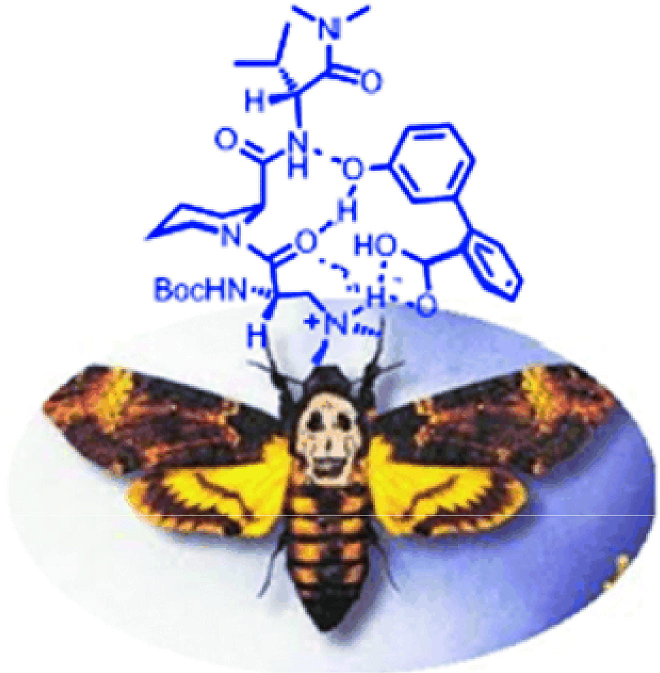


Science 2010, *328*, 1251

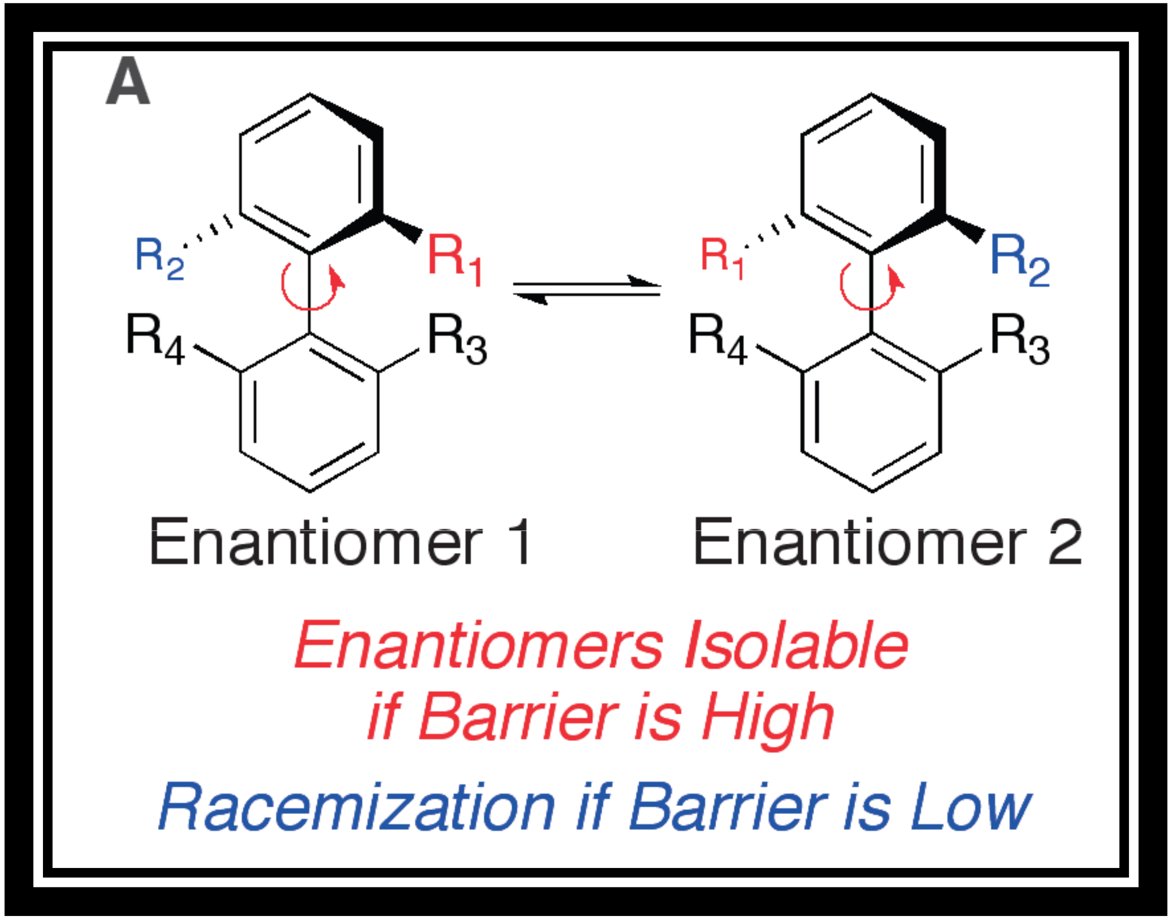
RCC- Kishor Mohanan

Dynamic Kinetic Resolution