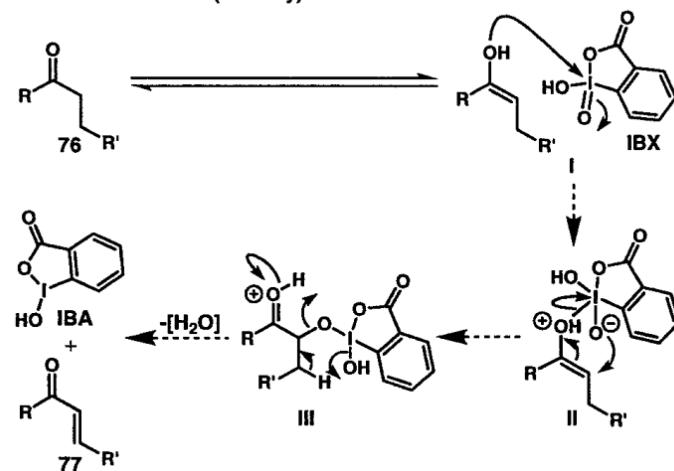




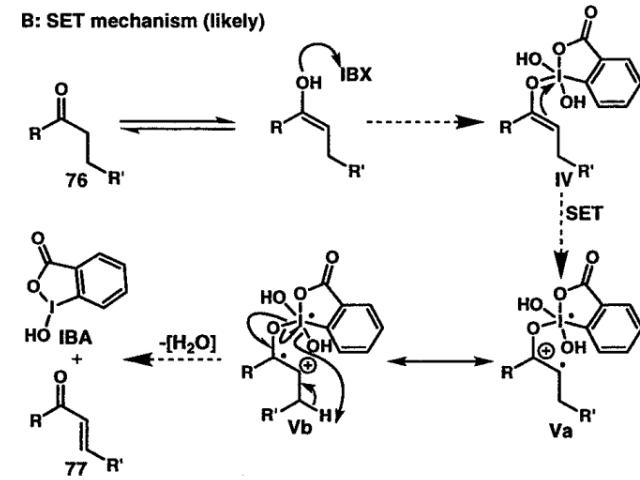
酮到 α,β -不饱和酮的合成

1、IBX氧化

A: Ionic mechanism (unlikely)



B: SET mechanism (likely)

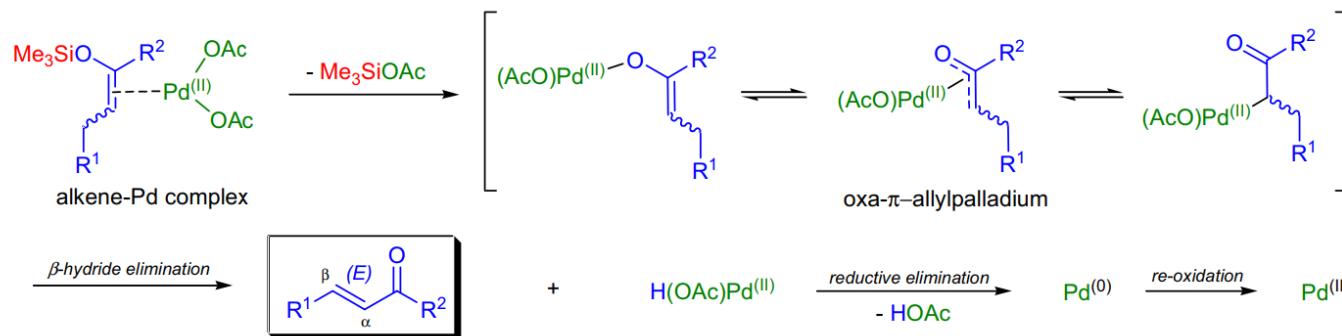


2、Saegusa氧化

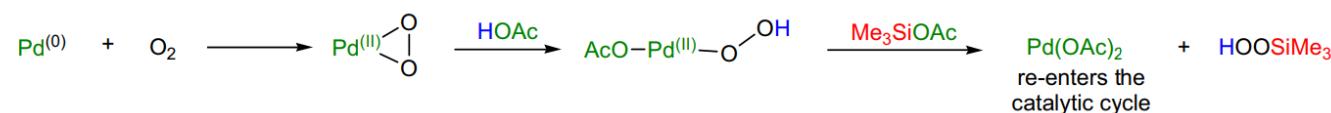
Angew. Chem. Int. Ed., 2002, 41, 996

Mechanism:^{15,7}

When substoichiometric/stoichiometric amounts of $\text{Pd}(\text{OAc})_2$ is used:

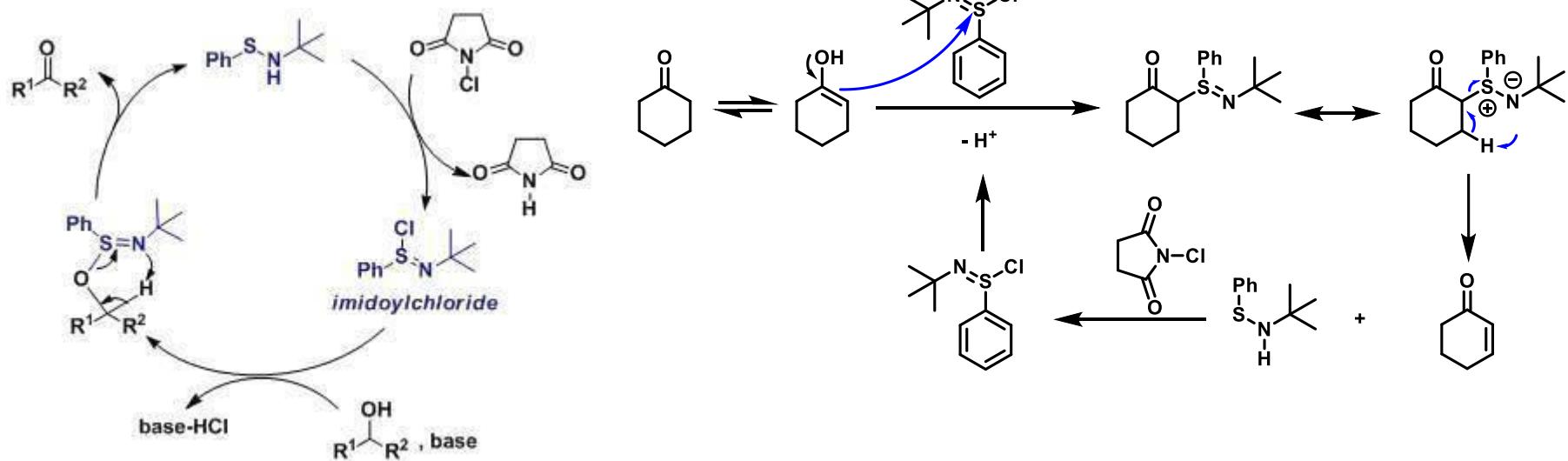


When the oxidation takes place under an oxygen atmosphere with catalytic amounts of $\text{Pd}(\text{OAc})_2$:

