Broadly Applicable NHC−Cu-Catalyzed Approach for Efficient, Site-, and Enantioselective Coupling of Readily Accessible (Pinacolato)alkenylboron Compounds to Allylic Phosphates and Applications to Natural Product Synthesis

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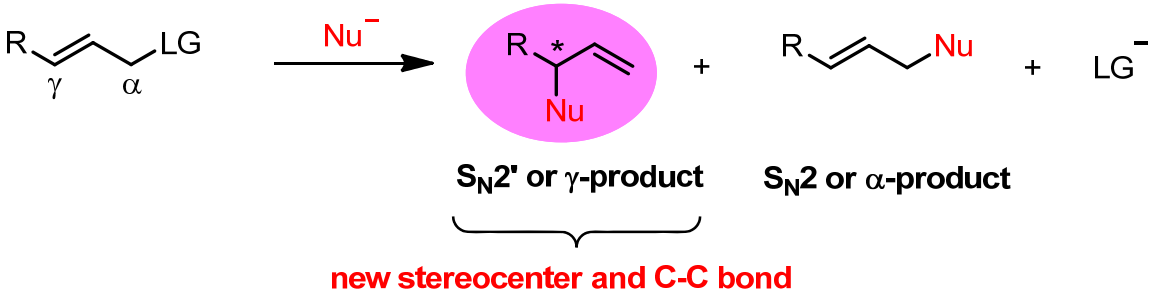
J. Am. Chem. Soc. **2014**, *136*, 2149−2161

Juan-Carlos Castillo Millán
07-04-2014

1. State of the Art

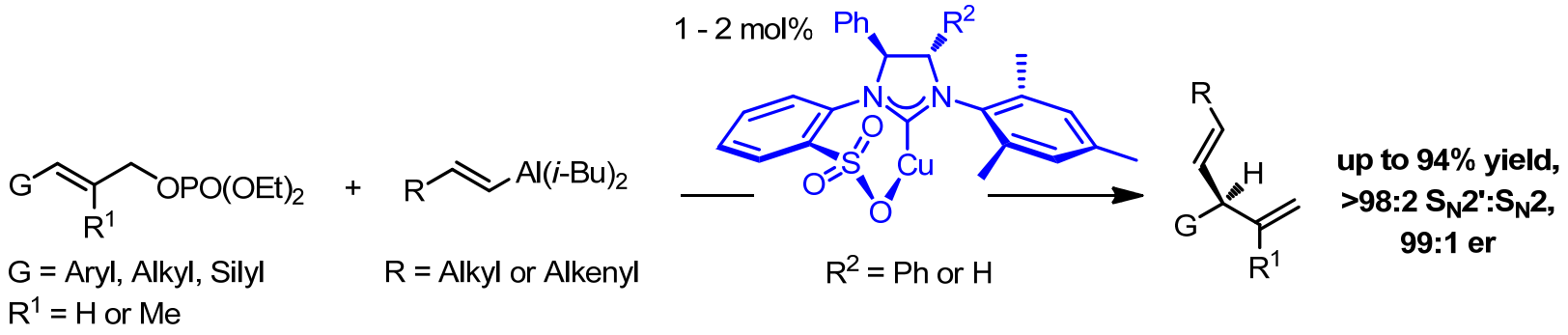
The Allylic Alkylation



1969 Copper-catalyzed allylic alkylation was discovered (sp^3-carbon)

2008 Enantioselective allylic substitutions with sp^2-hybridized carbon nucleophiles

Enantioselective NHC-Cu-catalyzed allylic alkenylation with vinylaluminum



[1] Ronal, P.; Tökes, J. T.; Crabeé, P. *J. Chem. Soc. D* **1969**, *8*, 43–44. [2] Lee, Y.; Akiyama, K.; Gillingham, D. G.; Brown, M. K.; Hoveyda, A. H. *J. Am. Chem. Soc*. **2008**, *130*, 446–447.

