ASYMMETRIC PALLADIUM-CATALYZED ALKENE CARBOAMINATION REACTIONS FOR THE SYNTHESIS OF CYCLIC SULFAMIDES

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Chem. Eur. J. **2016**, 22, 5919 – 5922
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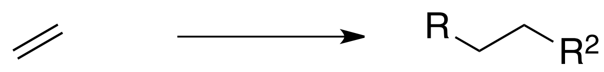
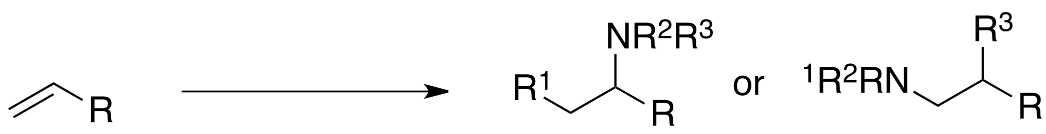
James Johnson
Wipf Group Current Literature
2-11-17

Alkene Difunctionalization: Carboamination

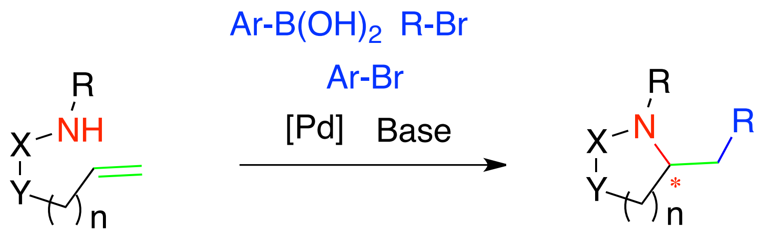


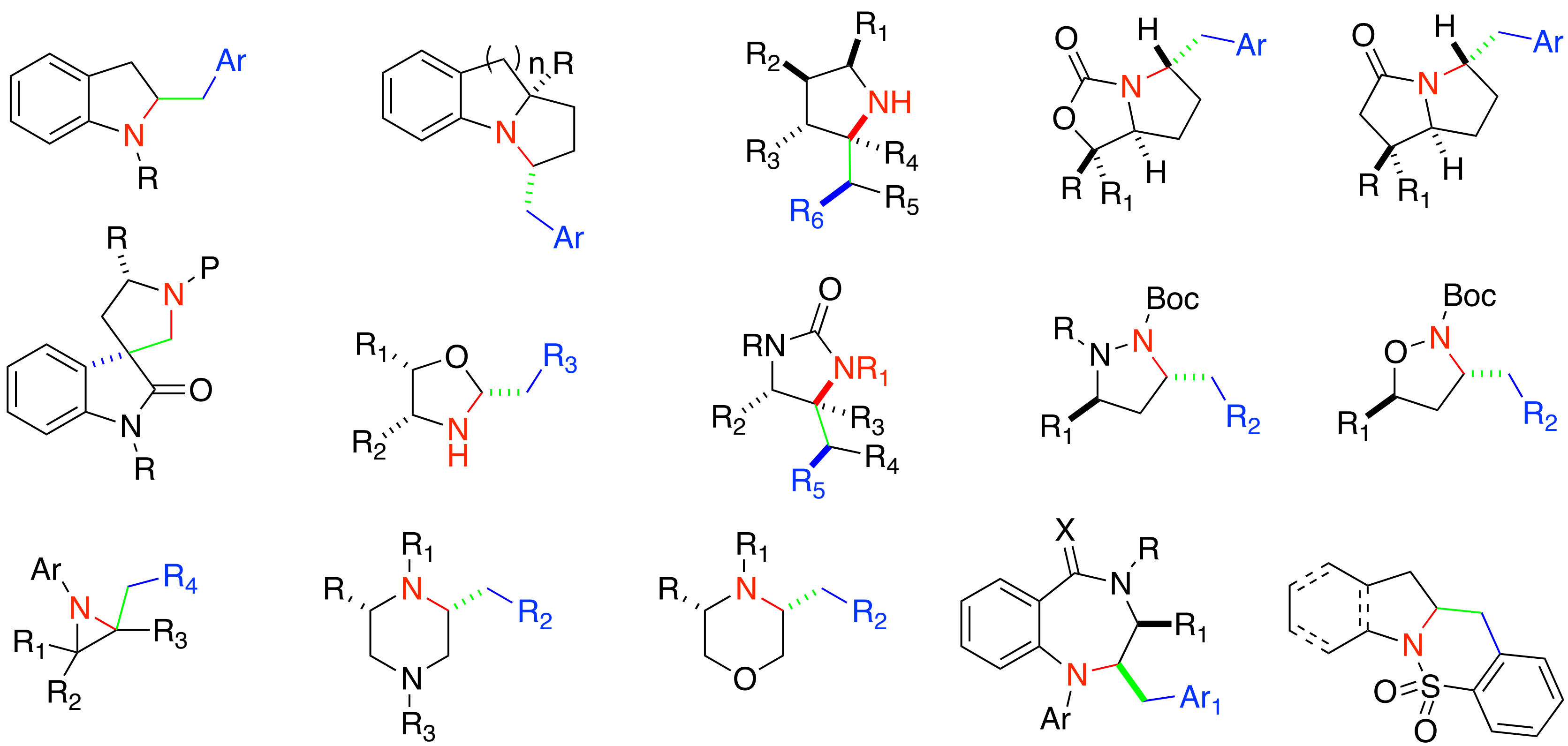
- Ethylene is produced from from petroleum and natural gas by thermal cracking.
  - Largest chemical produced organic compound.
- Alkenes used extensively in the polymer industry.
- Carboamination



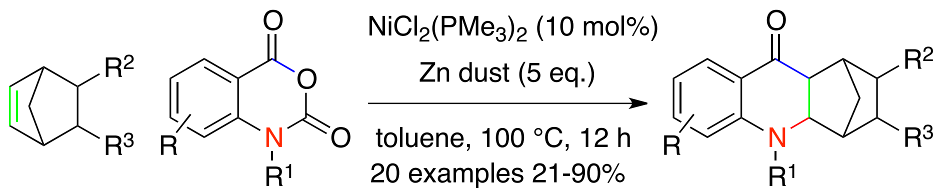
- Inexpensive starting materials are rapidly functionalized in a single step
- Easily accessed heterocycles and amine building blocks (amino acids).