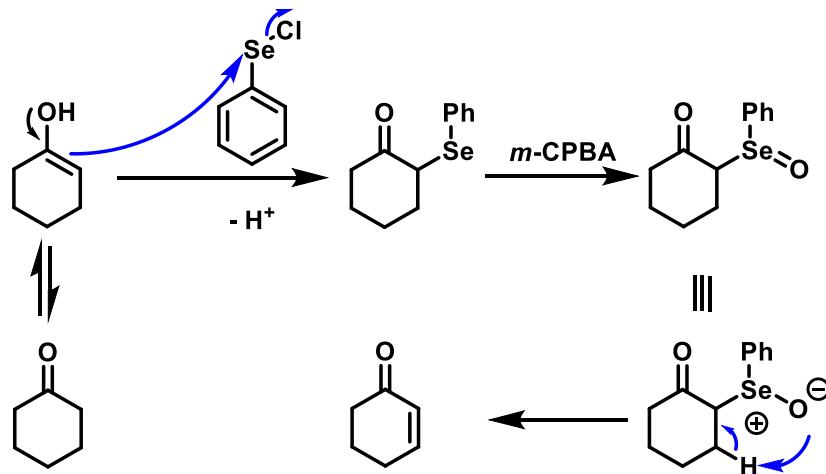


酮到 α,β -不饱和酮的合成

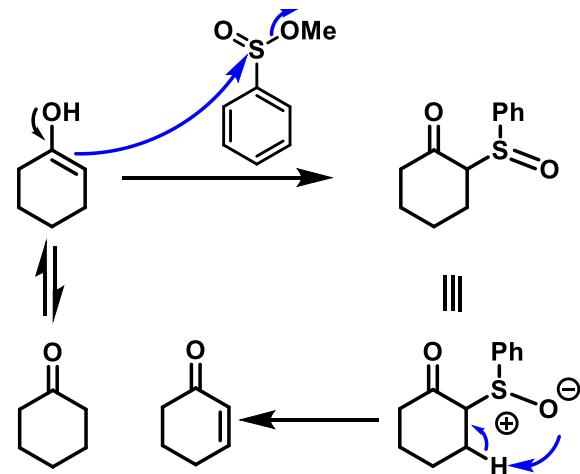
3、Mukaiyama试剂



4、SePhCl&*m*-CPBA



5、 $Ph(SO)OMe$ 试剂



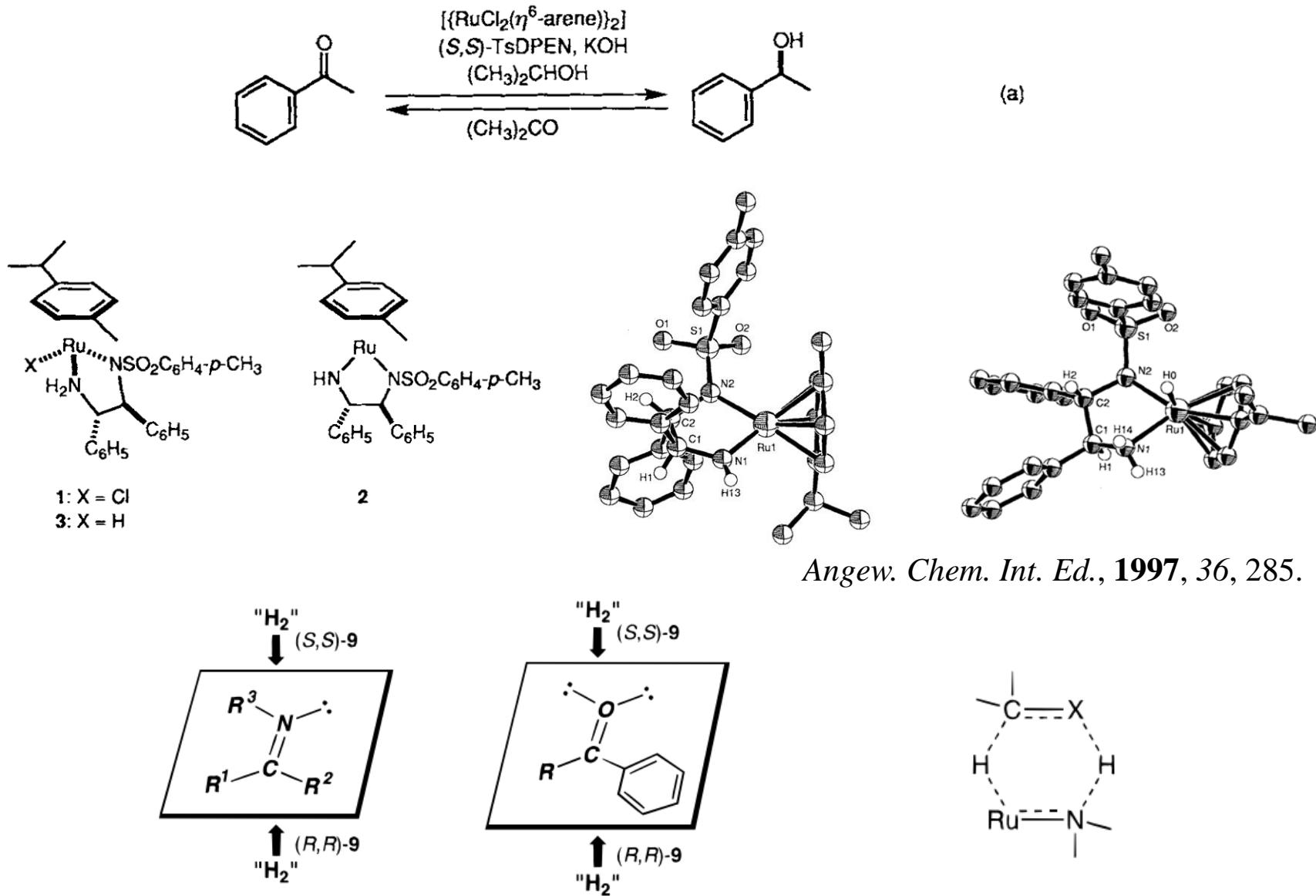


FIGURE 2. General sense of asymmetric transfer hydrogenation catalyzed by the Ru complex 9.

