Quaternary stereocentres via an enantioconvergent catalytic SN1 reaction

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Wipf Group Current Literature
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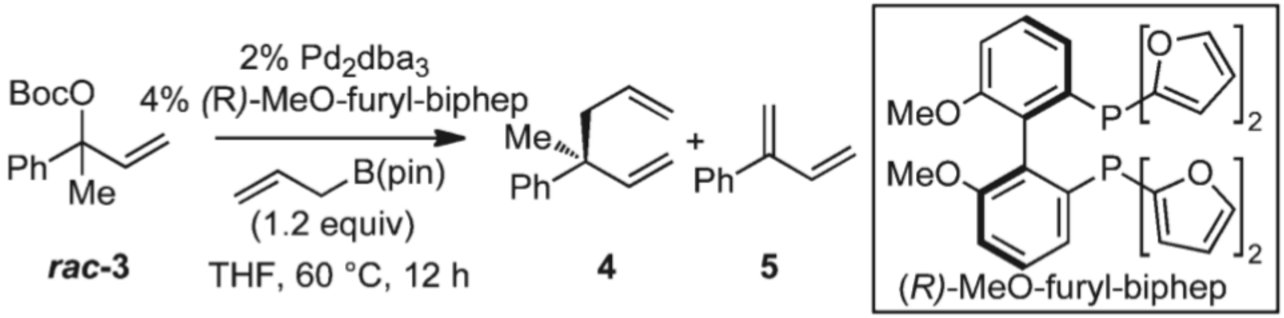
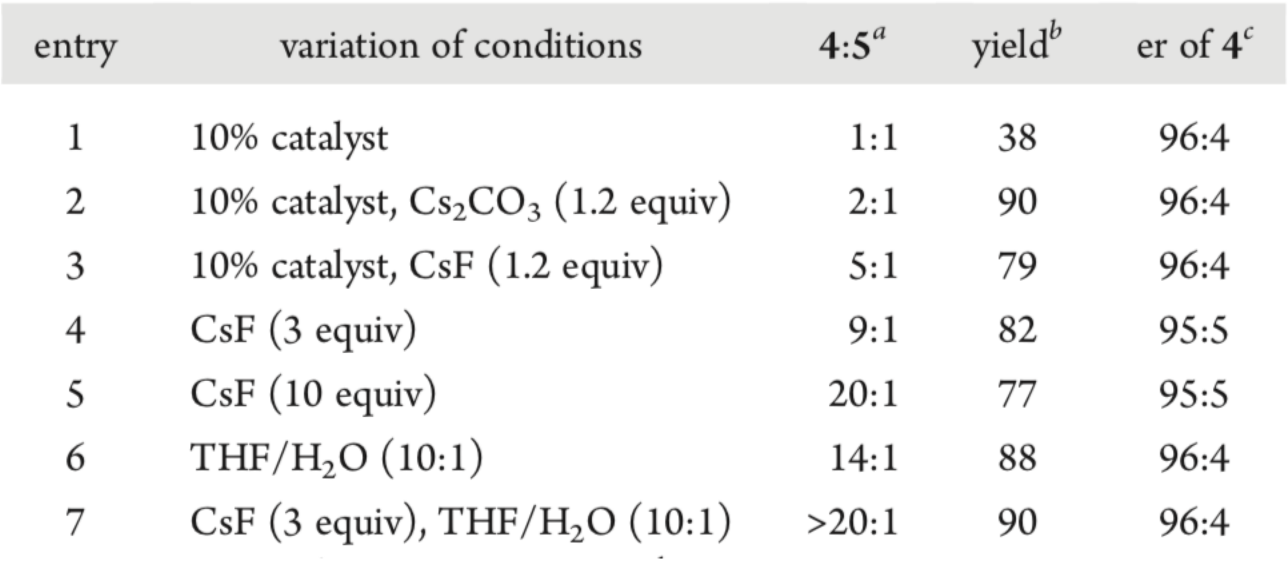
Quaternary Stereocenter

- ➢ Formation
- Carbonyl α-functionalization
- Alkene cross coupling
- Conjugate addition
- Rearrangement or Sn2’ reaction
- Cycloaddition
- ➢ Downsides: requires the preparation of stereochemically well-defined starting materials (such as trisubstituted olefins) and subsequent enantioselective bond formation

Previous Studies



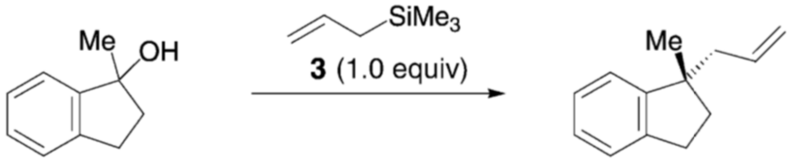
rac-3 **4** **5** (R)-MeO-furyl-biphep



entry	variation of conditions	**4**:**5**[a]	yield[b]	er of **4**[c]
1	10% catalyst	1:1	38	96:4
2	10% catalyst, Cs_2CO_3 (1.2 equiv)	2:1	90	96:4
3	10% catalyst, CsF (1.2 equiv)	5:1	79	96:4
4	CsF (3 equiv)	9:1	82	95:5
5	CsF (10 equiv)	20:1	77	95:5
6	THF/H_2O (10:1)	14:1	88	96:4
7	CsF (3 equiv), THF/H_2O (10:1)	>20:1	90	96:4