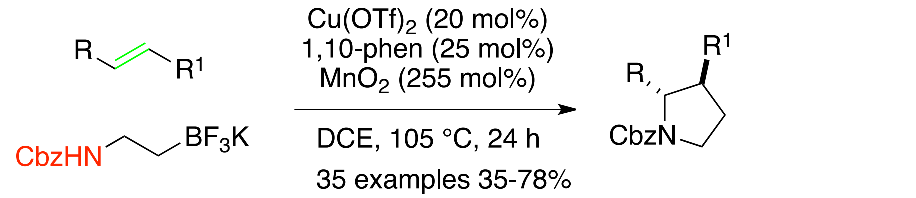
Intramolecular Palladium-Catalyzed Carboamination Reactions

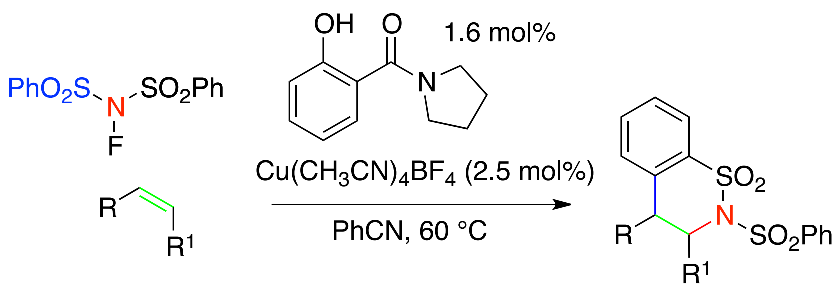


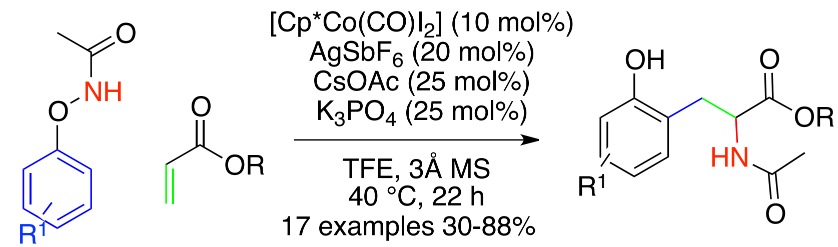


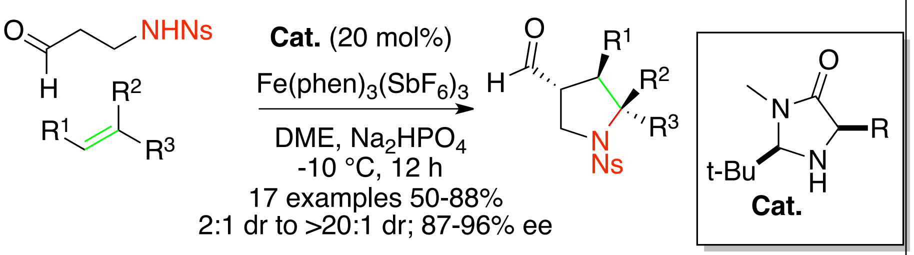
Intermolecular Carboamination

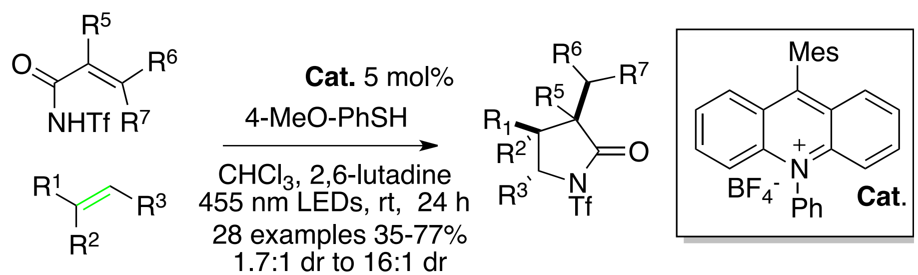


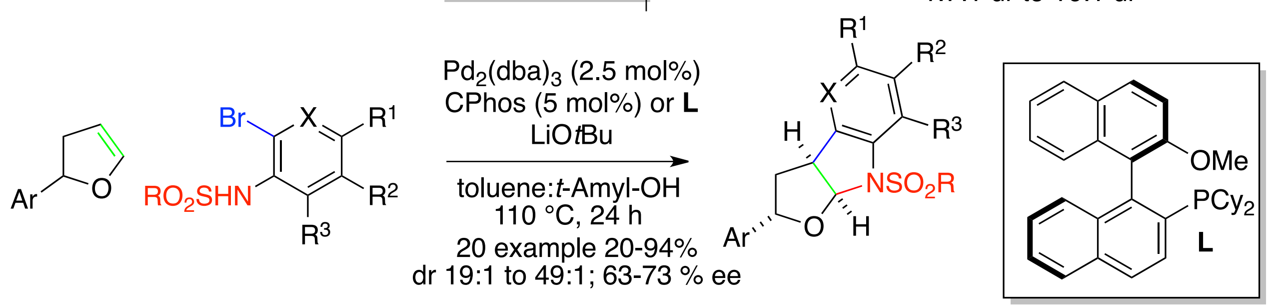






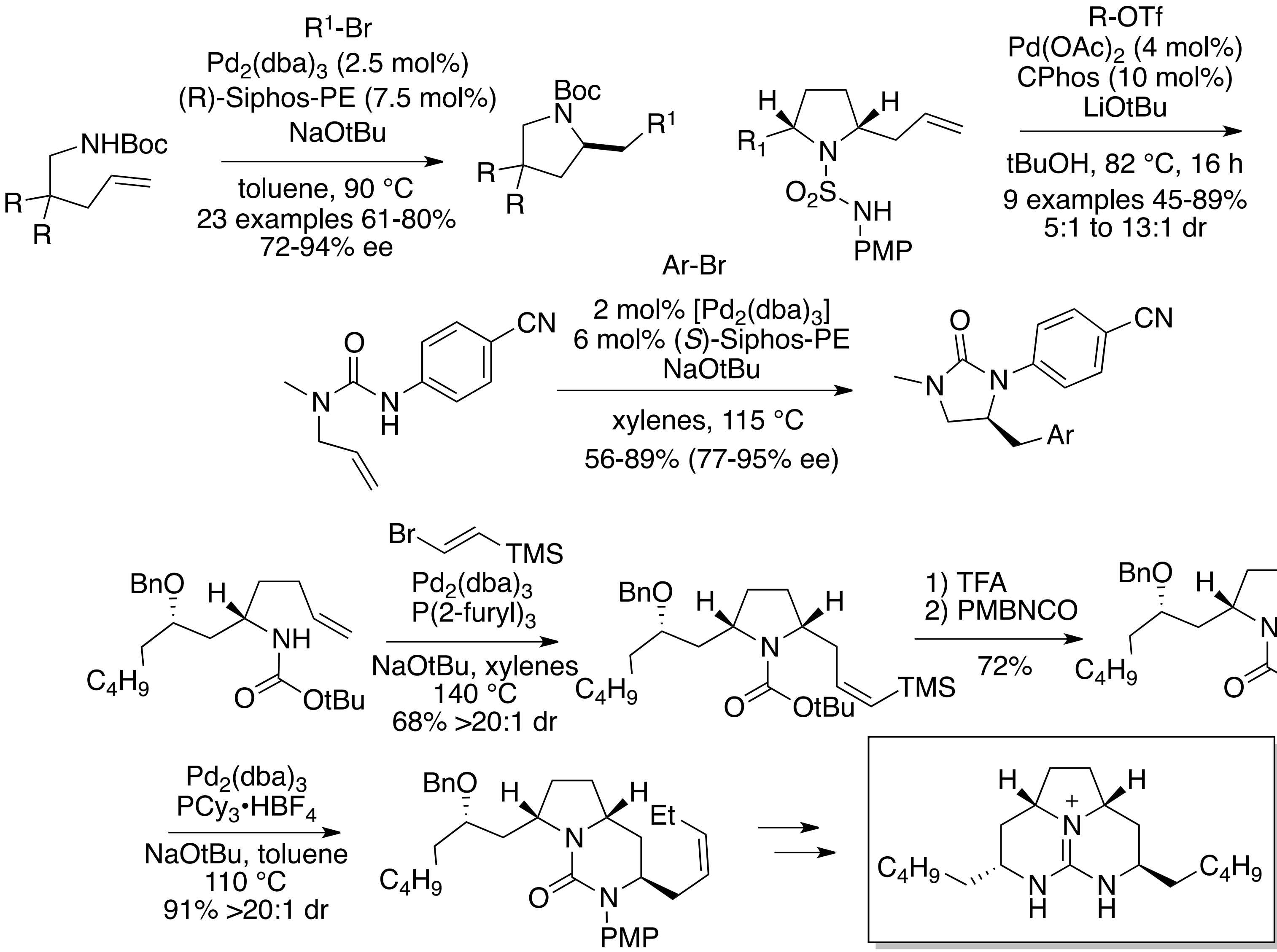




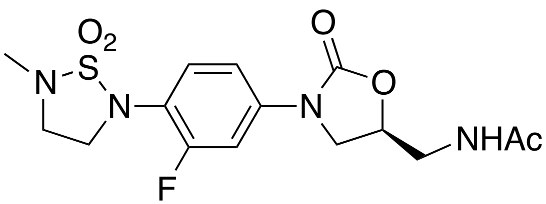


Org. Lett. ***2013***, *15, 2502-2505; ACS Catal.*, **2016**, *6* (10), pp 7183–7187