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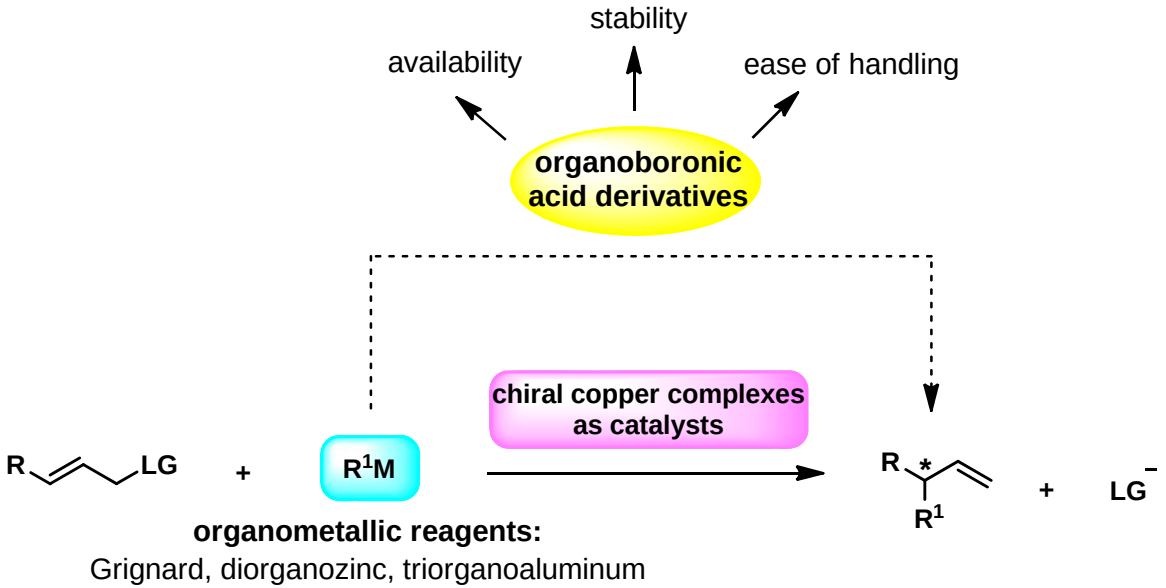