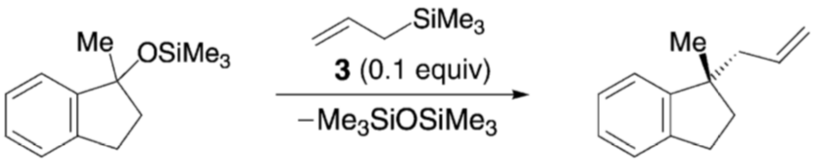
J. Am. Chem. Soc. 2011, 133, 9716–9719

Previous Studies



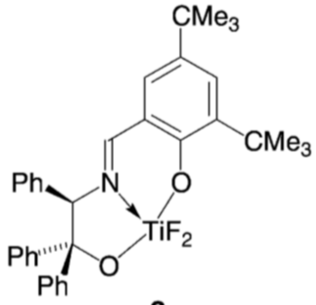
rac-**1a**

(*S*)-**2**
94% (81% *ee*)



rac-**1b**

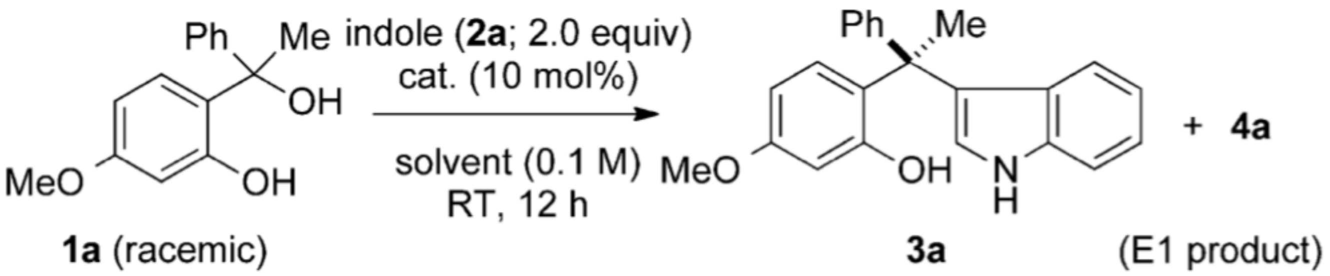
(*S*)-**2**
96% (98.9% *ee*)



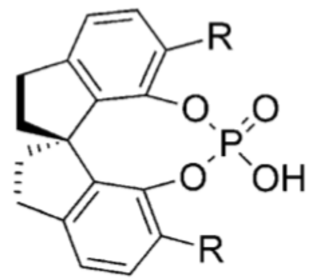
3

Angew. Chem. Int. Ed. 2004, 43, 514 –517

Previous Studies



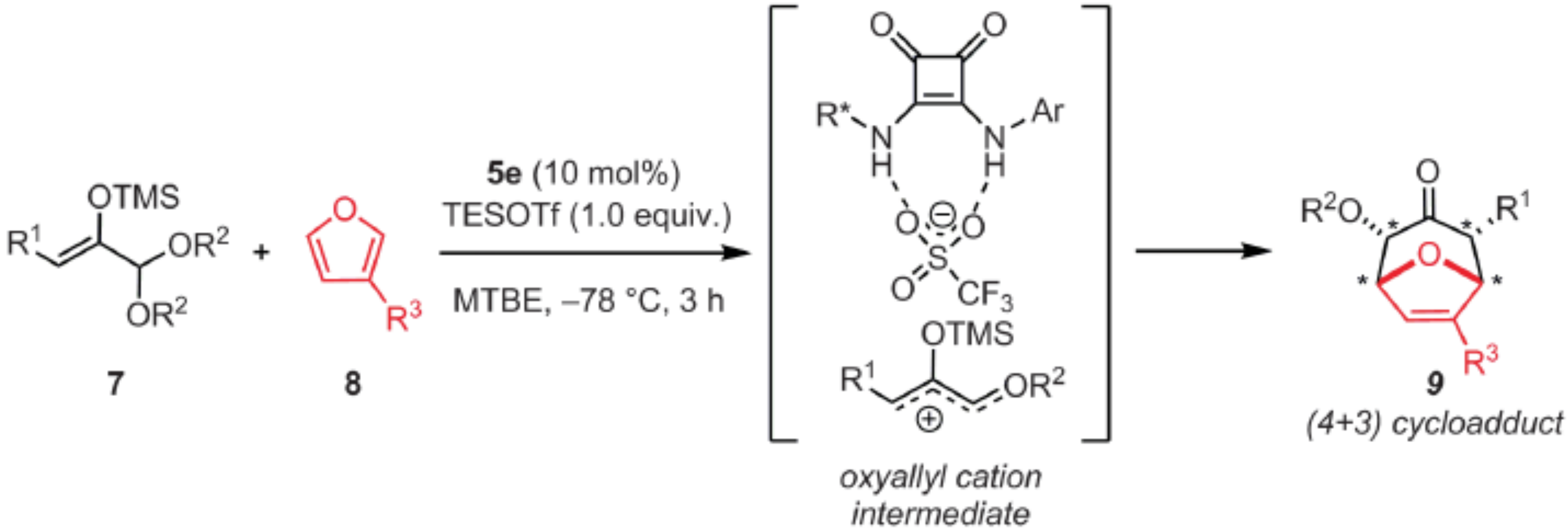
Entry	Cat.	Solvent	**3a**/**4a**[a]	**3a** Yield [%][a]	**3a** *ee* [%][b]
9	**B5**	CH_2Cl_2	> 20:1	87	80