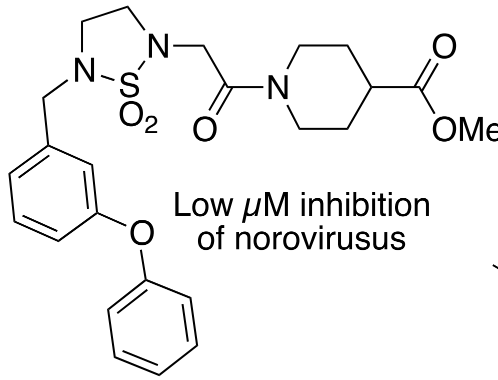
Wolfe Group Chemistry



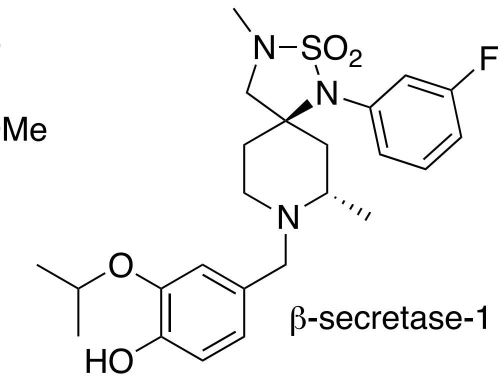
Cyclic Sulfamides



Active against gram-positive methicillin and vancomycin resistant bacteria

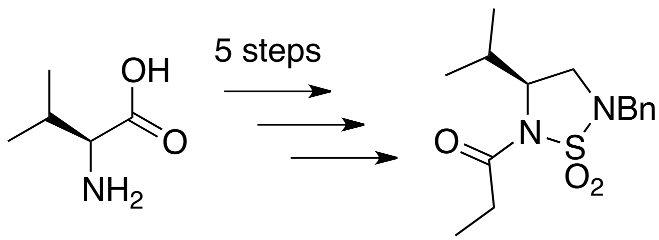


Low μM inhibition of norovirusus

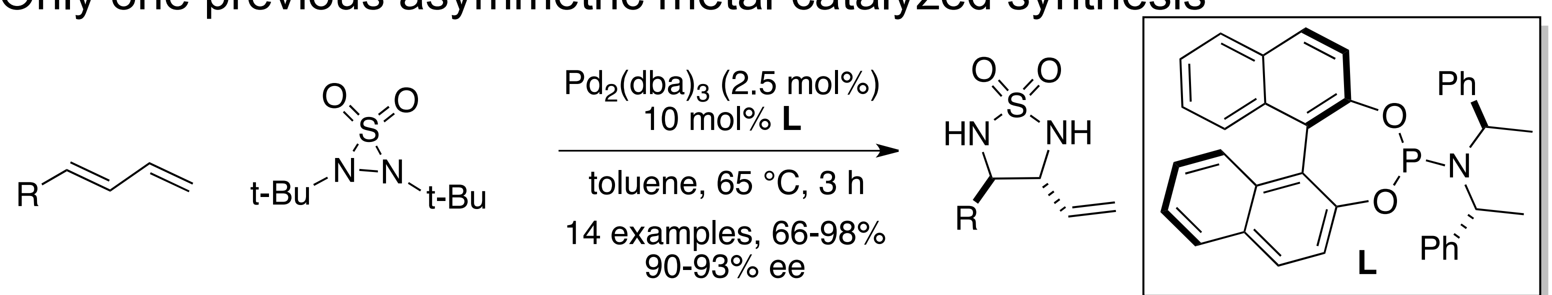


β-secretase-1 inhibitor

- Biologically active
- Enantioselective synthesis usually multi-step starting from amino acids