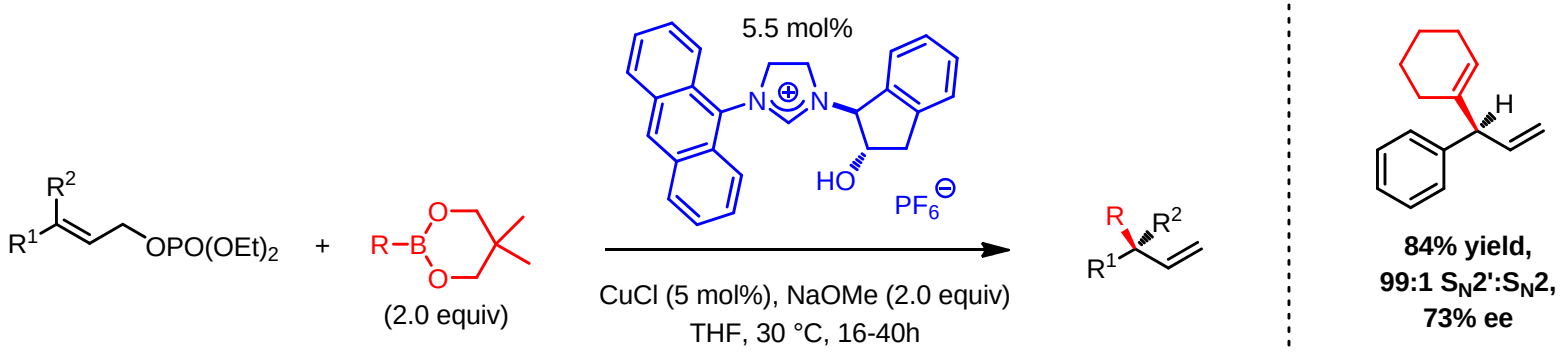
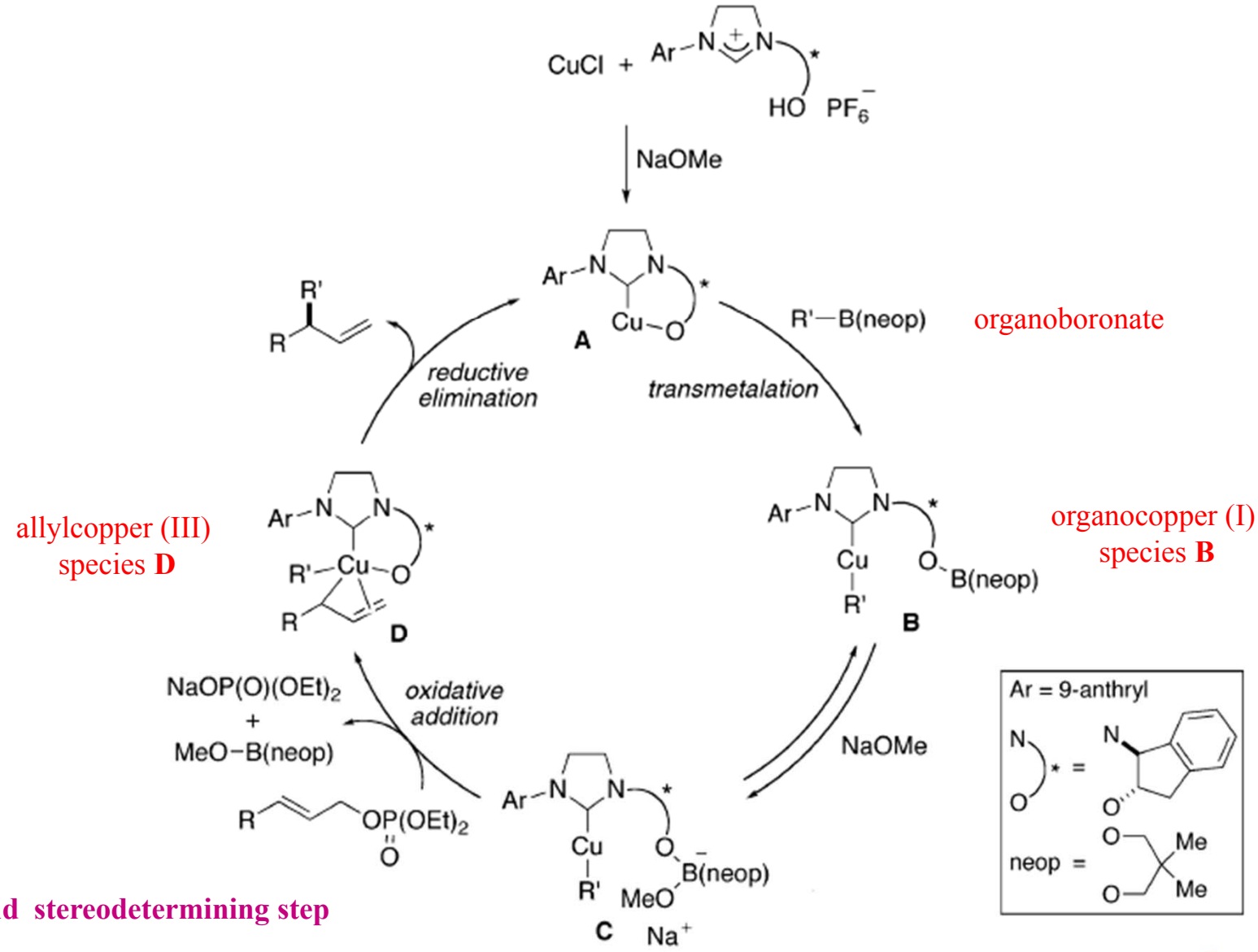