of Biaryl Atropisomers via Peptide-Catalyzed Asymmetric Bromination

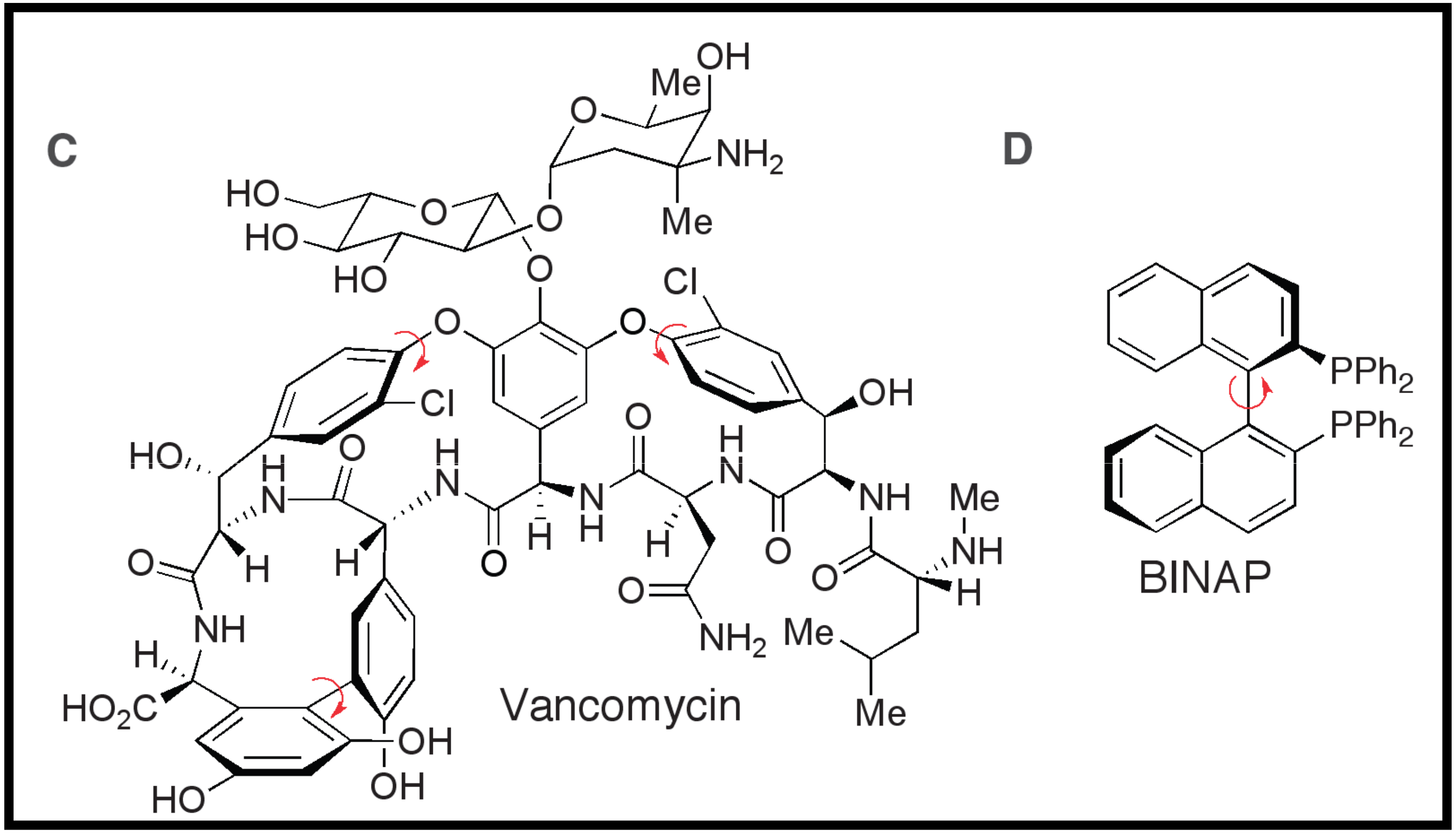
Scott J. Miller and co-workers
Yale University