(*R*)-**B5:** R = 9-phenanthryl

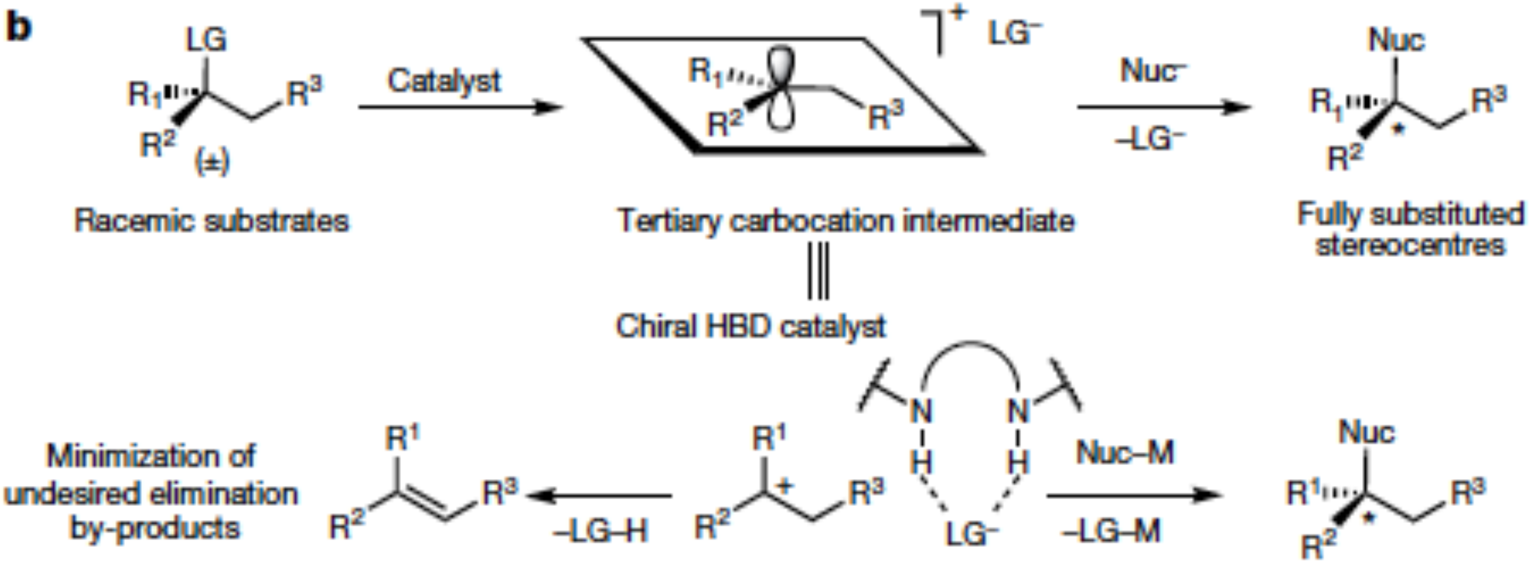
Angew. Chem. Int. Ed. 2015, 54, 1910 –1913

Lewis acid enhancement HBD for asymmetric catalysis



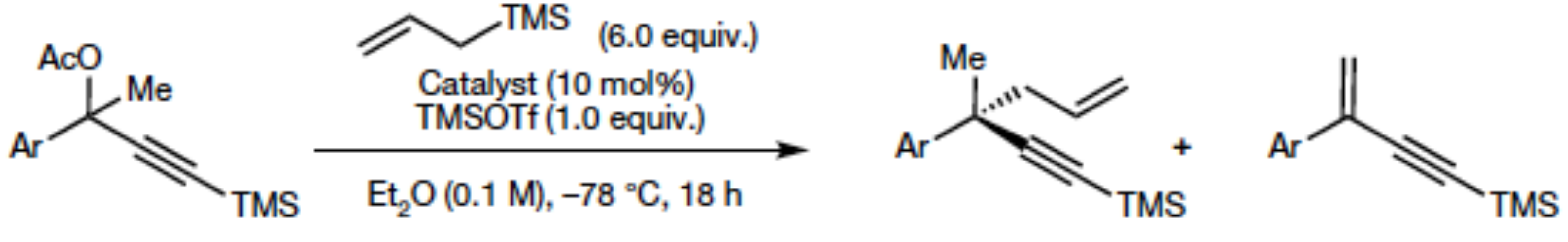
Banik et al., Science 358, 761–764 (2017)

Jacobsen’s approach from SN1 reaction



b, The SN1 approach to the construction of quaternary stereocentres described here. c, Enantioselective allylation of propargyl acetates using chiral squaramide catalysts and TMSOTf as a promoter. LG, leaving group; Np, naphthyl; TMS, trimethylsilyl.