2011 Enantioselective NHC-Cu-catalyzed allylic substitution of allyl phosphates with aryl- and alkenylboronic acid esters.



[3] Shintani, R.; Takatsu, K.; Takeda, M.; Hayashi, T. *Angew. Chem. Int. Ed.* **2011**, *50*, 8656 –8659.

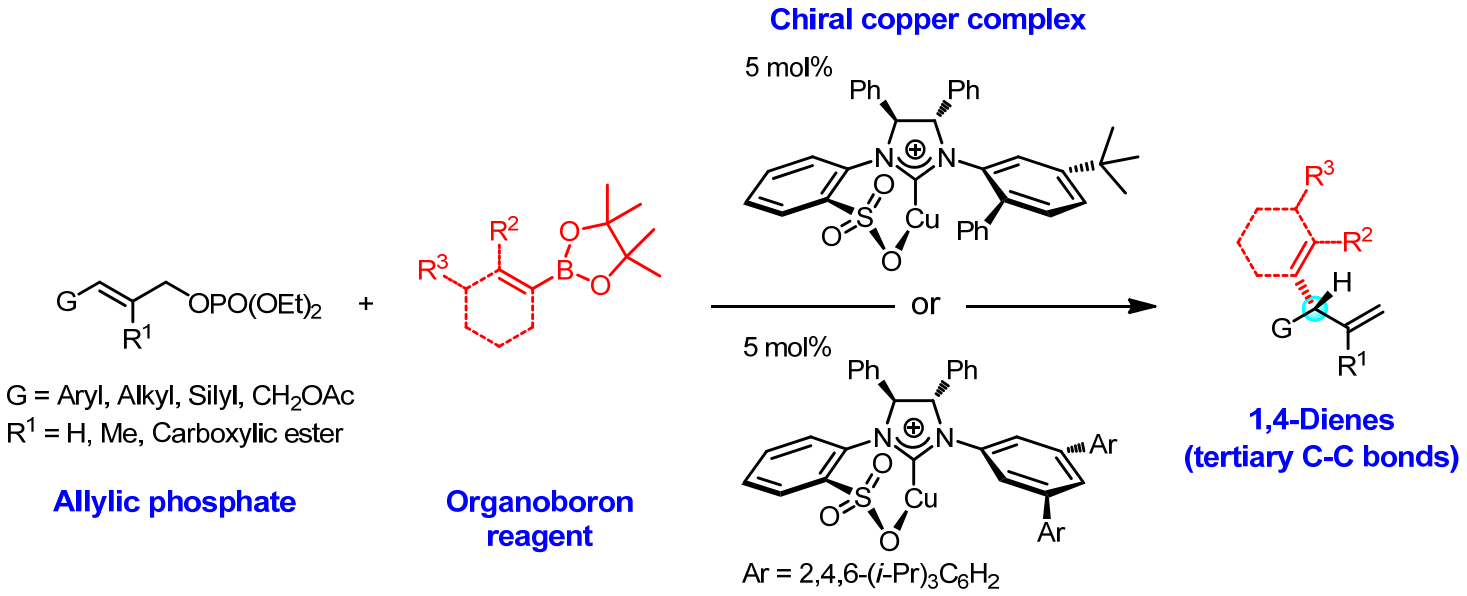
1. State of the Art



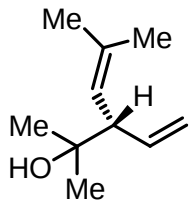
[3] Shintani, R.; Takatsu, K.; Takeda, M.; Hayashi, T. *Angew. Chem. Int. Ed*. **2011**, *50*, 8656 –8659.

2. NHC−Cu-Catalyzed EAS with Alkenyl−B(pin) Reagents Developed in This Study and Related Applications

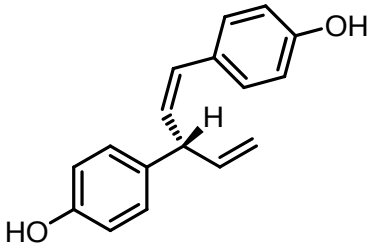
2.1 A Broadly Applicable Method:



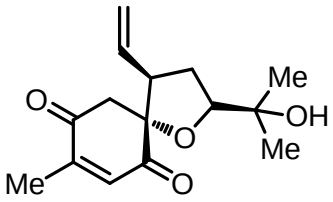
2.2 Natural products can be synthesized through the NHC-Cu-catalyzed protocol:



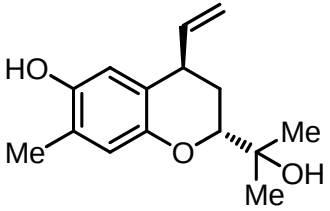
santolina alcohol



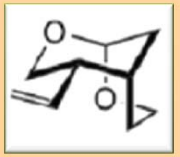
nyasol



heliespirone A



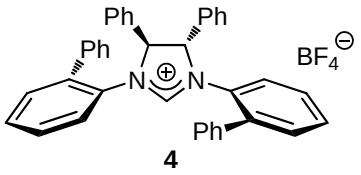
heliannuol E



semburin

3. Catalyst Screening

Selection of chiral NHC−Cu complexes to promote the EAS involving allylic phosphate **1a** and *n*-alkyl-substituted alkenyl−B(pin) **2** to afford diene **3**.



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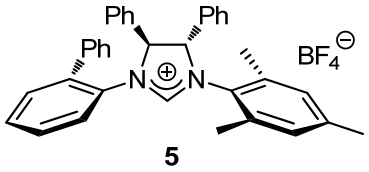

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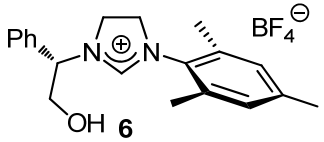

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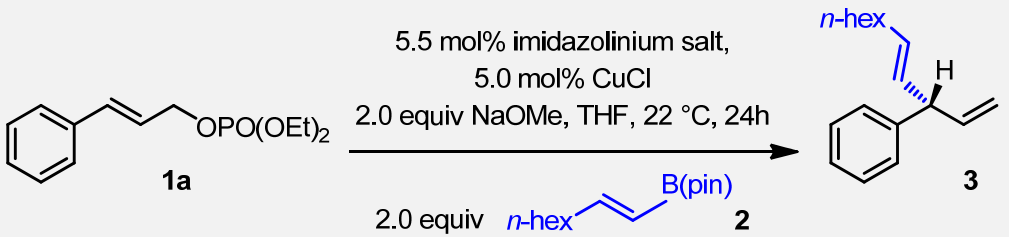
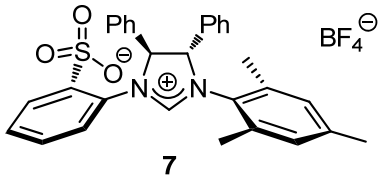


entry	imidazolinium salt	conv (%)	yield (%)	$S_N2':S_N2^a$	er
1	**4**	38	31	67:33	45:55
2	**5**	76	59	79:21	74:26
3	**6**	38	30	>98:2	78:22
4	**7**	91	90	>98:2	41:59
5	**8**	72	70	98:2	34:66
6	**9a**	98	93	98:2	87:13
7[b]	**9b**	**97**	**97**	**98:2**	**92:8**



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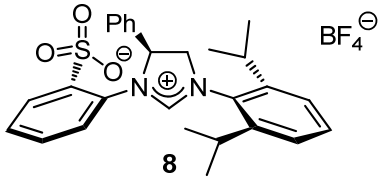