Highlighted in Angew. Chem. Int. Ed. 2011, *50, early view*

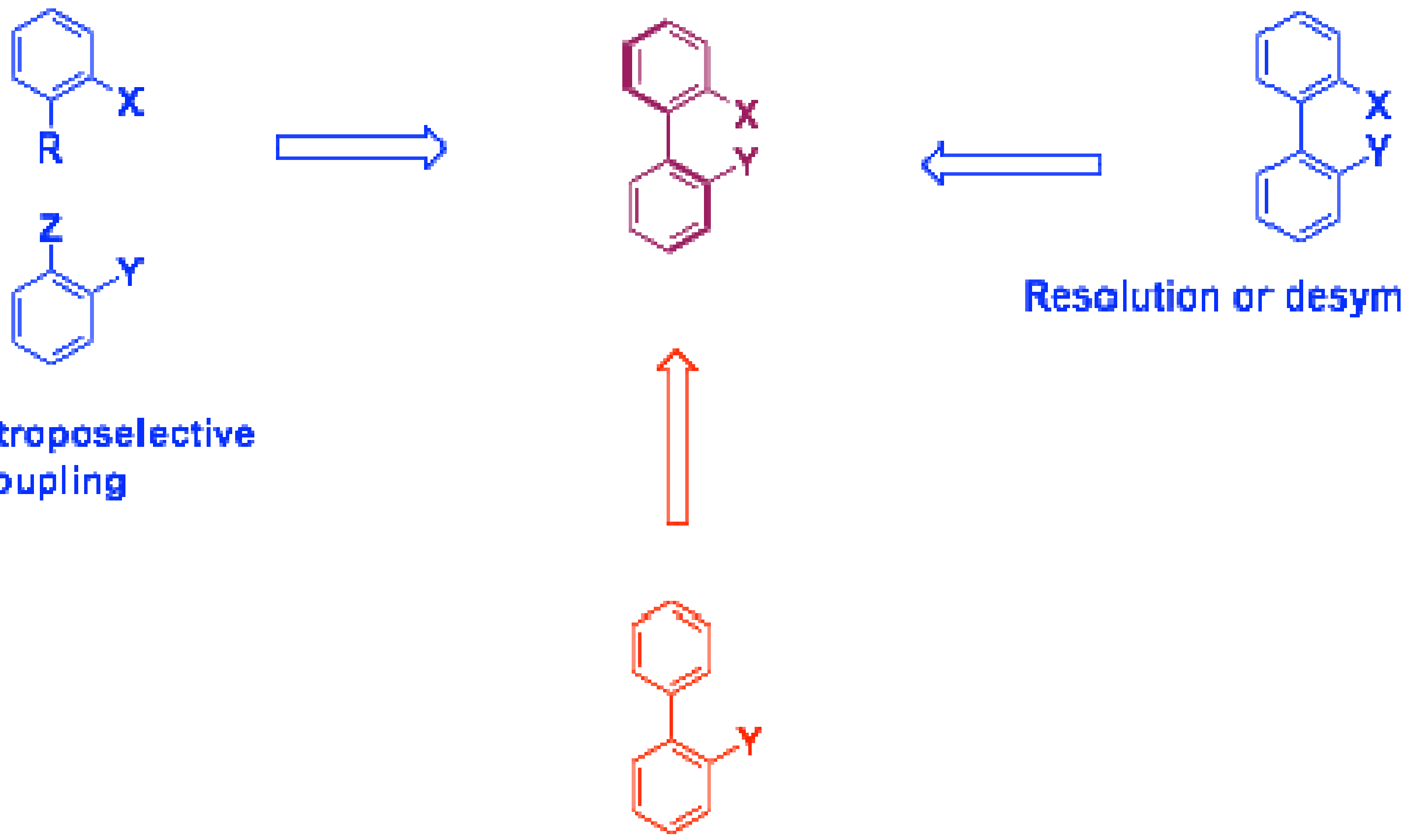
Atropisomers…



Atropisomers *are stereoisomers resulting from hindered rotation about single bonds where the steric strain barrier to rotation is high enough to allow for the isolation of the conformers*


C
D
Vancomycin
BINAP
PPh2
PPh2

Atroposelective reactions..