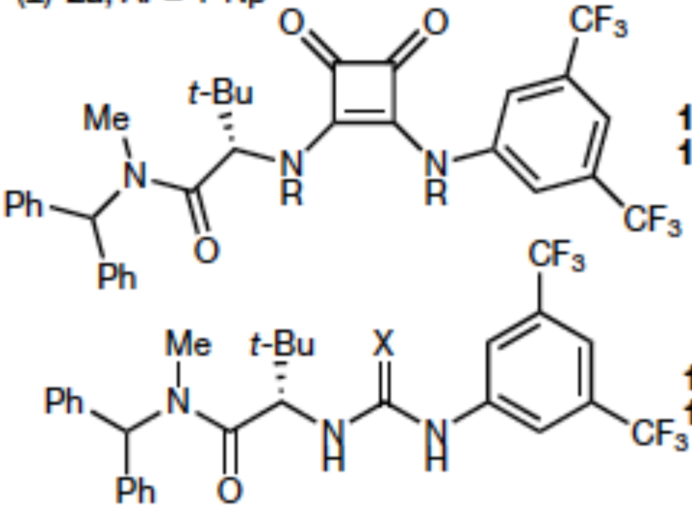
Reaction Optimation



(±)-**2a**, Ar = 1-Np

3a

4a

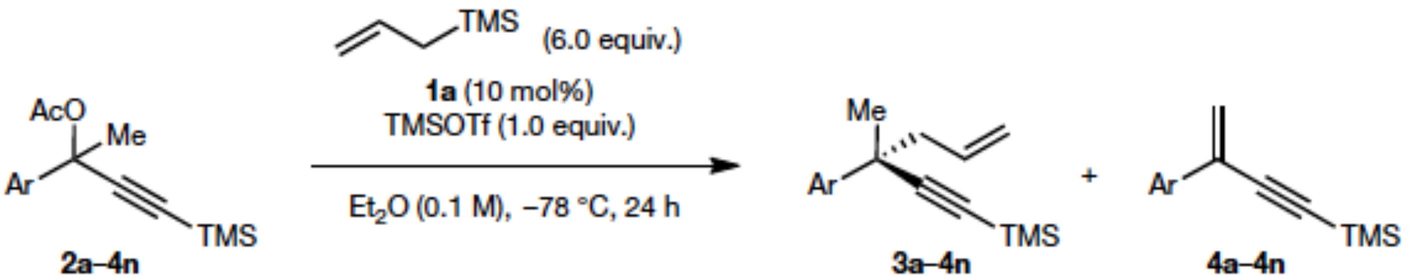


1a: R = H
1b: R = Me

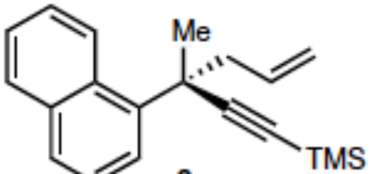
1c: X = S
1d: X = O

Entry	Catalyst	**3a**:**4a**	e.e. **3a** (%)
1	None	1:1	0
2	**1a**	40:1	91
3	**1b**	3.4:1	1
4	**1c**	2.9:1	20
5	**1d**	3.3:1	–3

Substrate Scope

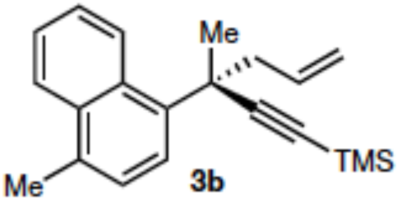


Substituent effects



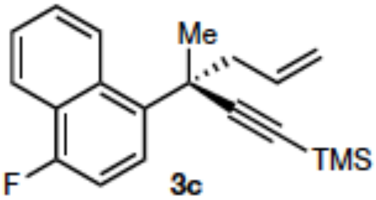
3a

95%, 91% e.e.
40:1 (**3a**:**4a**)



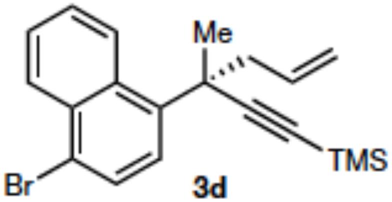
3b

91%[a], 94% e.e.
40:1 (**3b**:**4b**)



3c

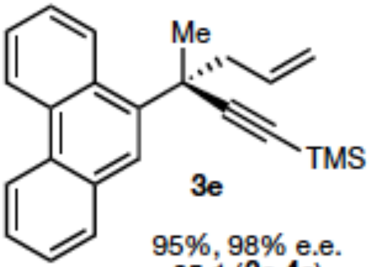
91%, 93% e.e.
40:1 (**3c**:**4c**)



3d

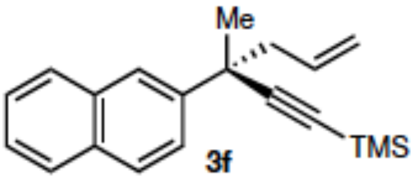
82%[b], 91% e.e.
30:1 (**3d**:**4d**)

Polarizability of aromatic ring



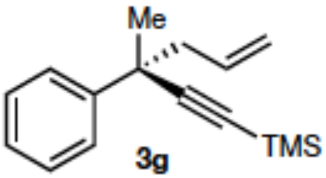
3e

95%, 98% e.e.
85:1 (**3e**:**4e**)



3f

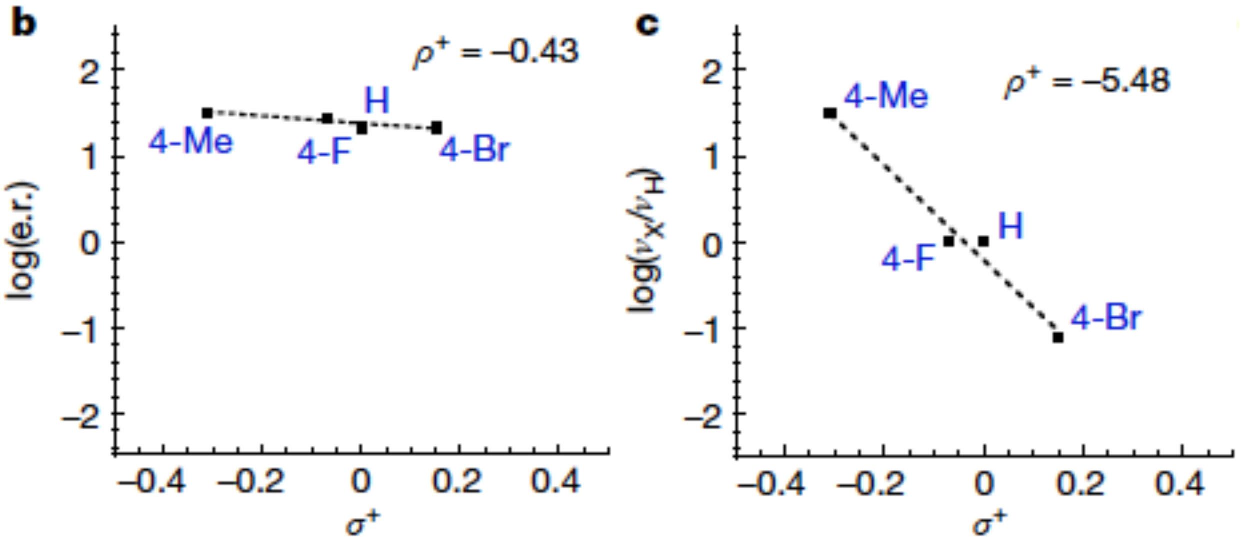
74%, 86% e.e.
70:1 (**3f**:**4f**)