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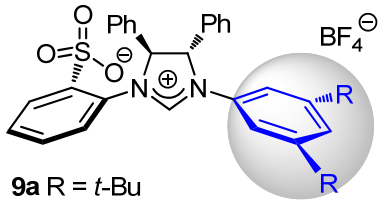
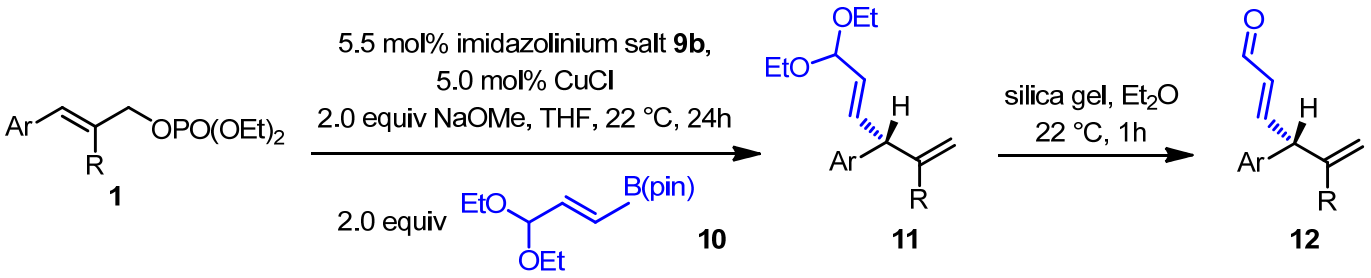


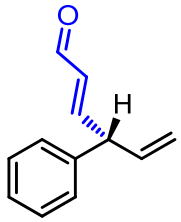
9a R = *t*-Bu
9b R = 2,4,6-(*i*-Pr)$_3$C$_6$H$_2$

[a]Conversion and site selectivity were determined by analysis of ^{1}H NMR spectra of product mixtures. [b]Reaction at lower temperatures resulted in reduced efficiency and similar selectivity.

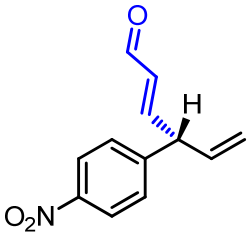
4. NHC-Cu-Catalyzed Enantioselective Allylic Substitution (EAS) Involving Organoboron Reagents

4.1 Transformations with Acetal-Substituted Alkenyl−B(pin)

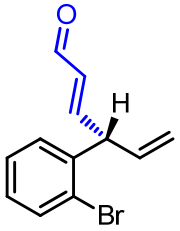




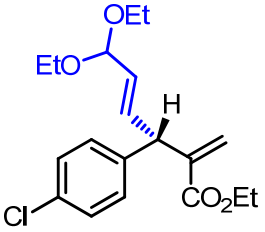
12a
88% conv, 85% yield,
>98% S_N2', 91:9 er



12b
>98% yield,
96% S_N2', 93:7 er



12c
91% conv, 86% yield,
95% S_N2', 94:6 er

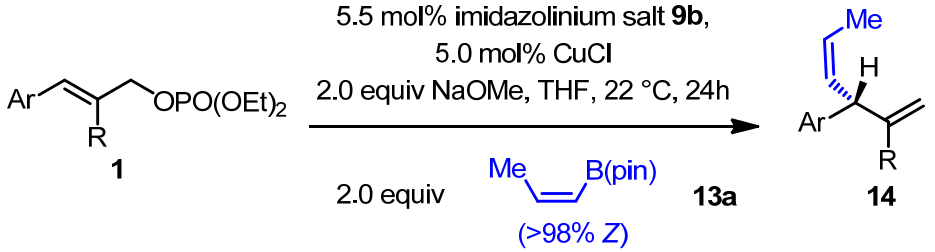


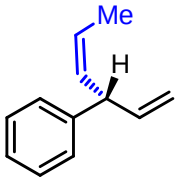
11a
93% conv, 52% yield,
>98% S_N2', 92:8 er

Stereogenic center survives NHC-Cu-Catalyzed EAS and subsequent hydrolysis to an enal