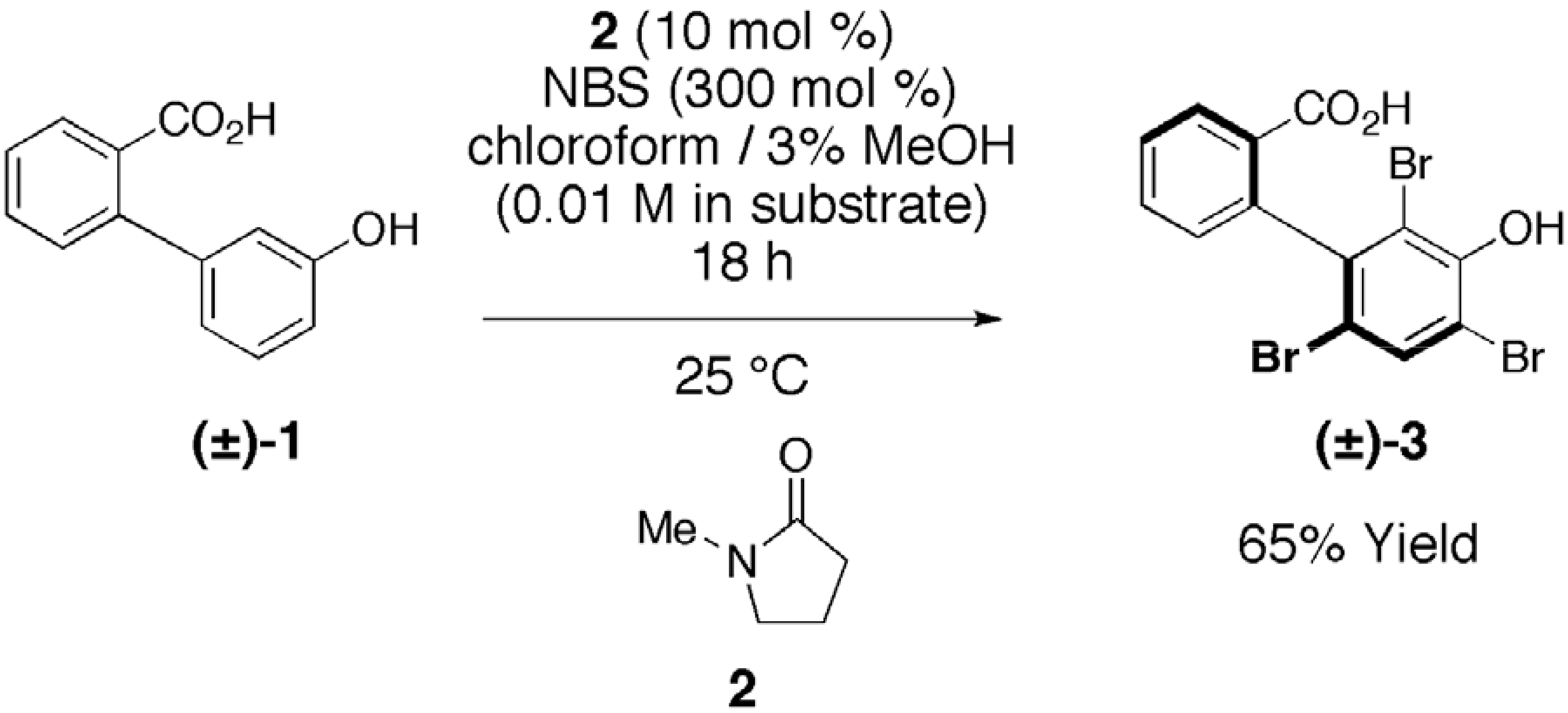


Atroposelective coupling

Resolution or desymmetrization

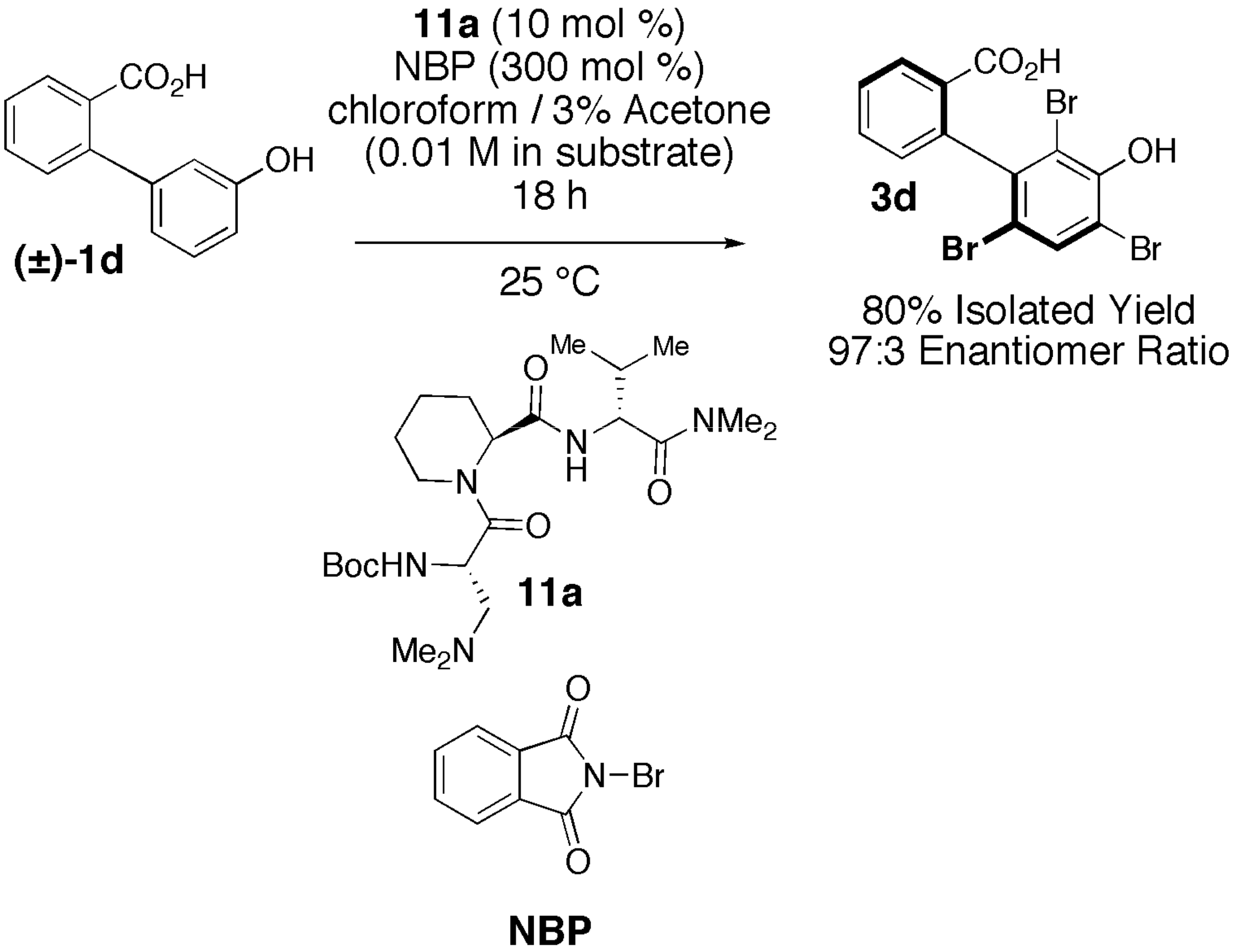
Atroposelective biaryl formation

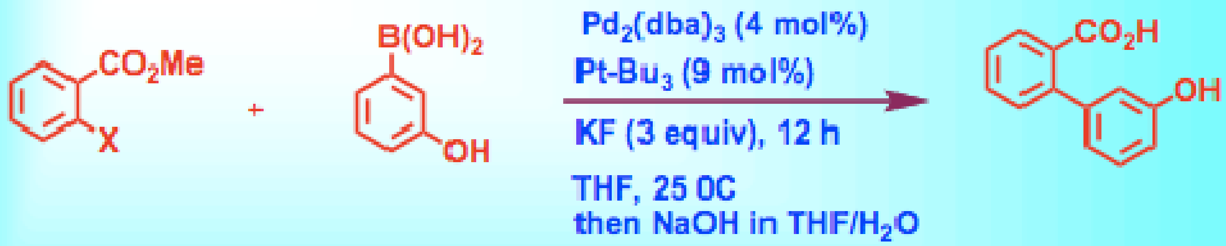