3g

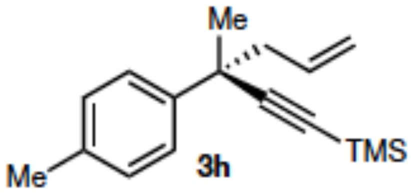
71%[c], 60% e.e.
3.3:1 (**3g**:**4g**)

SN1-type ionization mechanism



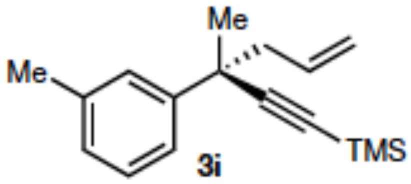
Substrate Scope

Steric effects



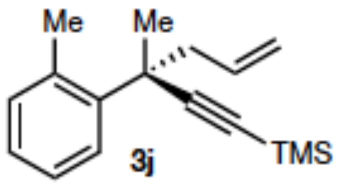
3h

40%^{c}, 66% e.e.
6.9:1 (**3h**:**4h**)



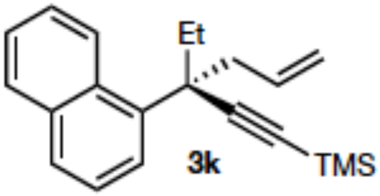
3i

58%^{c}, 67% e.e.
3.2:1 (**3i**:**4i**)



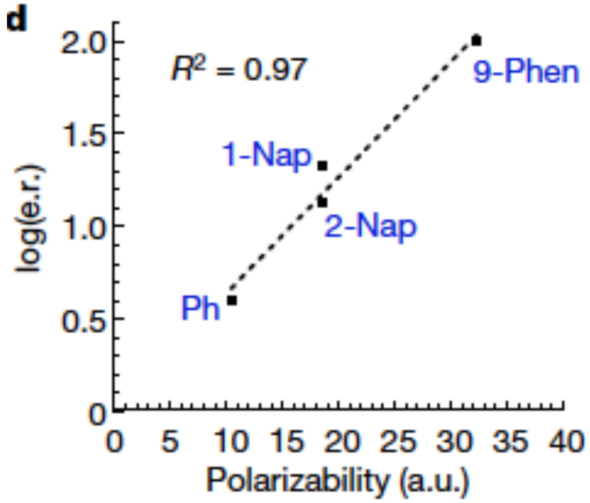
3j

78%^{c}, 82% e.e.
5.0:1 (**3j**:**4j**)



3k

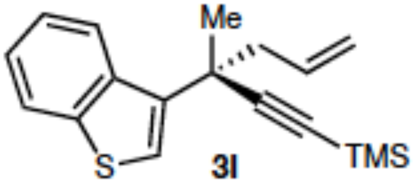
64%^{c}, 94% e.e.
2.3:1 (**3k**:**4k**)



- stabilizing aromatic interactions are likely to serve as a contri-buting factor in enantiodifferentiation
- Steric congestion near the reaction site also correlates with enantioselectivity.

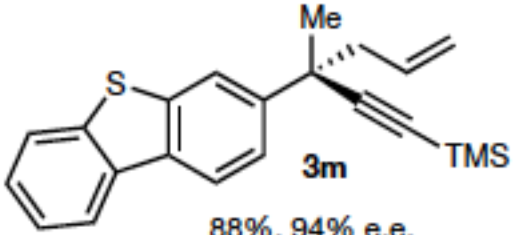
Substrate Scope

Heterocyclic substrates



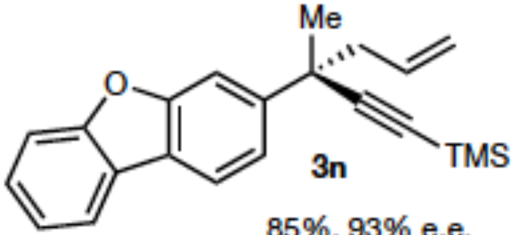
3l

95%, 92% e.e.
>100:1 (**3l**:**4l**)



3m

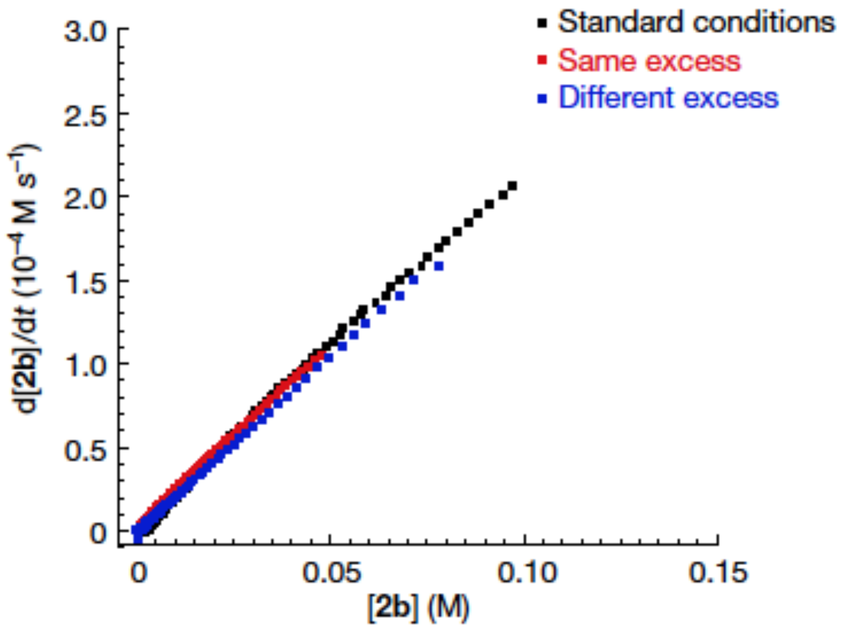
88%, 94% e.e.
>100:1 (**3m**:**4m**)