4. NHC-Cu-Catalyzed Enantioselective Allylic Substitution (EAS) Involving Organoboron Reagents

4.2 Transformations with Z-Alkenyl−B(pin)

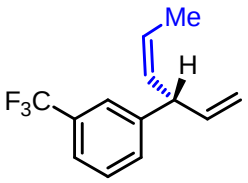




14a

90% conv, 76% yield,

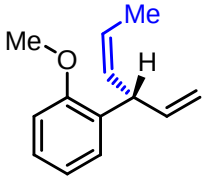
>98% S_N2', >98% *Z*, 95:5 er



14b

95% conv, 76% yield,

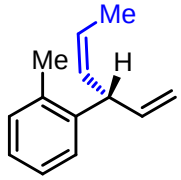
>98% S_N2', >98% *Z*, 98:2 er



14c

98% conv, 82% yield,

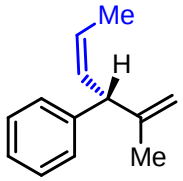
>98% S_N2', >98% *Z*, 97:3 er



14d

92% conv, 78% yield,

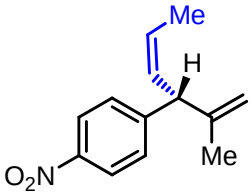
>98% S_N2', >98% *Z*, 98:2 er



14e

86% conv, 77% yield,

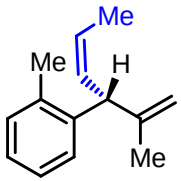
>98% S_N2', >98% *Z*, 91:9 er



14f

98% conv, 96% yield,

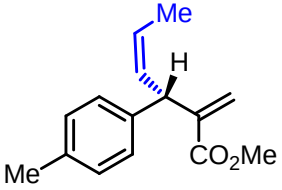
>98% S_N2', >98% *Z*, 95:5 er



14g

89% conv, 87% yield,

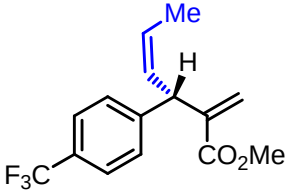
>98% S_N2', >98% *Z*, 87:13 er



14h

93% conv, 90% yield,

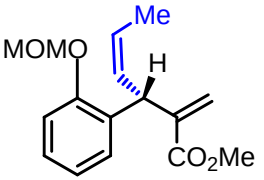
>98% S_N2', >98% *Z*, 96:4 er



14i

98% conv, 81% yield,

>98% S_N2', >98% *Z*, 97:3 er

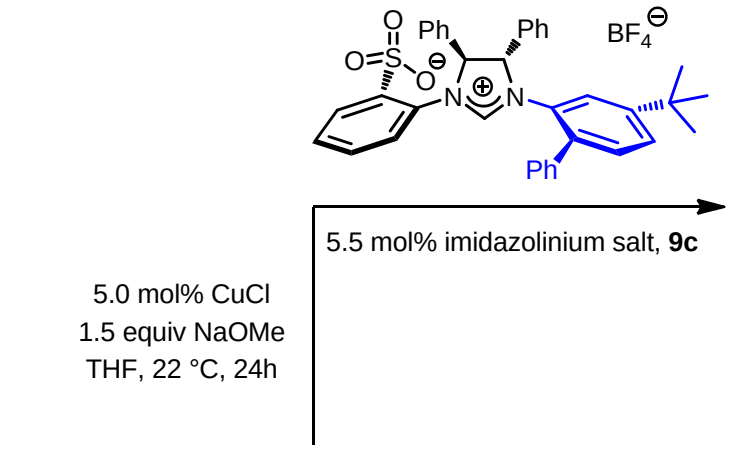


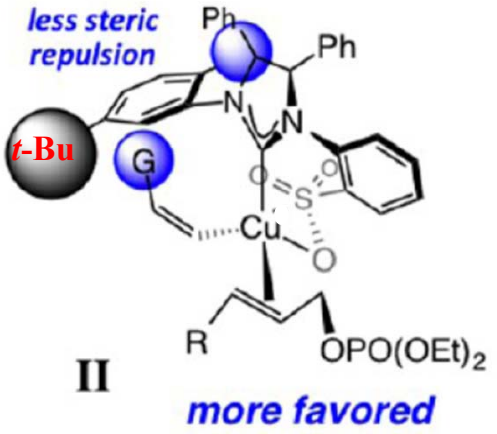
14j

95% conv, 74% yield,

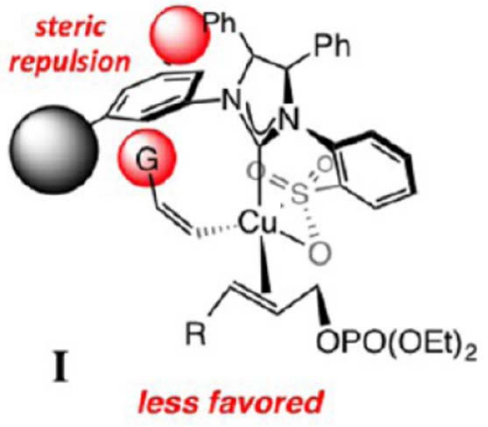