Acc. Chem. Res., 1997, 30, 97.



Weix 偶联

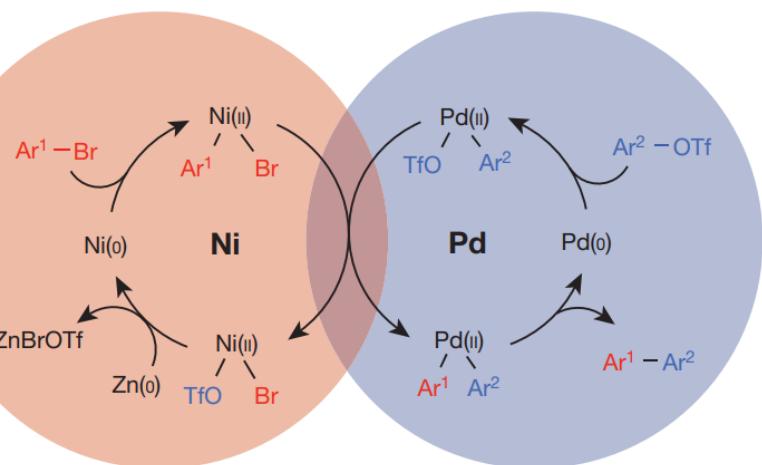
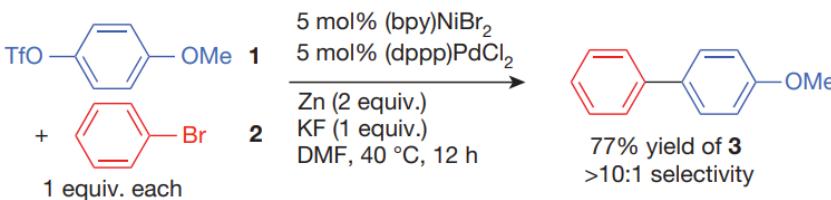
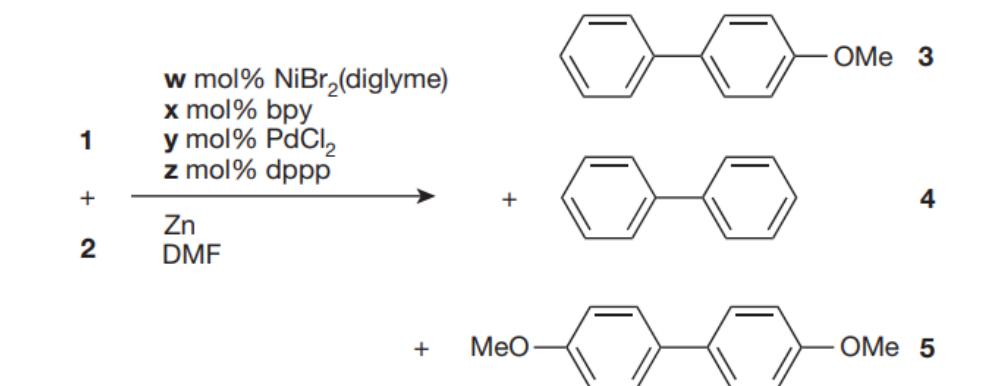


Figure 1 | A general cross-Ullmann reaction catalysed by a combination of nickel and palladium. 1, 4-methoxyphenyltriflate; 2, bromobenzene; 3, the main cross-product, 4-methoxybiphenyl. Although a nickel(0/II) and palladium (0/II) cycle is depicted, alternative mechanisms are also possible, such as a nickel(I/III) cycle³⁰. OTf, triflate; DMF, *N,N*-dimethylformamide (solvent).

(Fig. 1). We propose that, after the two arylmetal intermediates are formed by oxidative addition, a mechanism analogous to the ‘persistent radical effect’ allows for the observed cross-selectivity in transmetalation^{27,28}. In the persistent radical effect, one radical is unreactive with itself and stable, while the other radical is highly reactive and

unselective. In our system, (dppp)Pd(Ar^2) triflate is stable to further reaction with itself (Fig. 2d) and accumulates in solution. By contrast, (bpy)Ni(Ar^1) bromide is a transient intermediate that quickly reacts with itself (Fig. 2c) or with (dppp)Pd(Ar^2) triflate (Fig. 2b).

Table 1 | Conditions for the multimetal-catalysed cross-Ullmann reaction



Entry	w	x	y	z	3*	4*	5*
1†	5	5	5	5	77	7	4
2	5	5	5	5	62	21	14
3	10	10	10	10	70	17	10
4	0	0	10	10	3	4	1
5	0	10	10	0	0	15	0
6	10	10	0	0	6	42	6
7	10	0	0	10	1	1	0
8	0	5	10	5	4	7	1
9	10	5	0	5	1	16	0
10‡	10	10	10	10	67	13	12
11	5	5	10	10	61	20	14
12	10	10	5	5	66	18	13
13§	10	10	10	10	65	12	10
14	0	0	0	0	0	0	0