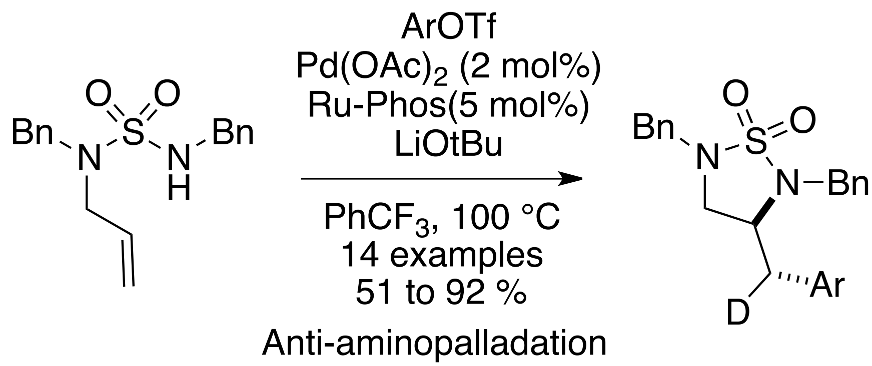


- Only one previous asymmetric metal-catalyzed synthesis



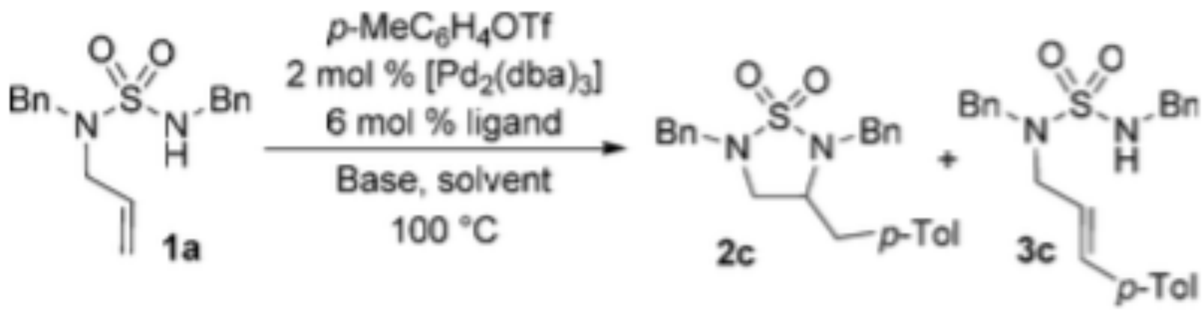
Org. Lett., **2013**, *15* (4), pp 796–799

Anti-aminopalladation

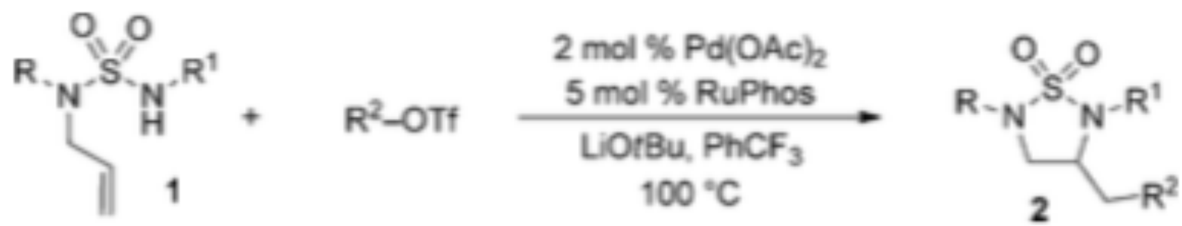


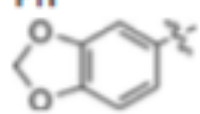
Chem. Eur. J. **2014**, 20, 8782 – 8790

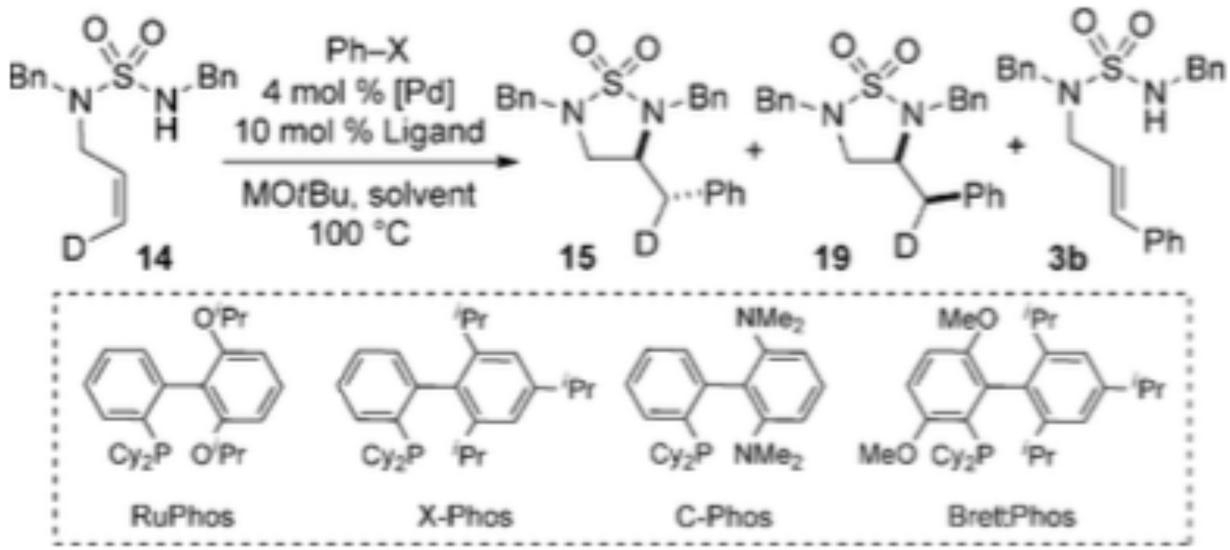
Optimization of Cyclization with Ar-OTf



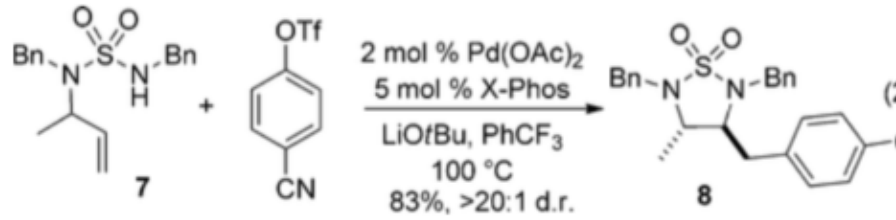
Entry	Ligand	Base	Solvent	2c/3c	Conversion [%][b]
1	X-Phos	NaO*t*Bu	toluene	1:1	81
2	RuPhos	NaO*t*Bu	toluene	9:1	90
3	RuPhos	LiO*t*Bu	toluene	19:1	100
4	RuPhos	LiO*t*Bu	$PhCF_3$	>25:1	100[c]