>98% S_N2', >98% *Z*, 97:3 er

4. NHC-Cu-Catalyzed Enantioselective Allylic Substitution (EAS) Involving Organoboron Reagents





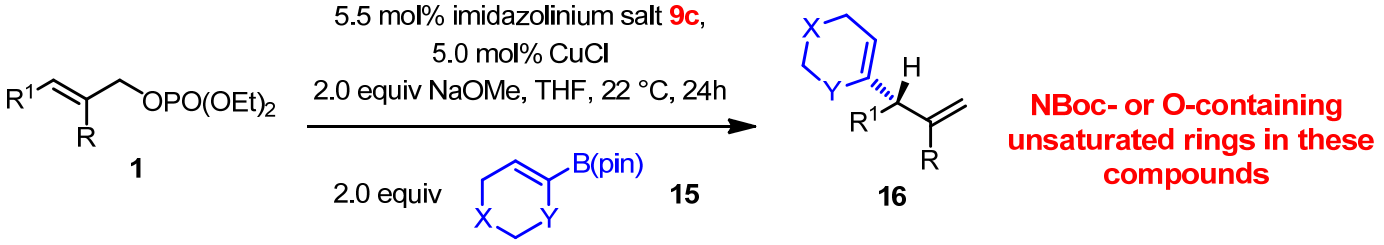
¿ Which modification of catalyst structure will improve selectivity ?



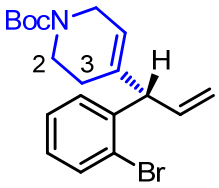
EAS proceed with lower site and enantioselectivity

4. NHC-Cu-Catalyzed Enantioselective Allylic Substitution (EAS) Involving Organoboron Reagents

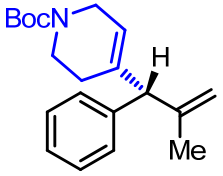
4.3 Transformations with heterocyclic alkenyl−B(pin)



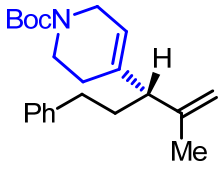
NBoc- or O-containing unsaturated rings in these compounds



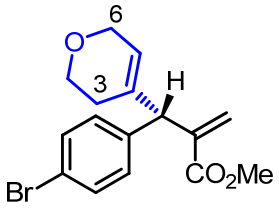
16a
>98% conv, 87% yield,
97% S_N2', 93:7 er



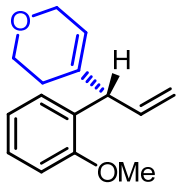
16b[a]
>98% conv, 98% yield,
>98% S_N2', 98:2 er



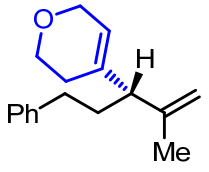
16c[a]
>98% conv, 98% yield,
>98% S_N2', 91:9 er



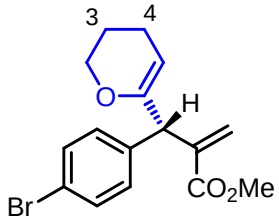
16d
>98% conv, 52% yield,
93% S_N2', 95:5 er



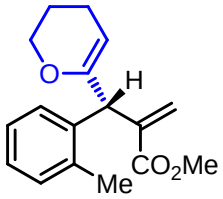
16e
81% conv, 80% yield,
>98% S_N2', 93:7 er



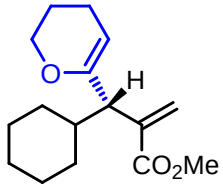
16f[a]
82% conv, 73% yield,
>98% S_N2', 91:9 er