3n

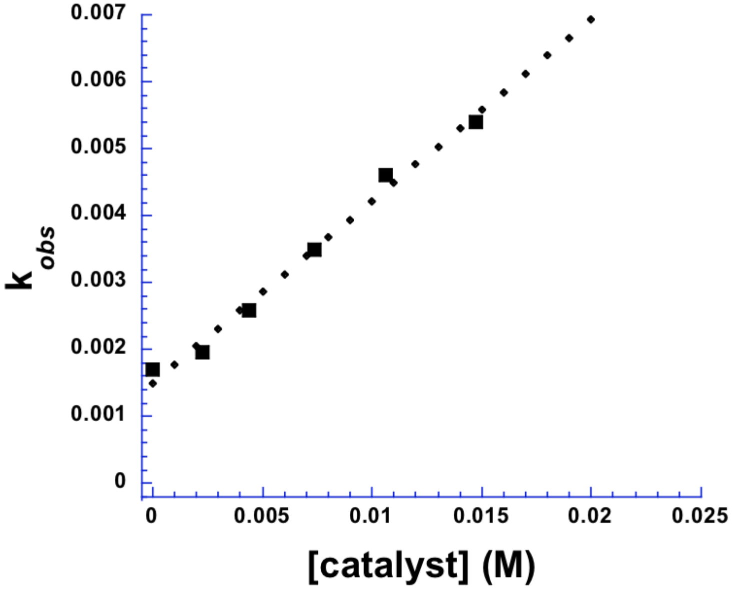
85%, 93% e.e.
>100:1 (**3n**:**4n**)

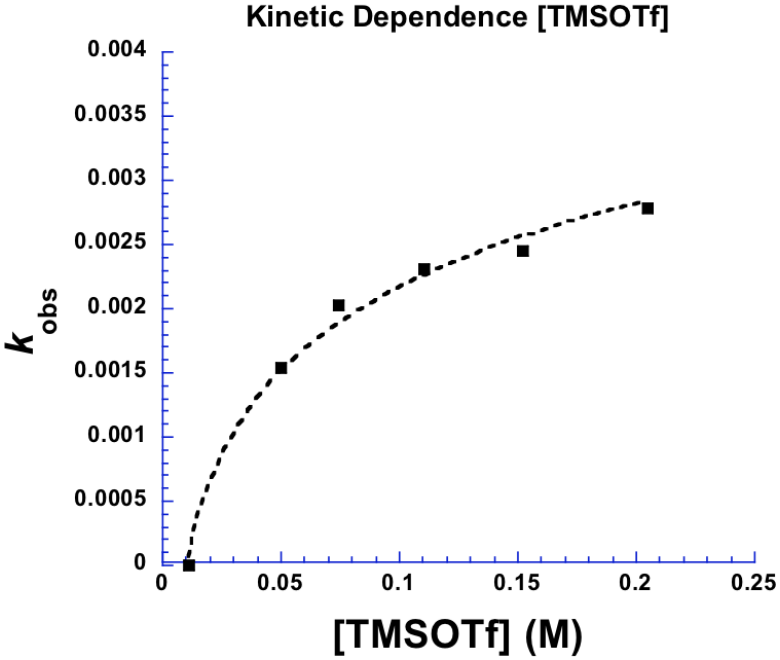
Mechanistic studies



- Monitoring disappearance of **2b** using in situ infrared spectroscopy reaction obeys a first-order rate
- Reaction hasdependence on the concentration of **2b** and has no rate dependence on the concentration of allyltrimethylsilane