Entry	R	R1	R2	Product	Yield [%][b]
1	Bn	Bn	*p*-Me-C_6H_4	**2c**	85
2	Bn	Bn	*p*-NC-C_6H_4	**2a**	90
3	Bn	Bn	*p*-MeO-C_6H_4	**2d**	90
4	Bn	Bn	*o*-Me-C_6H_4	**2e**	85
5	Bn	Bn	1-cyclohexenyl	**2f**	87[c]
6	Bn	Bn	(*E*)-1-decenyl[e]	**2g**	80[d,e,f]
7	Me	Bn	*p*-Cl-C_6H_4	**2h**	79
8	Bn	PMB	*p*-Me-C_6H_4	**2i**	90
9	Bn	Me	*m*-F_3C-C_6H_4	**2j**	86
10	Bn	*t*Bu	*p*-MeO-C_6H_4	**2k**	92
11	Bn	PMP	Ph	**2l**	90[g]
12	Me	Bn		**2m**	84
13	*t*Bu	Bn	*m*-F_3C-C_6H_4	**2n**	88[h]
14	H	allyl	Ph	**2o**	51[i]

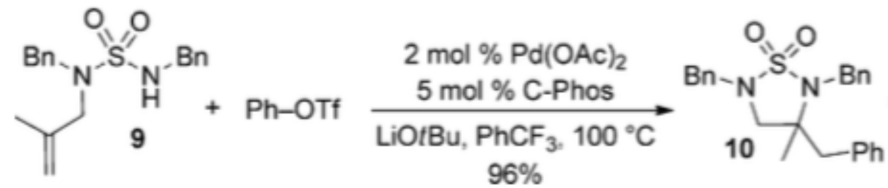


Entry	X	Ligand	M	Solvent	15/19[b]	(15+19)/3b[c]
1	**OTf**	**RuPhos**	**Li**	**$PhCF_3$**	**>20:1**	**99:1**
2	OTf	RuPhos	Na	toluene	7:1	94:6[d]
3	OTf	X-Phos	Na	toluene	1:7	72:28[d]
4	**OTf**	**X-Phos**	**Li**	**dioxane**	**1:10**	**60:40**
5	OTf	X-Phos	Li	$PhCF_3$	10:1	93:7
6	**Br**	**X-Phos**	**Na**	**toluene**	**1:4**	**70:30[d]**
7	Br	RuPhos	Na	toluene	1:1	60:40[d]
8	Br	RuPhos	Na	toluene	1:1	60:40
9	Br	RuPhos	Na	$PhCF_3$	10:1	93:7
10	Br	X-Phos	Na	$PhCF_3$	1:1	60:40
11	Br	BrettPhos	Na	$PhCF_3$	10:1	98:2
12	**Br**	**C-Phos**	**Na**	**$PhCF_3$**	**>20:1**	**99:1**



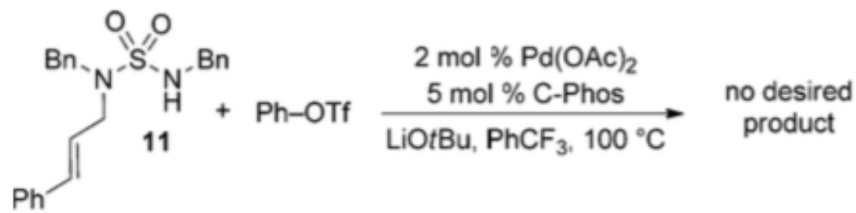
Bn N S N Bn H
OTf
CN
2 mol % Pd(OAc)$_2$
5 mol % X-Phos
LiO*t*Bu, PhCF$_3$
100 °C
83%, >20:1 d.r.
7
8
CN

(2)



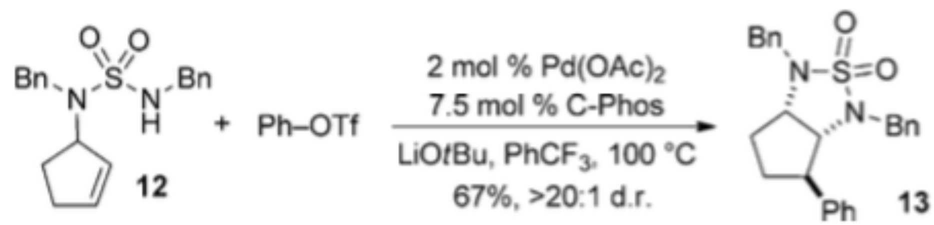
Ph–OTf
2 mol % Pd(OAc)$_2$
5 mol % C-Phos
LiO*t*Bu, PhCF$_3$, 100 °C
96%
9
10
Ph

(3)

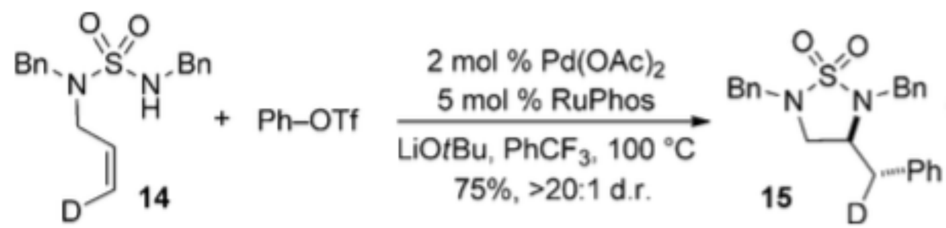


Ph–OTf
2 mol % Pd(OAc)$_2$
5 mol % C-Phos
LiO*t*Bu, PhCF$_3$, 100 °C
no desired product
11
Ph

(4)