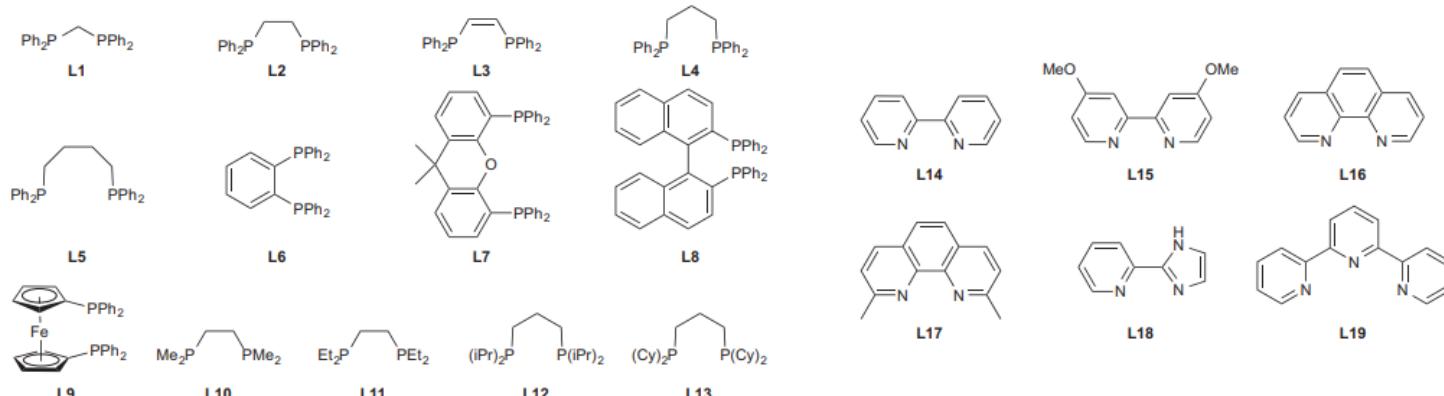
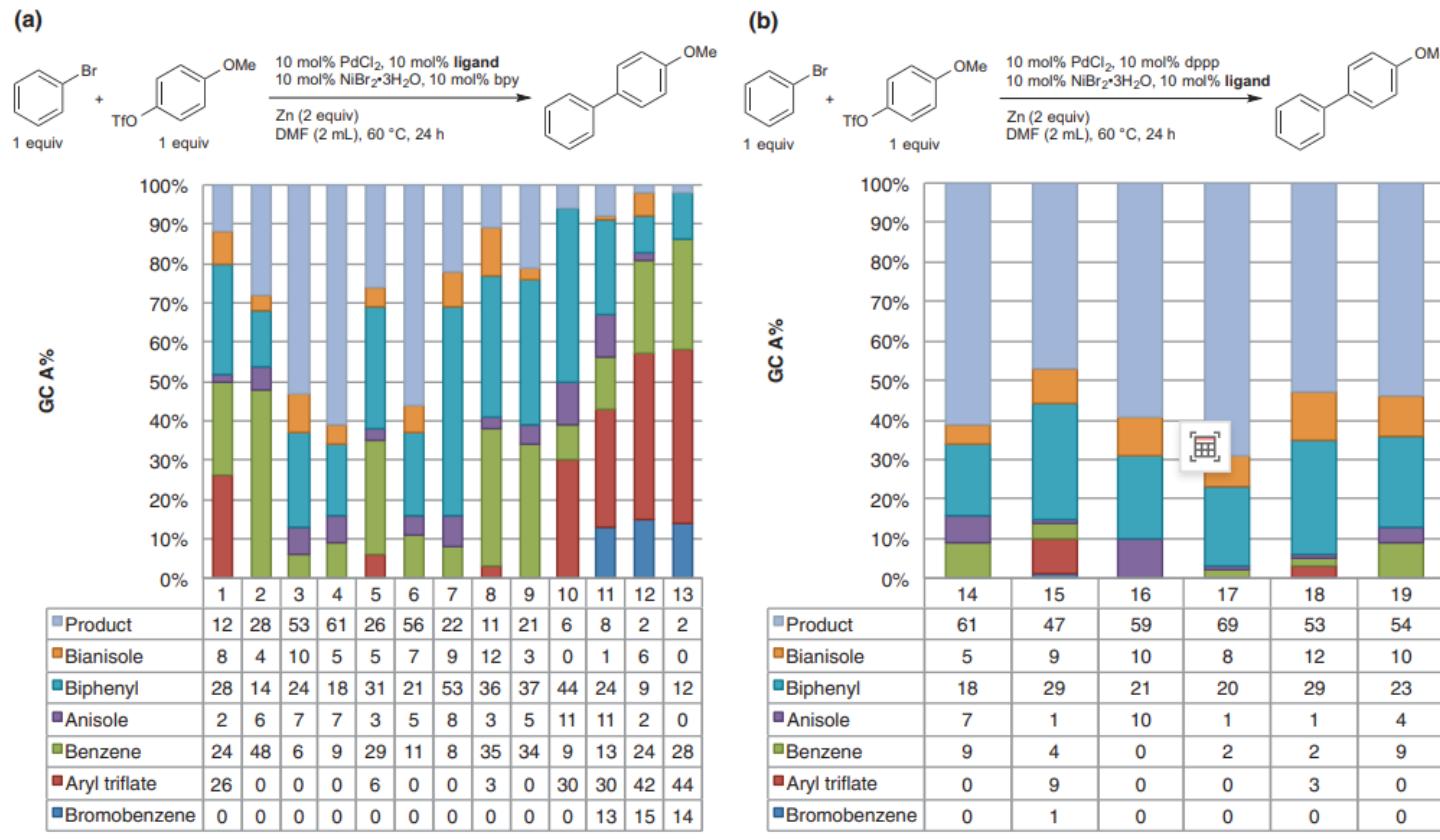
Reactions were run on a 0.5 mmol scale in 2 ml DMF.

*Yields were determined by gas chromatography and are expressed as area per cent, uncorrected. Remaining yields consist of unreacted starting material or hydrodehalogenation byproducts.

†One equivalent of KF was added.