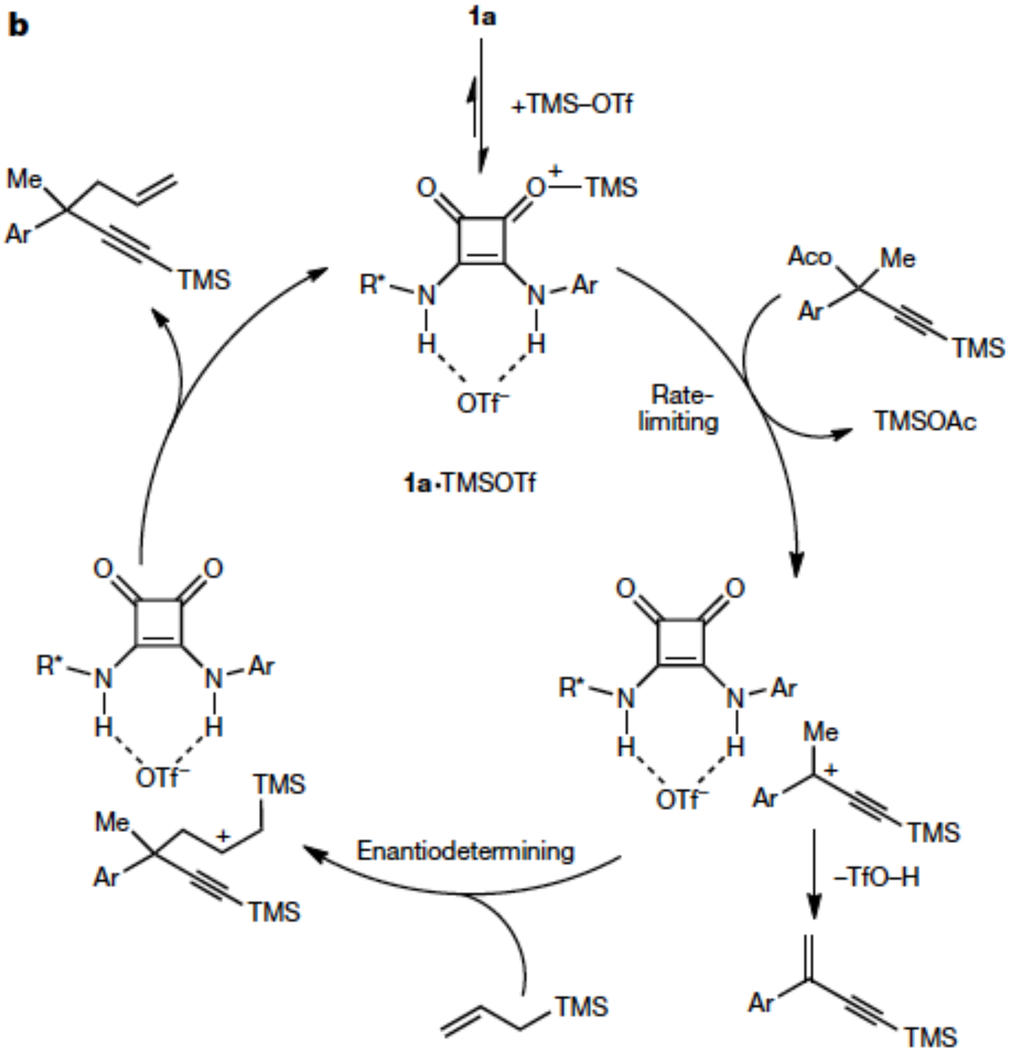
Mechanistic studies



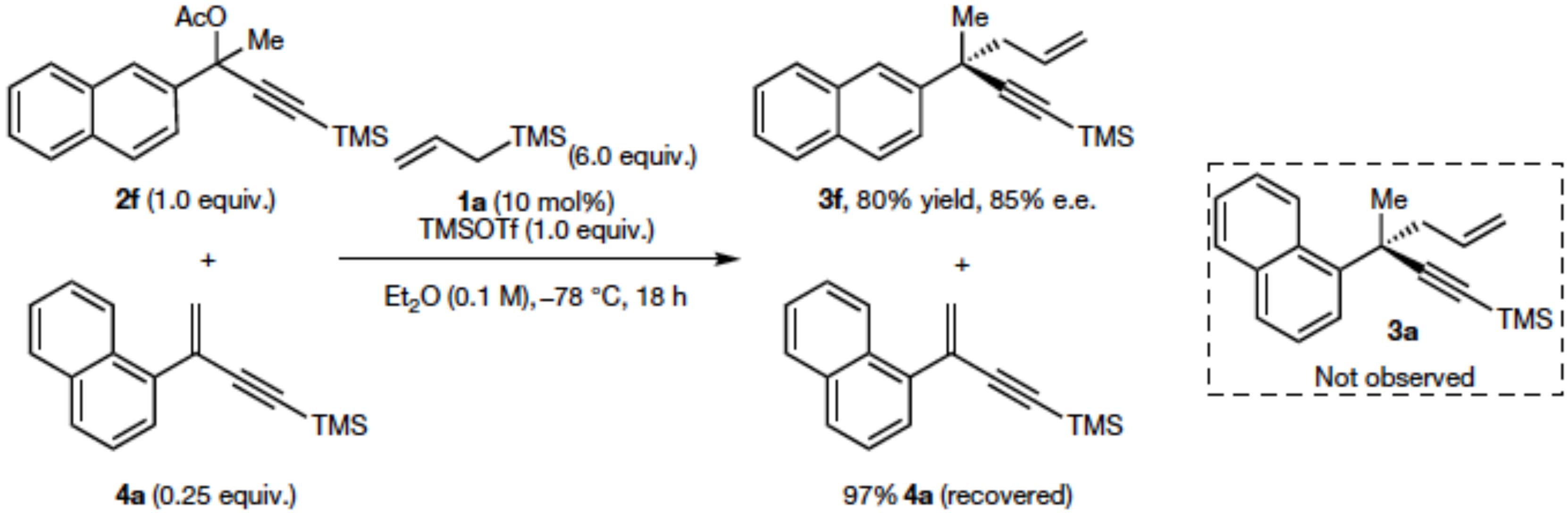


sub-first-order dependence of the reaction rate on the concentration of TMSOTf, and a first-order dependence of the reaction rate on the concentration of **1a**