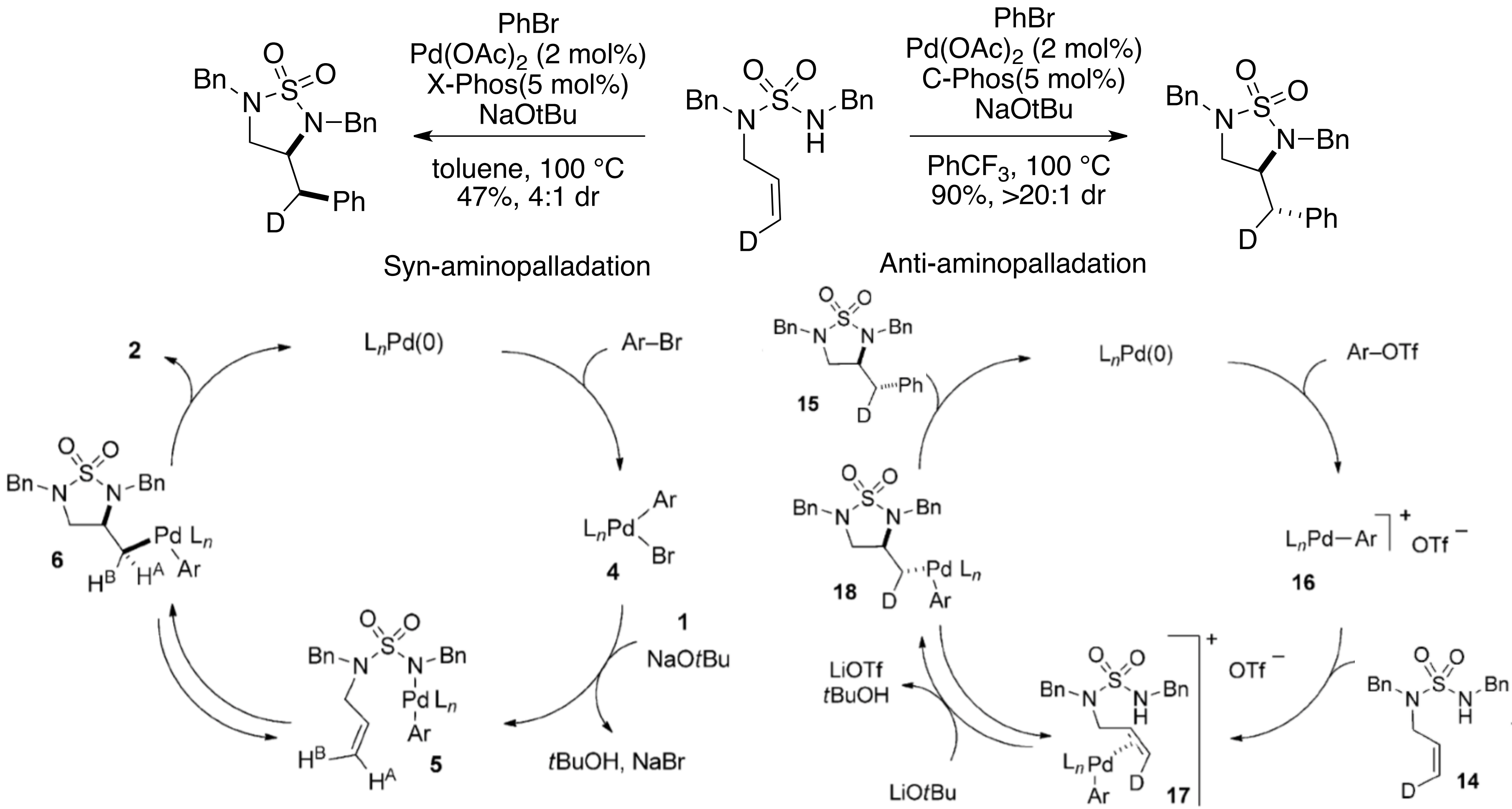


Ph–OTf
2 mol % Pd(OAc)$_2$
7.5 mol % C-Phos
LiO*t*Bu, PhCF$_3$, 100 °C
67%, >20:1 d.r.
12
13
Ph



Ph–OTf
2 mol % Pd(OAc)$_2$
5 mol % RuPhos
LiO*t*Bu, PhCF$_3$, 100 °C
75%, >20:1 d.r.
14
15
D
Ph

Syn vs Anti-aminopalladation



Mechanism highly solvent and ligand dependent

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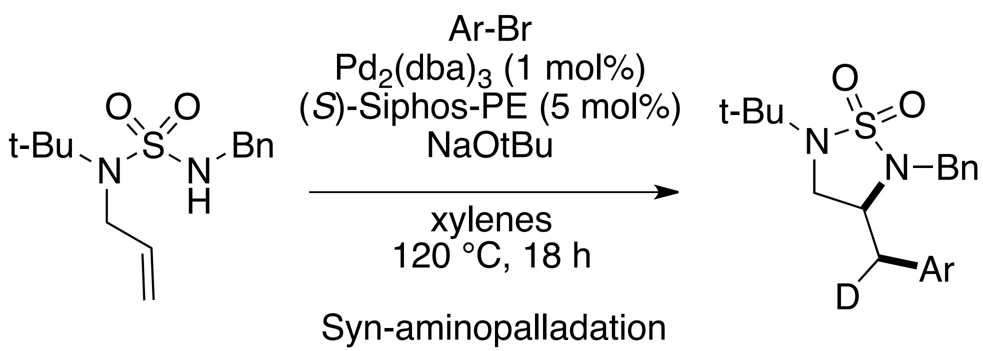
Title Paper