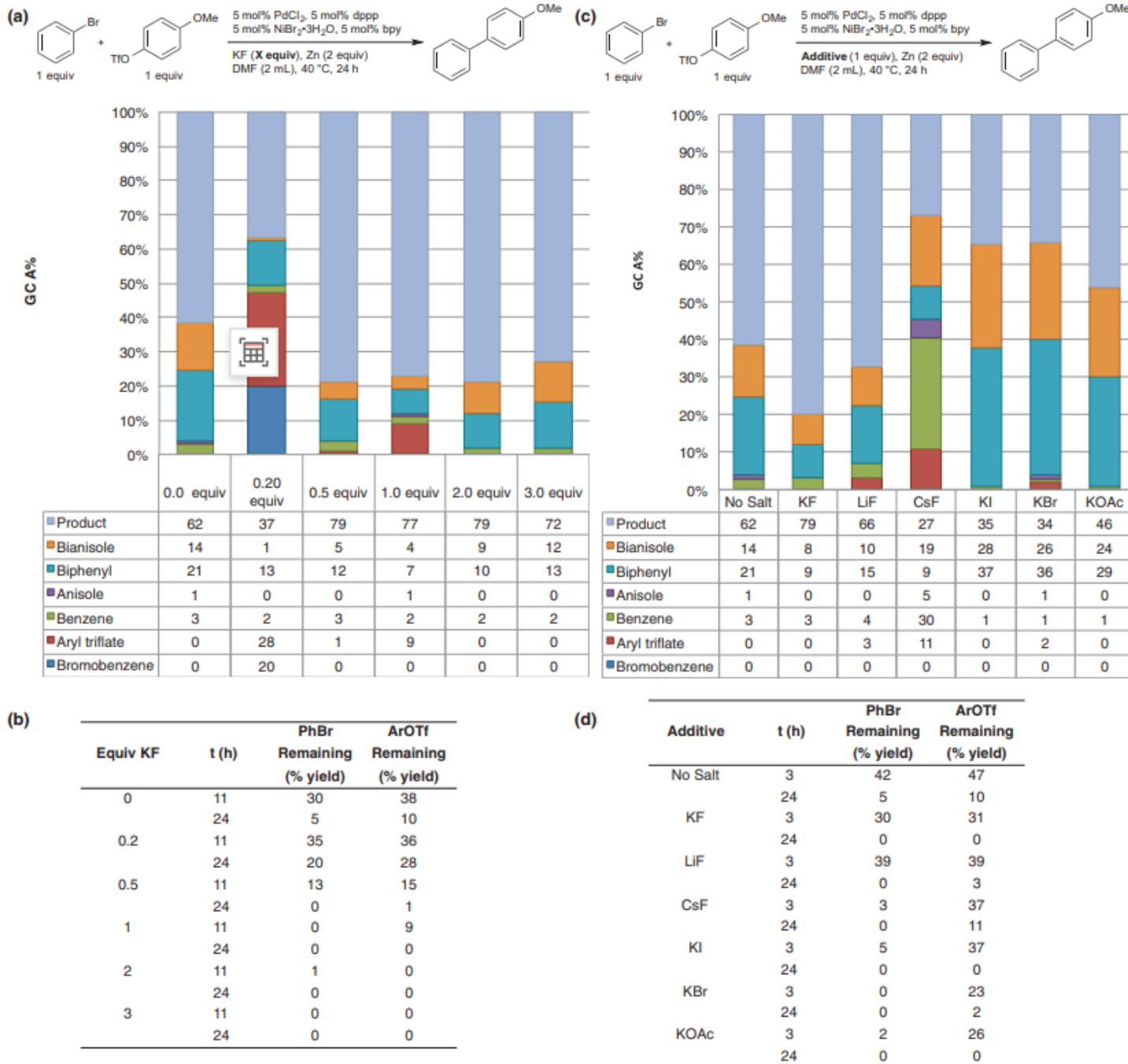
‡Ligands and metal salts were not individually pre-stirred to ensure ligation. All solid reagents were added together, followed by solvent and liquids.

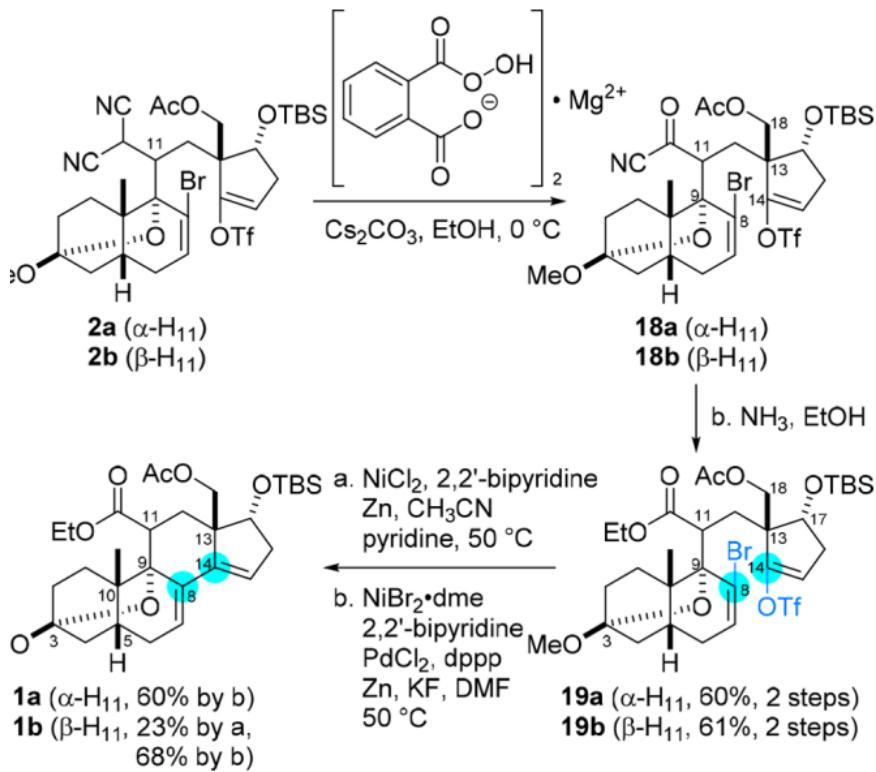
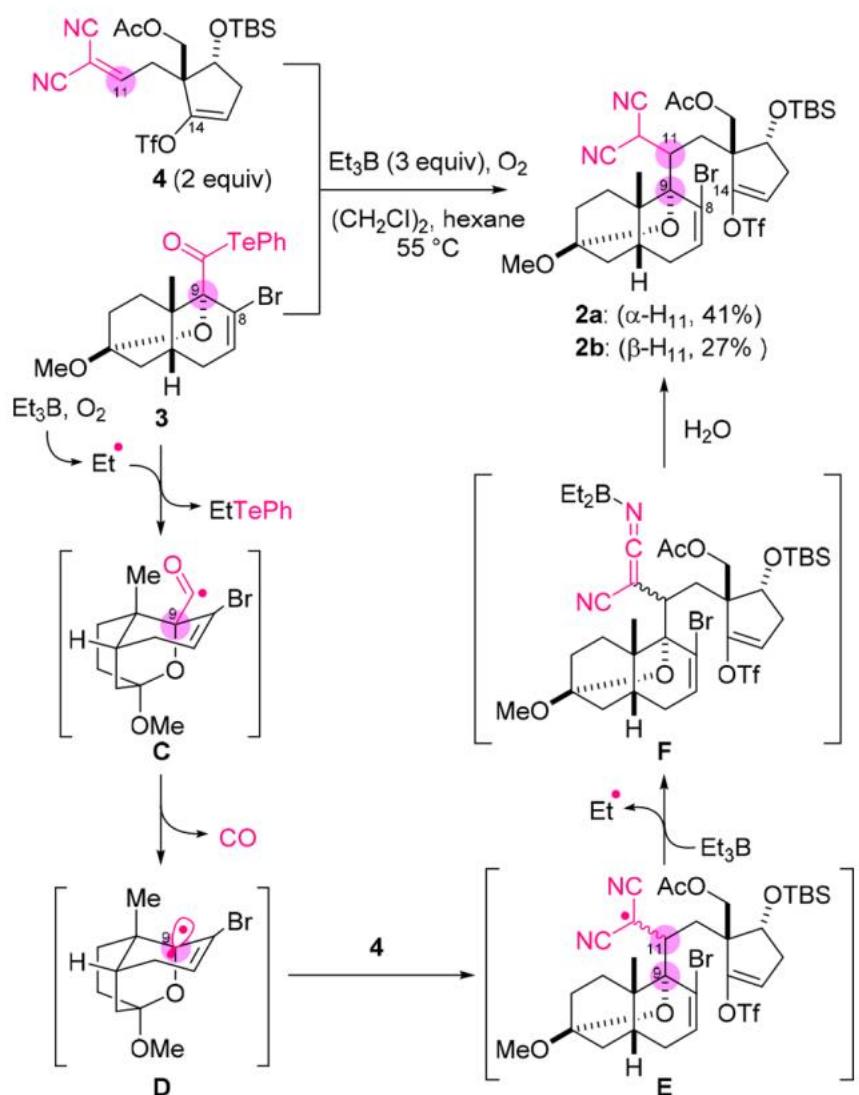
§Instead of being set up in a glove box, the reaction was set up on the bench top using standard inert atmosphere techniques.