The present reaction



7 kcal/mol ← **Rotation energy barrier** → ***30 kcal/mol***

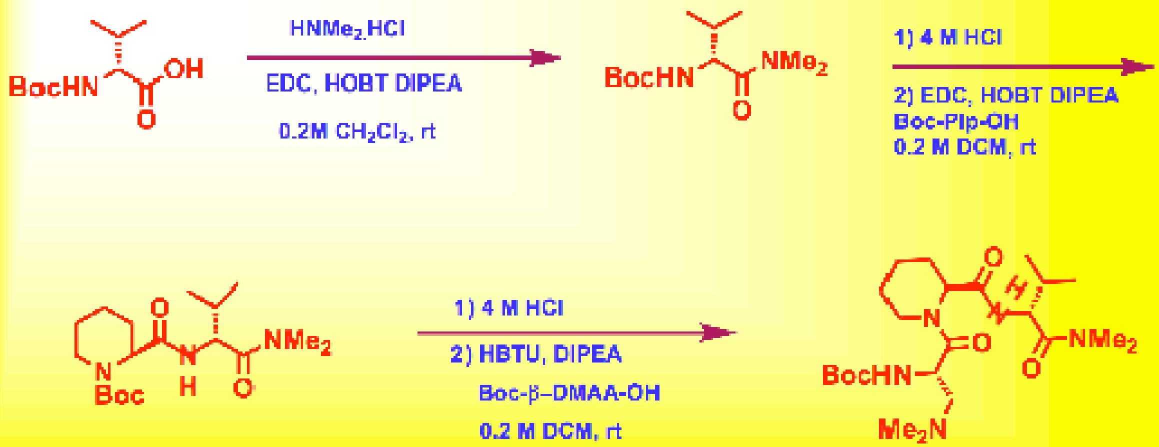
The present reaction

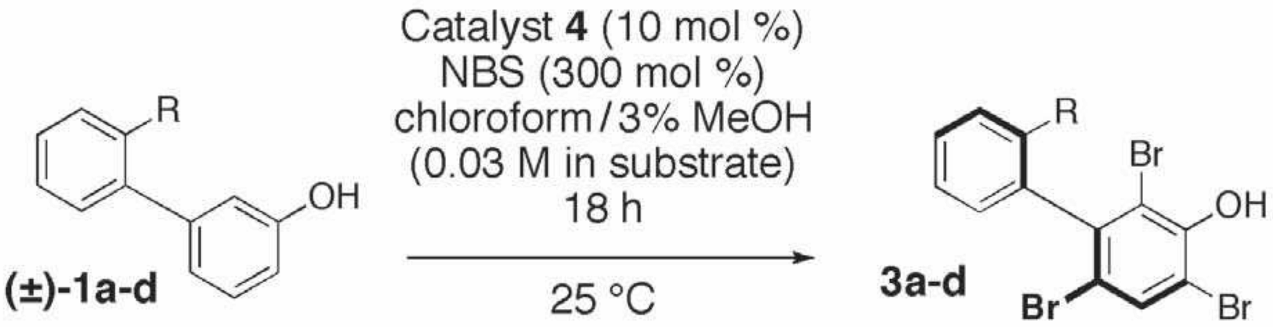