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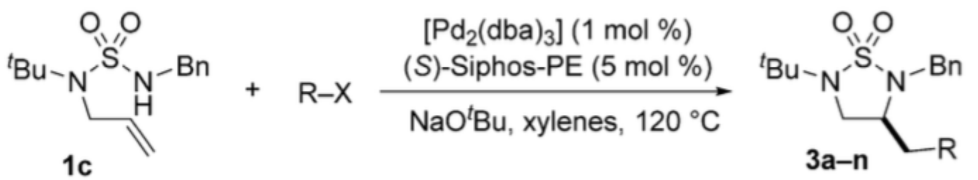
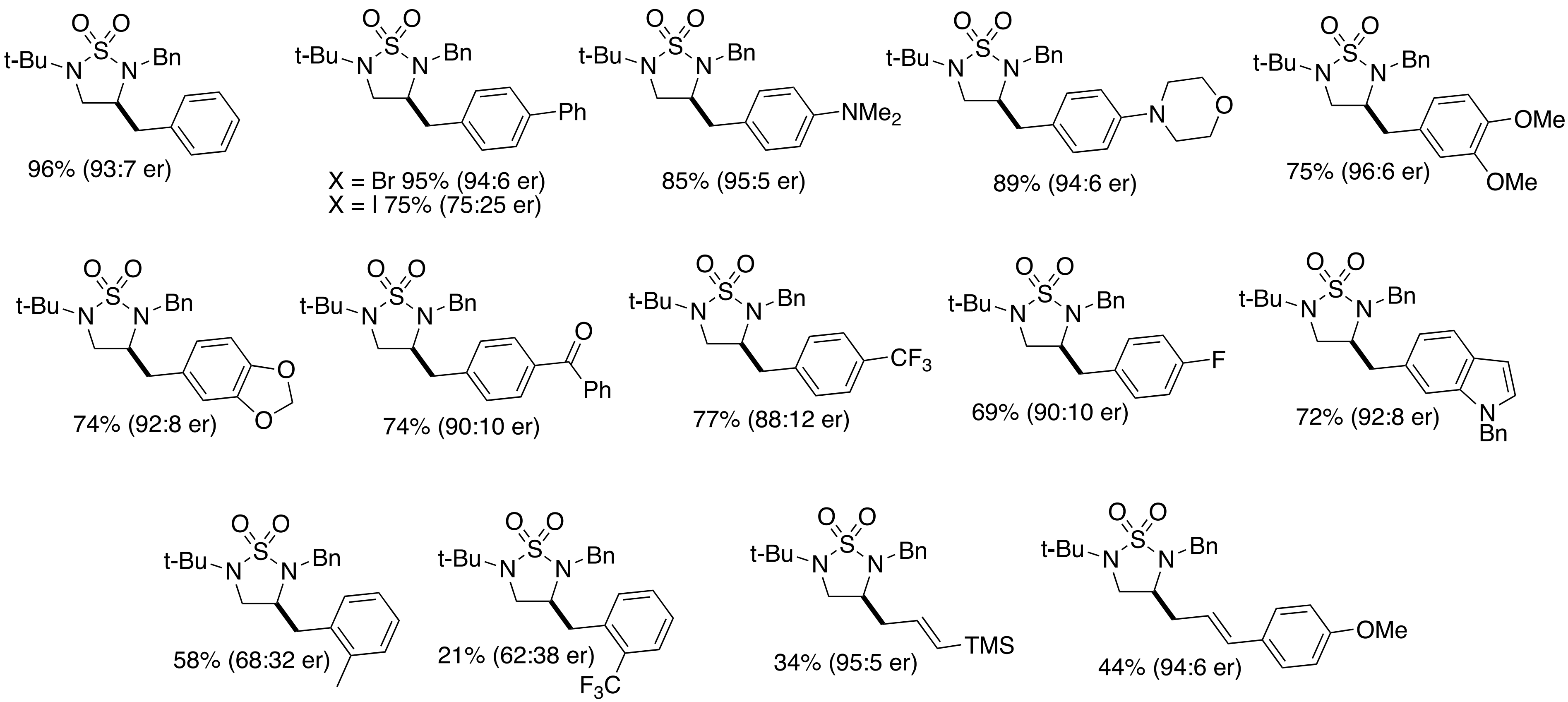
Optimization of Protecting Groups

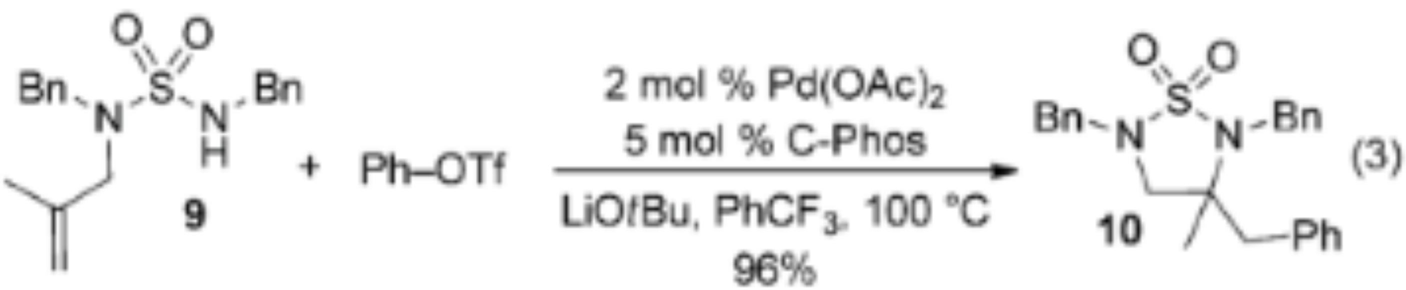
Entry	R^1	R^2 (substrate)	Yield [%][b]	e.r.[c]
1	*t*Bu	C_6H_4-*p*-OMe (**1a**)	47 (**2a**)	78:22
2	*t*Bu	C_6H_4-*p*-Cl (**1b**)	11 (**2b**)	73:27
3	*t*Bu	Bn (**1c**)	70 (**2c**)	93:7
4	*t*Bu	*p*-MeO-Bn (**1d**)	77 (**2d**)	91:9
5	*t*Bu	*m*-MeO-Bn (**1e**)	60 (**2e**)	91:9
6	Bn	Bn (**1f**)	0 (**2f**)	–
7	C_6H_4-*p*-OMe	Bn (**1g**)	0 (**2g**)	–
8	C_6H_4-*p*-Cl	Bn (**1h**)	0 (**2h**)	–
9	Ph_2CH	Bn (**1i**)	0 (**2i**)	–