16g[b]
95% conv, 78% yield,
97% S_N2', 98:2 er



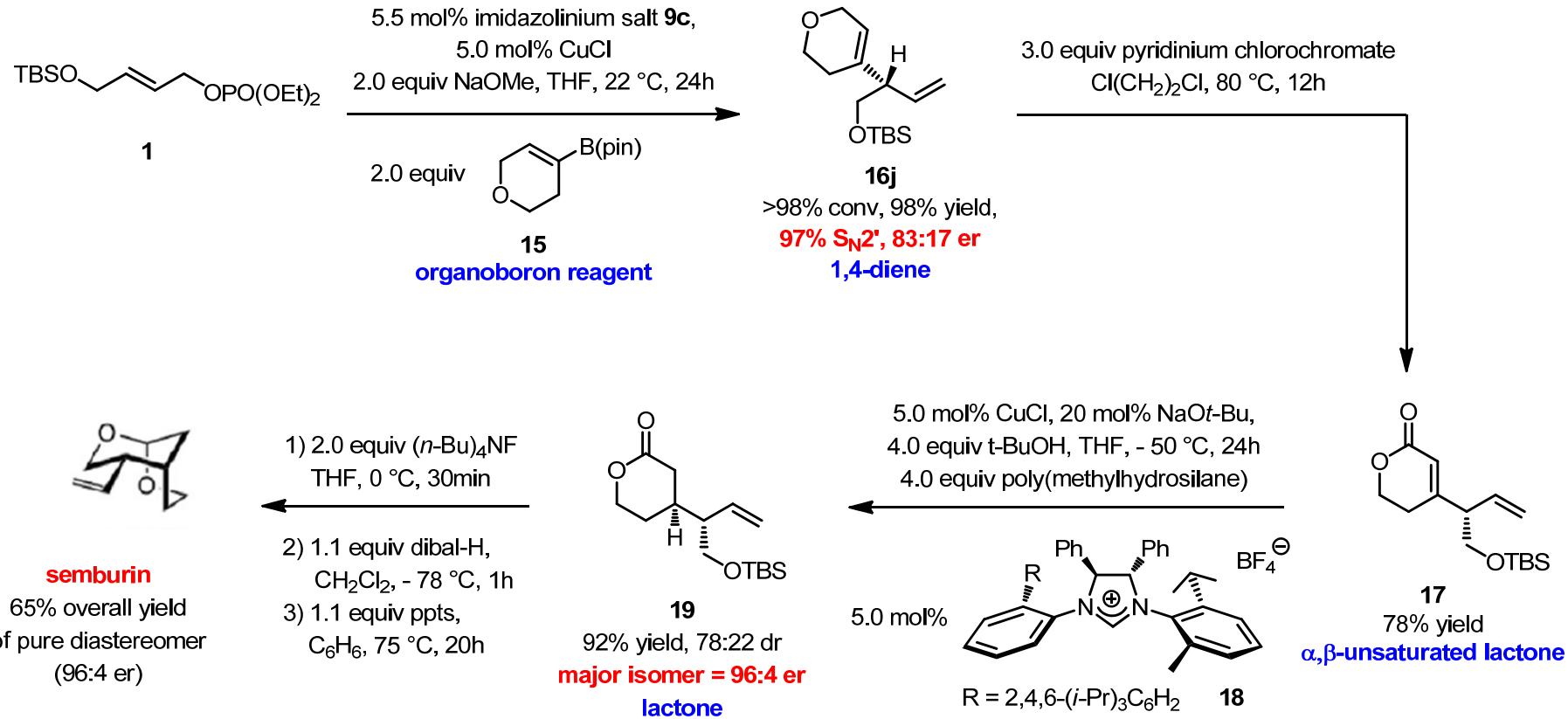
16h[b]
88% conv, 69% yield,
94% S_N2', 94:6 er



16i[b]
>98% conv, 81% yield,
>98% S_N2', 95:5 er

[a]Reaction performed at 60 °C. [b]Reaction performed at 60 °C with 2.5 mol% **9b** (for 16g and 16i) or **9c** (for 16h) and 25 mol% CuCl .

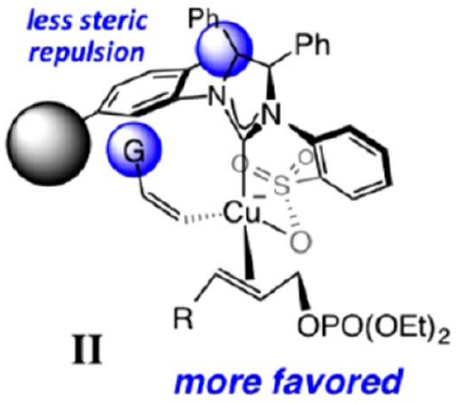
5. Application to Diastereo- and Enantioselective Synthesis of Semburin



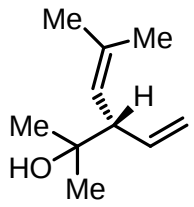
NHC-Cu-catalyzed stereoselective conjugate reduction

7. Conclusion

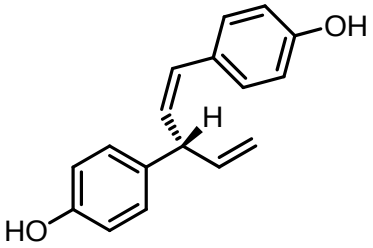
➢ A variety of robust alkenyl−(pinacolatoboron) [alkenyl−B(pin)] can be reacted with aryl- or alkyl-containing allylic electrophiles to afford enantiomerically enriched 1,4-dienes that contain a tertiary carbon stereogenic site using 5.0 mol% of a copper complex of an N-heterocyclic carbene (NHC).



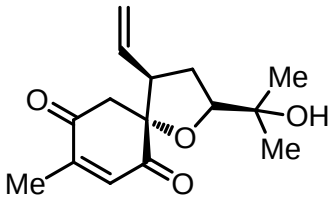
➢ Representative natural products can be synthesized through the NHC-Cu-catalyzed protocol .



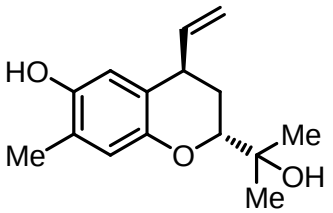
santolina alcohol



nyasol



heliespirone A



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