Extended Data Figure 1 | Varying ligands on the nickel and palladium catalysts. Several different phosphine ligands for palladium (a) and amine ligands for nickel (b) were investigated. Although selectivity and yield of cross-product were sensitive to the identity of the phosphine ligand (a), a variety of

different amine ligands were effective (b). Reactions conducted with L15, L17, and L18 used 5 mol% catalyst loadings, were heated to 40 °C, and were monitored for 64 h. GC, gas chromatography; area per cent, uncorrected.





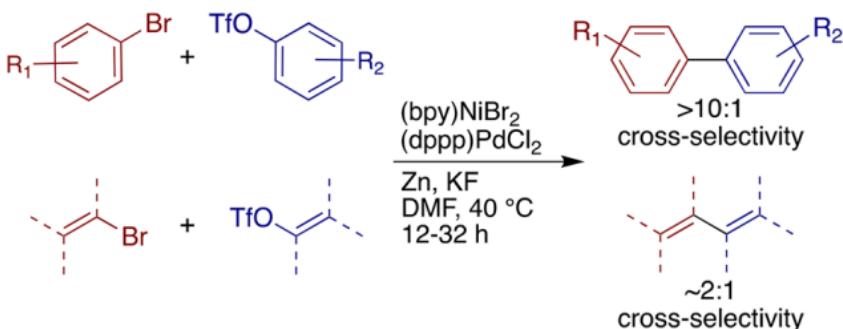
The C-ring cyclization necessitated a powerful C–C bond formation because the reacting C8 and C14 positions were hindered by the adjacent fully substituted carbons C9 and C13. To achieve this, the Ni-promoted Ullmann reaction was first explored using one C11-isomer, **19b**. Treatment of **19b** with NiCl₂ (5 equiv), 2,2'-bipyridine (6 equiv), and Zn (7.5 equiv) in CH₃CN and pyridine permitted the formation of cyclized diene **1b**, albeit in only 23% yield.²⁹ Isolation of the C8-debrominated derivative of **19b** as a byproduct indicated the slow oxidative addition of Ni(0) to the C14–OTf bond. During this time, we noticed that the Weix group realized Ullmann cross-coupling reactions between aryl bromides and triflates by employing multimetallic Pd/Ni catalysts,³⁰ and we therefore expected that use of a Pd reagent would accelerate the

Multimetallic Ni- and Pd-Catalyzed Cross-Electrophile Coupling To Form Highly Substituted 1,3-Dienes

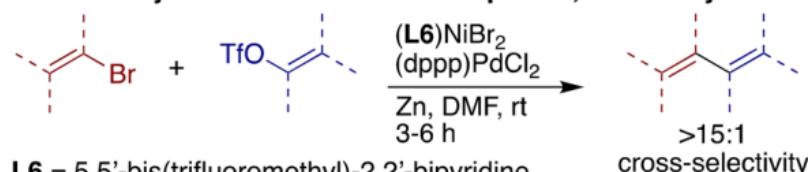
Astrid M. Olivares[†] and Daniel J. Weix^{*,†,‡,§,ID}

A. Previous Study: Cross-Ullman and 1,3-Diene Synthesis

Biaryls: [Ni] only reacts with Ar-Br, [Pd] only reacts with Ar-OTf



B. This Study: Selective Cross-Electrophile 1,3-Diene Synthesis

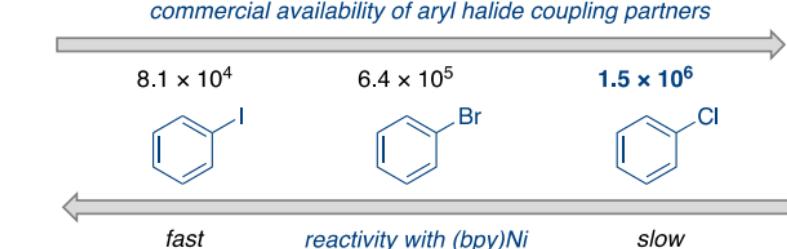
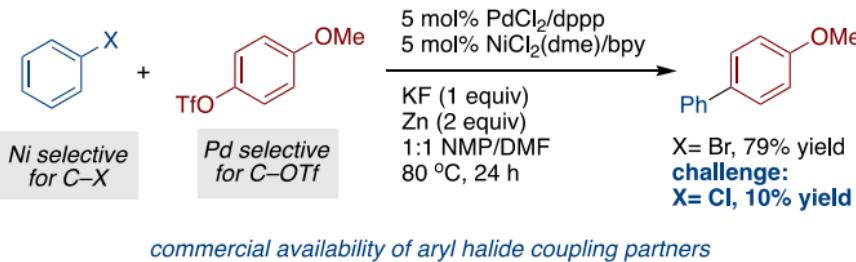