Reaction Scope

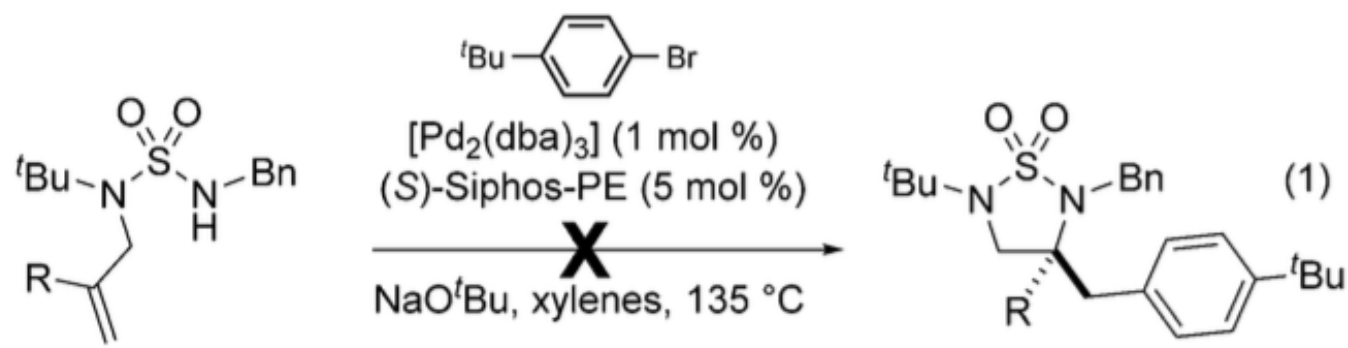




Anti-aminopalladation



Syn-aminopalladation

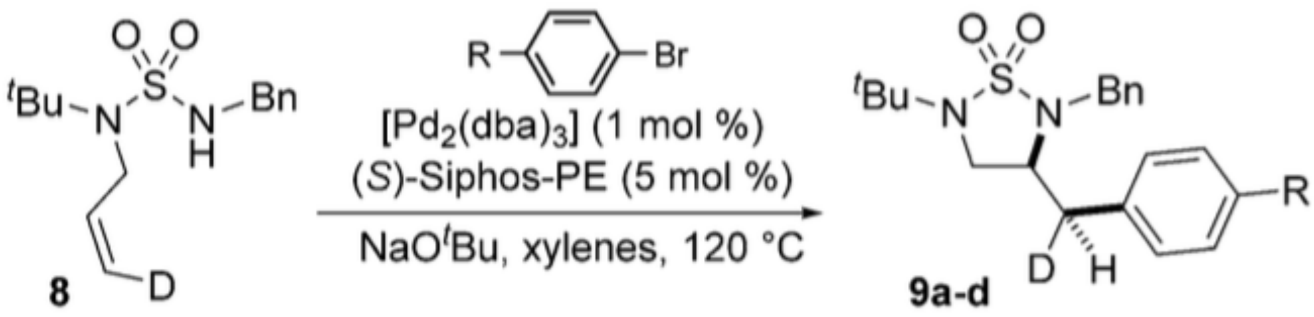


4a-b: R = Me, Ph

5 Not Observed

- Olefin substitution not tolerated

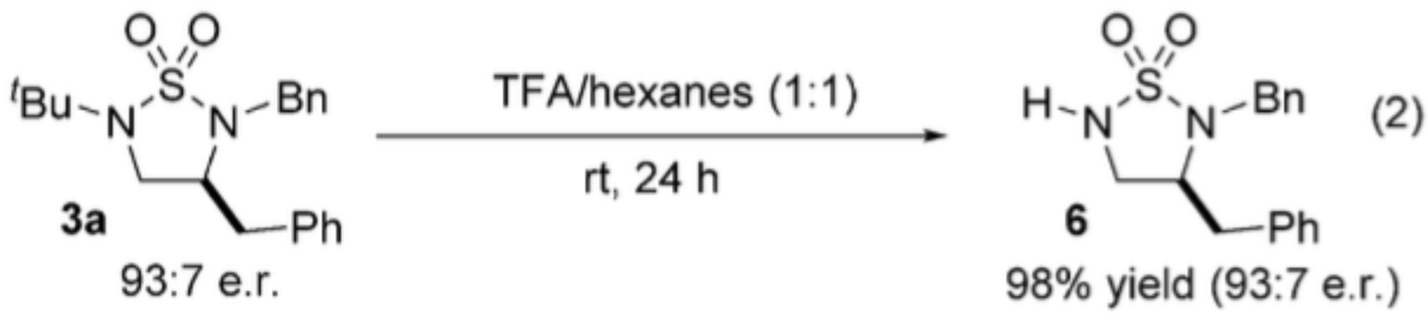
Deuterium Labeling Studies

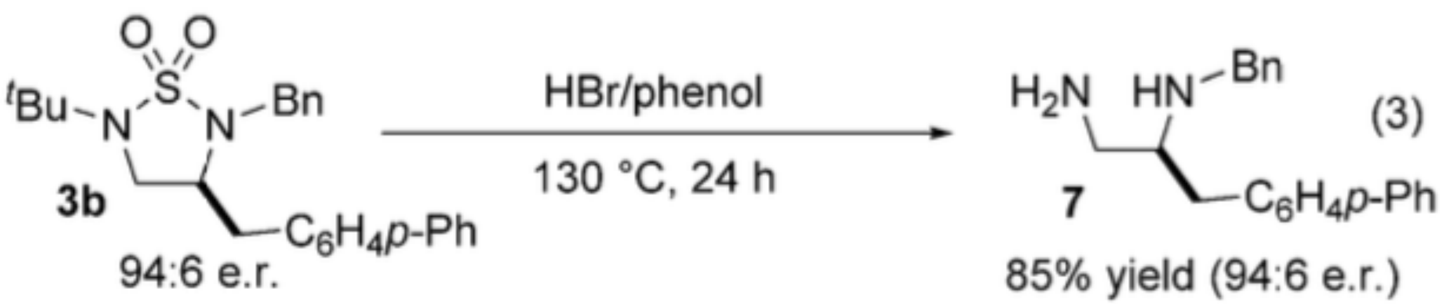


Entry	R	Yield [%][b]	d.r.[c]	e.r.[d]
1	*t*Bu	58 (**9a**)	17:1	94:6
2	H	67 (**9b**)	8:1	95:5
3	Ph	65 (**9c**)	9:1	92:8
4a	CF_3	58 (**9d**)	7:1	88:12
4b[e]		78 (**9d**)	5:1	89:11

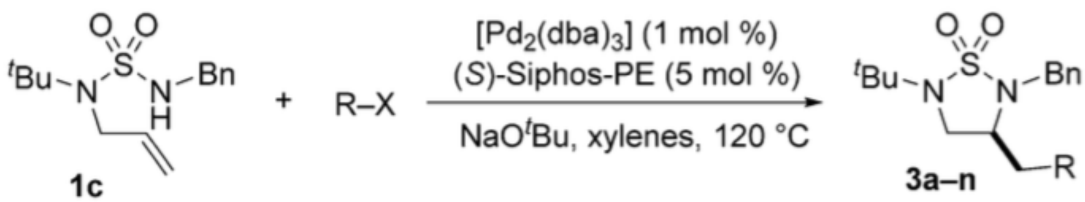
- EWD groups decrease dr
    - anti-aminopalladation pathway
- Addition of water (4b) improved yield.
    - No effect on dr or er

Deprotection





Conclusions



- Developed enantioselective Pd-catalyzed alkene carboamination with good to high enantio selectivity
- Example of controlling syn vs anti-aminopalladation

- Expansion to intermolecular variant?