Synthesis of starting material

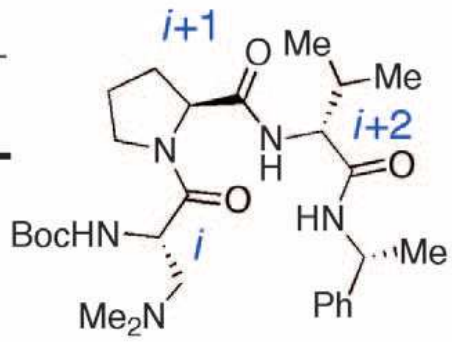
Catalyst synthesis





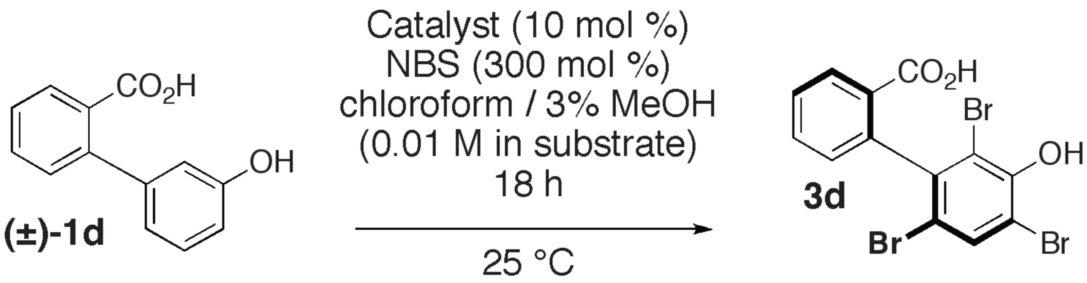
Entry	R	Yield (%)	Enantiomer Ratio (E.r.)*
1	CO_2Me (**1a**)	80	57.5:42.5
2	CONHBn (**1b**)	80	65.0: 35.0
3	NO_2 (**1c**)	80	52.0: 48.0
4	CO_2H (**1d**)	90	75.0: 25.0

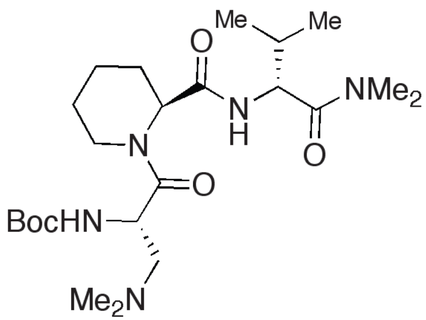
*The major atropisomer of **3d** was assigned to the *R*-configuration by X-ray analysis.