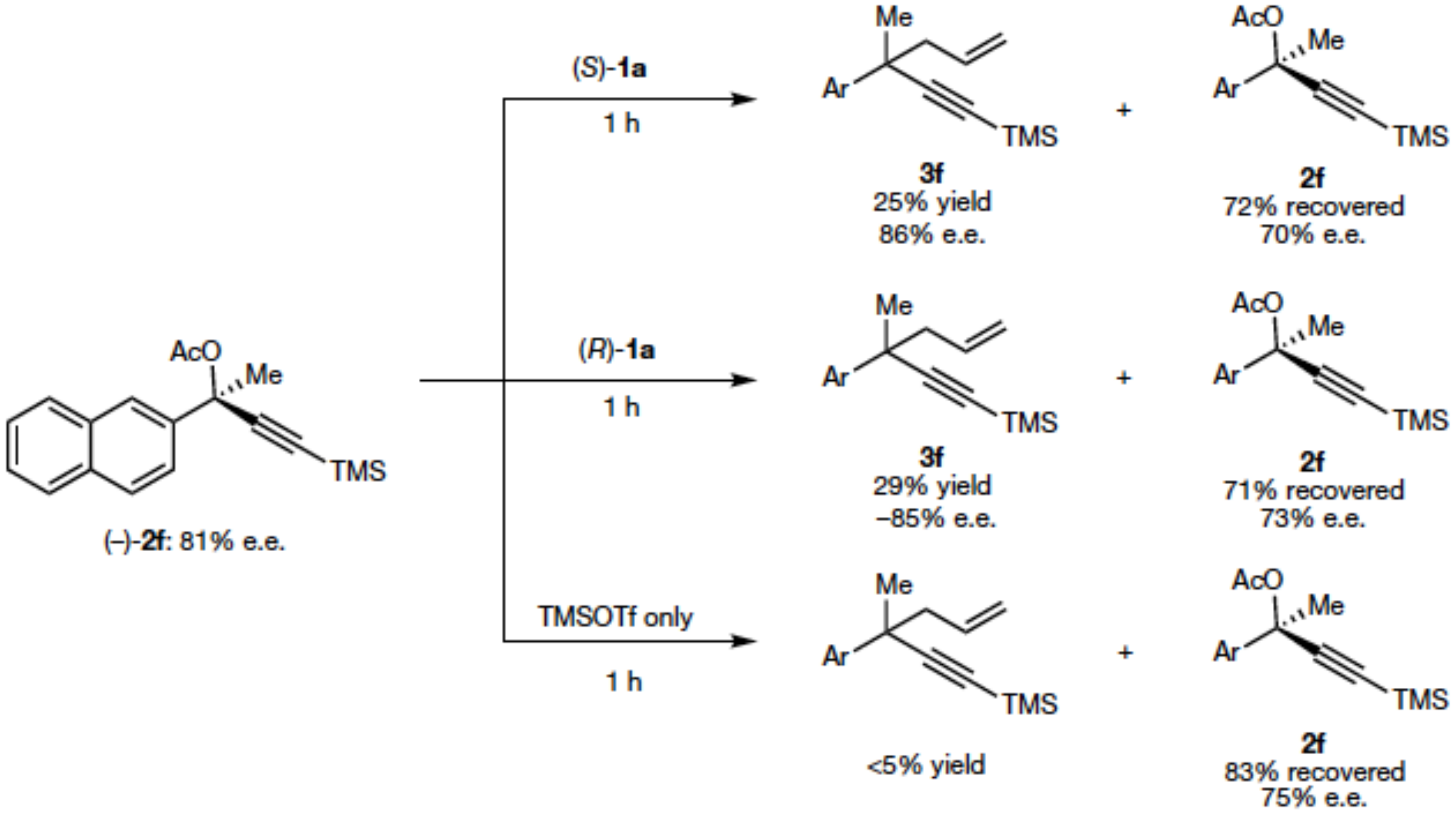
Proposed catalytic mechanism



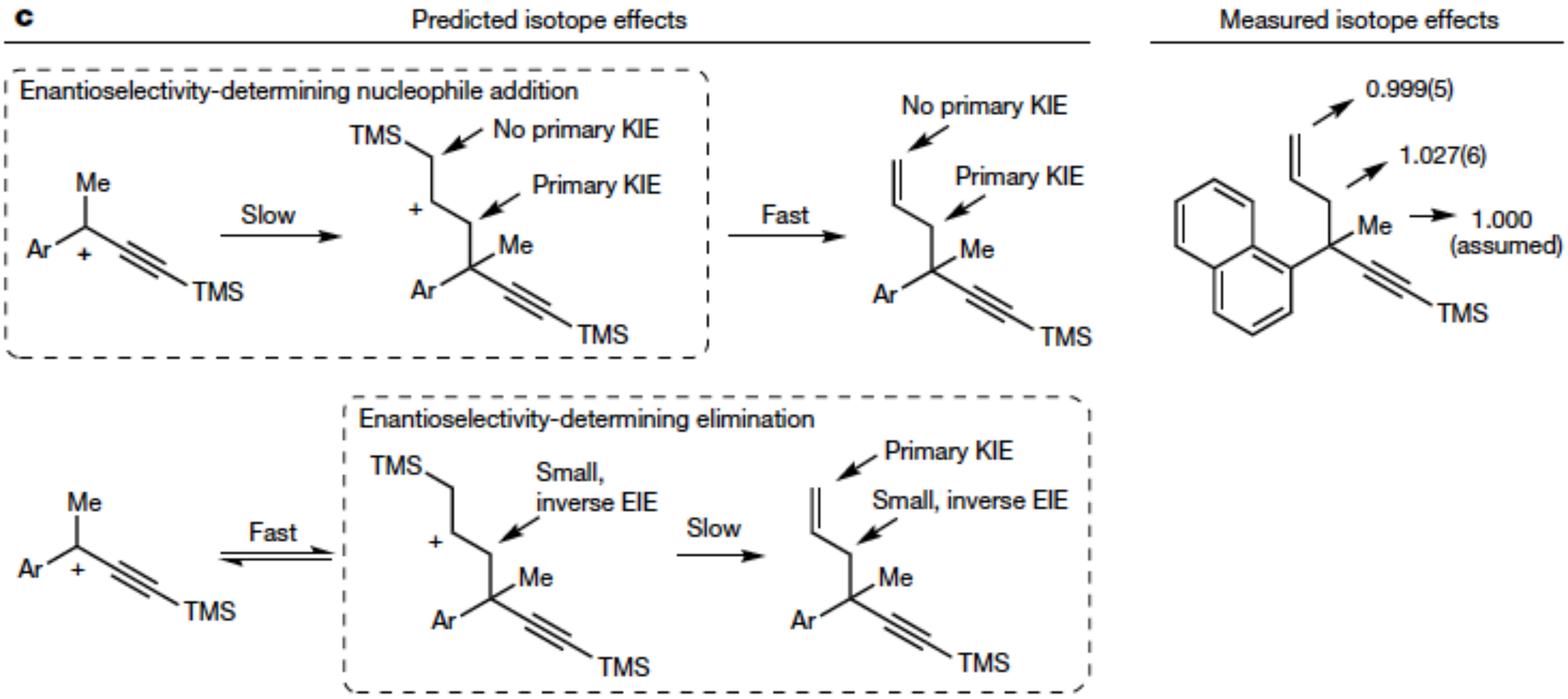
Elimination by-product was irreversible



Enantioselective



Enantiodetermining Step



the first C–C bond-forming step is irreversible and therefore enantiodetermining.

Conclusion

- Cooperative effect of chiral squaramides and TMSOTf generates tertiary carbocations that lack heteroatom stabilization from racemic precursors
- Controls enantioselectivity in additions of a carbon-centred nucleophile, and attenuates undesired elimination pathways.