J. Am. Chem. Soc., 2018, 140, 2446.

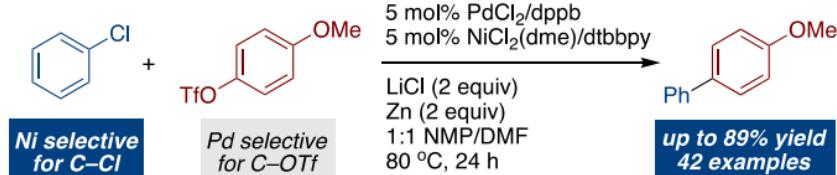
LiCl-Accelerated Multimetallic Cross-Coupling of Aryl Chlorides with Aryl Triflates

Liangbin Huang,^{†,§} Laura K. G. Ackerman,^{‡,||} Kai Kang,[†] Astrid M. Parsons,^{‡,ID} and Daniel J. Weix^{*,†,§,ID}

B. Previous report: coupling of aryl bromides with aryl triflates



C. This report: LiCl enabled coupling of aryl chlorides with aryl triflates



J. Am. Chem. Soc., 2019, 141, 10978.



6. Stereoselective reduction of the C11-ketone of 4

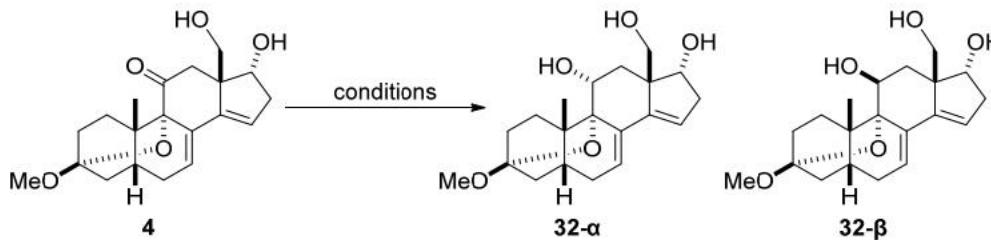
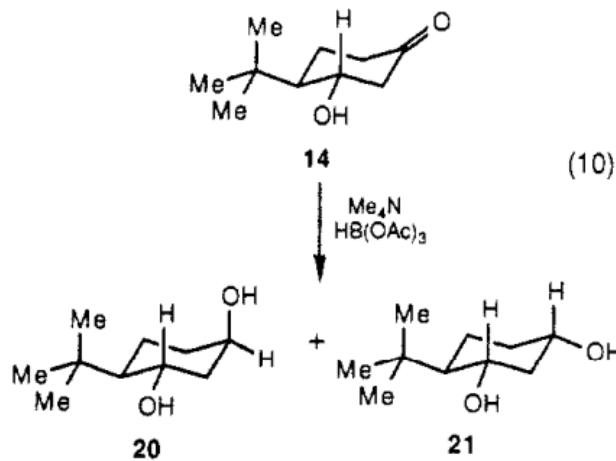
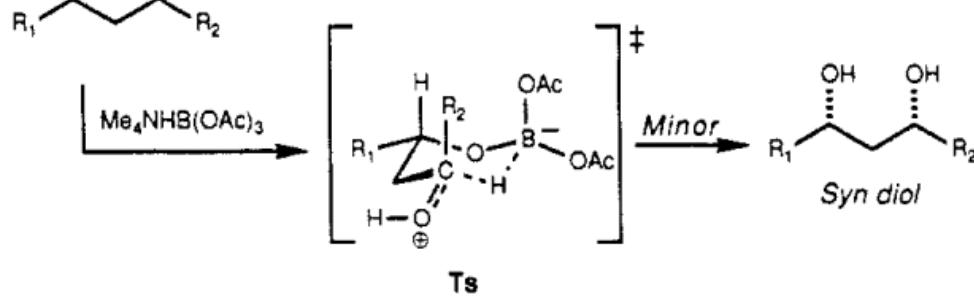
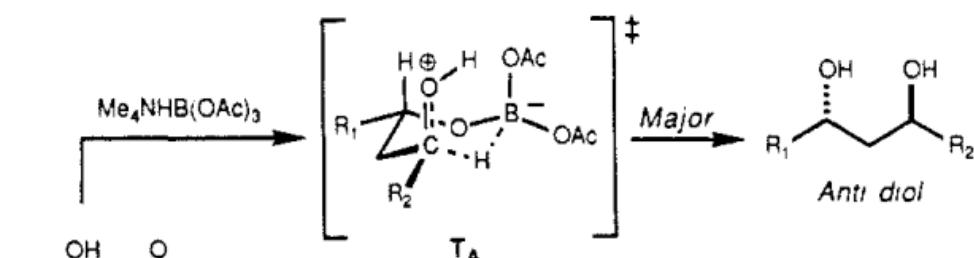


Table S3. Investigation of reductants and additives

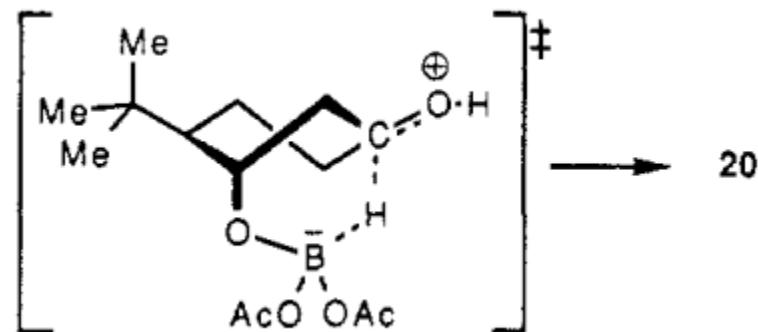
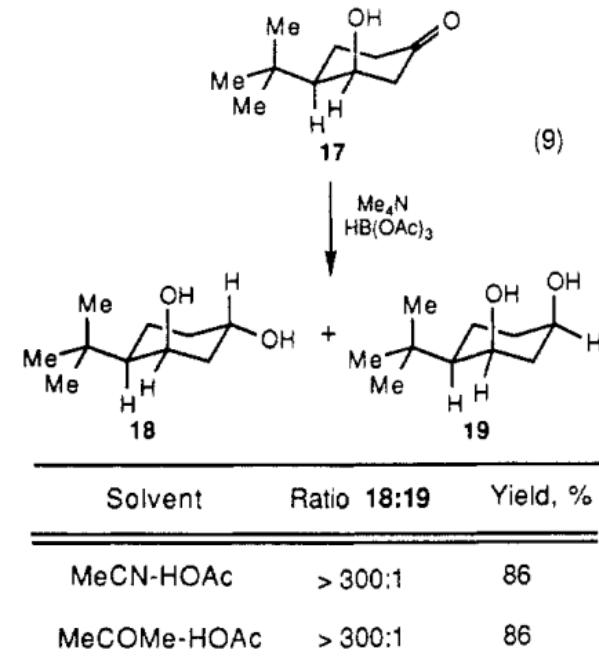
entry	conditions	yield		
		32- α	32- β	32- α :32- β
1 ^a	<i>i</i> -Bu ₂ AlH, CH ₂ Cl ₂ /Et ₂ O = 3/1, -78 °C	0%	35%	0:1
2 ^a	<i>t</i> -BuOK then <i>i</i> -Bu ₂ AlH, toluene, -78 °C	-	-	1:4
3 ^a	AlH ₃ , THF, -78 °C	-	-	1:3
4 ^a	NaAlH ₂ (OCH ₂ CH ₂ OCH ₃), toluene, -78 °C	-	-	1:3
5 ^a	Zn(BH ₄) ₂ , THF, 0 to 21 °C	0%	0%	-
6 ^a	NaBH ₃ CN, THF, 0 to 23 to 40 °C	trace	trace	-
7 ^a	NaBH(OAc) ₃ , THF, 22 °C	30%	16%	1.9:1
8 ^a	NaBH(OAc) ₃ , MeCN, 0 to 21 °C	45%	15%	3.0:1
9 ^a	NaBH(OAc) ₃ , Et ₃ N MeCN/DMF(2/1), 24 °C, 2 cycles	53%	11%	4.8:1
10 ^a	NaBH(OAc) ₃ , piperidine MeCN/DMF(2/1), 26 °C, 2 cycles	66%	12%	5.5:1
11 ^b	NaBH(OAc) ₃ , piperidine MeCN/DMF(2/1), 26 °C, 2 cycles	73%	18%	4.1:1

^a2~14 mg scale. ^b260 mg scale.

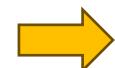


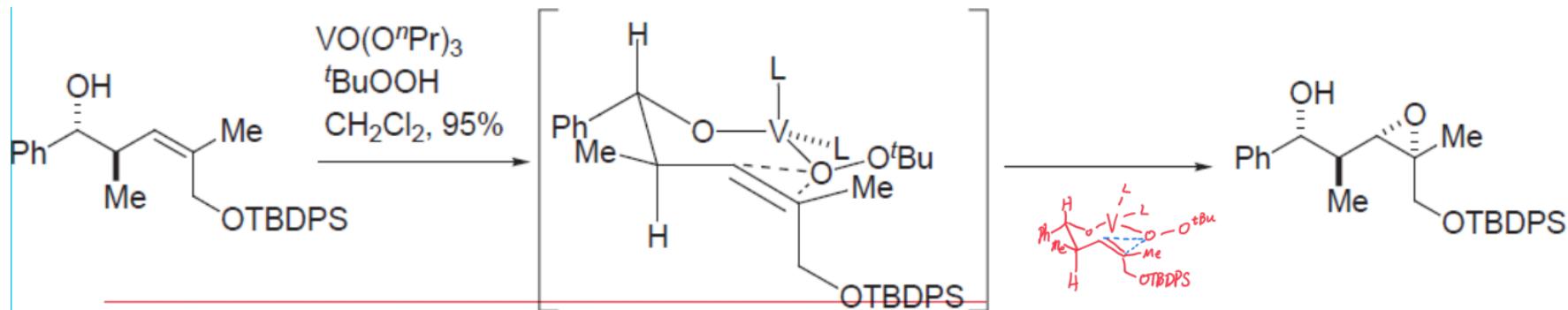


Solvent	Ratio 20:21	Yield, %
MeCN-HOAc	88:12	73
MeCOMe-HOAc	> 300:1	54



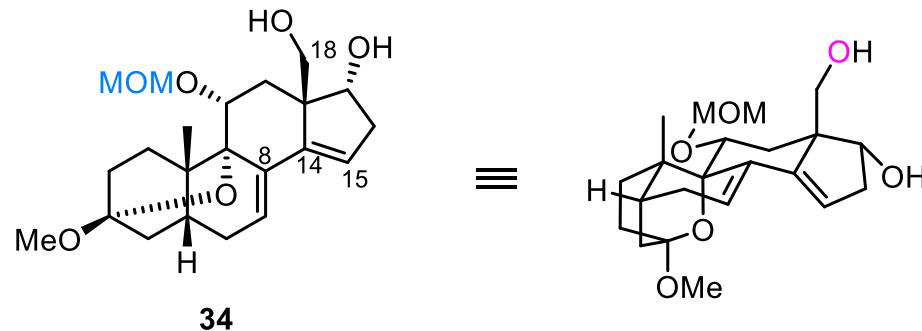
J. Am. Chem. Soc., 1988, 110, 3561.





- ❑ Alternative chair has **two axial substitutes**.
- ❑ Intramolecular oxygen delivery occurs through most stable **chair-like transition state**.

J. Am. Chem. Soc., **1990**, *112*, 5276.



高烯丙位羟基
导向的环氧化