Catalyst **4**

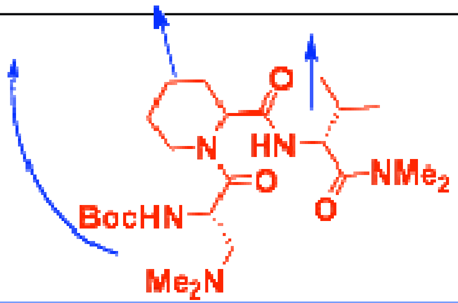
Catalyst screening…



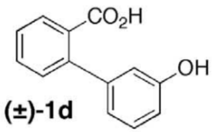
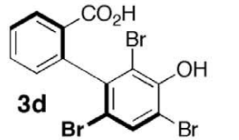
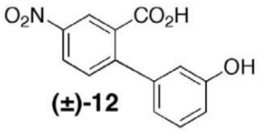
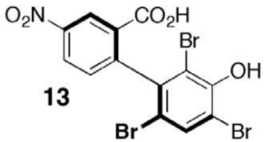
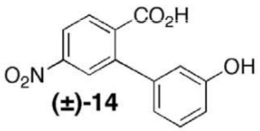
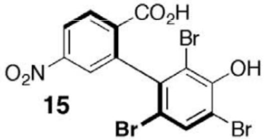
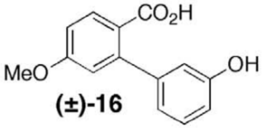
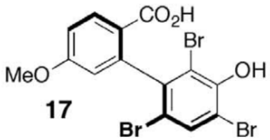
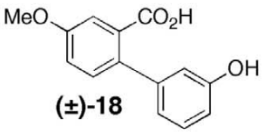
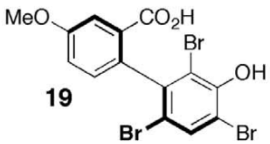
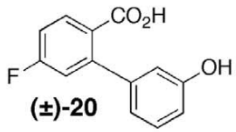
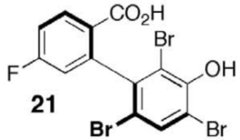
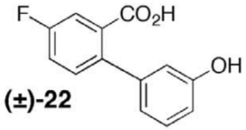
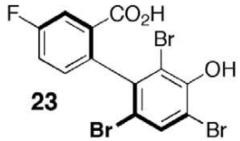
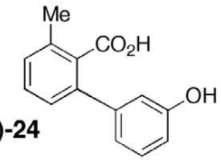
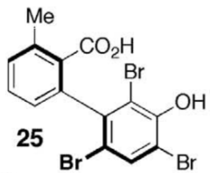
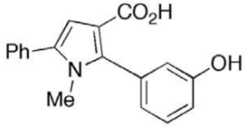
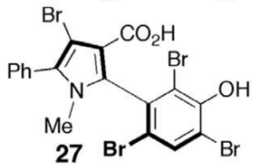
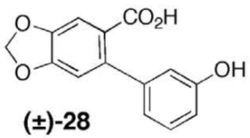


Lead Catalyst
11a

Entry	Catalyst	Yield (%)	E.r.
1	Boc-β-Dmaa-Pro-(D)Val-(*R*)-αMba (**4**)	90	75.0:25.0
2	Boc-β-Dmaa-Pip-(D)Val-(*R*)-αMba (**5**)	87	90.0:10.0
3	Boc-β-Dmaa-Pip-(D)Phe-(*R*)-αMba (**6**)	73	86.5:13.5
4	Boc–β-Dmaa-Pip-(D)Tle-(*R*)-αMba (**7**)	85	89.0:11.0
5	Boc-β-Dmaa-Pip-(D)Ile-(*R*)-αMba (**8**)	65	82.5:17.5
6	Boc-β-Dmaa-Pip-(L)Val-(*R*)-αMba (**9**)	95	75.0:25.0
7	Boc-β-Dmaa-Pip-(D)Val-(*S*)-αMba (**10**)	80	75.0:25.0
8	Boc-β-Dmaa-Pip-(D)Val-NMe_2 (**11a**)	90	**92.0:8.0**
9	Boc-β-Dmaa-Pip-(D)Val-OMe (**11b**)	90	65.0:35.0

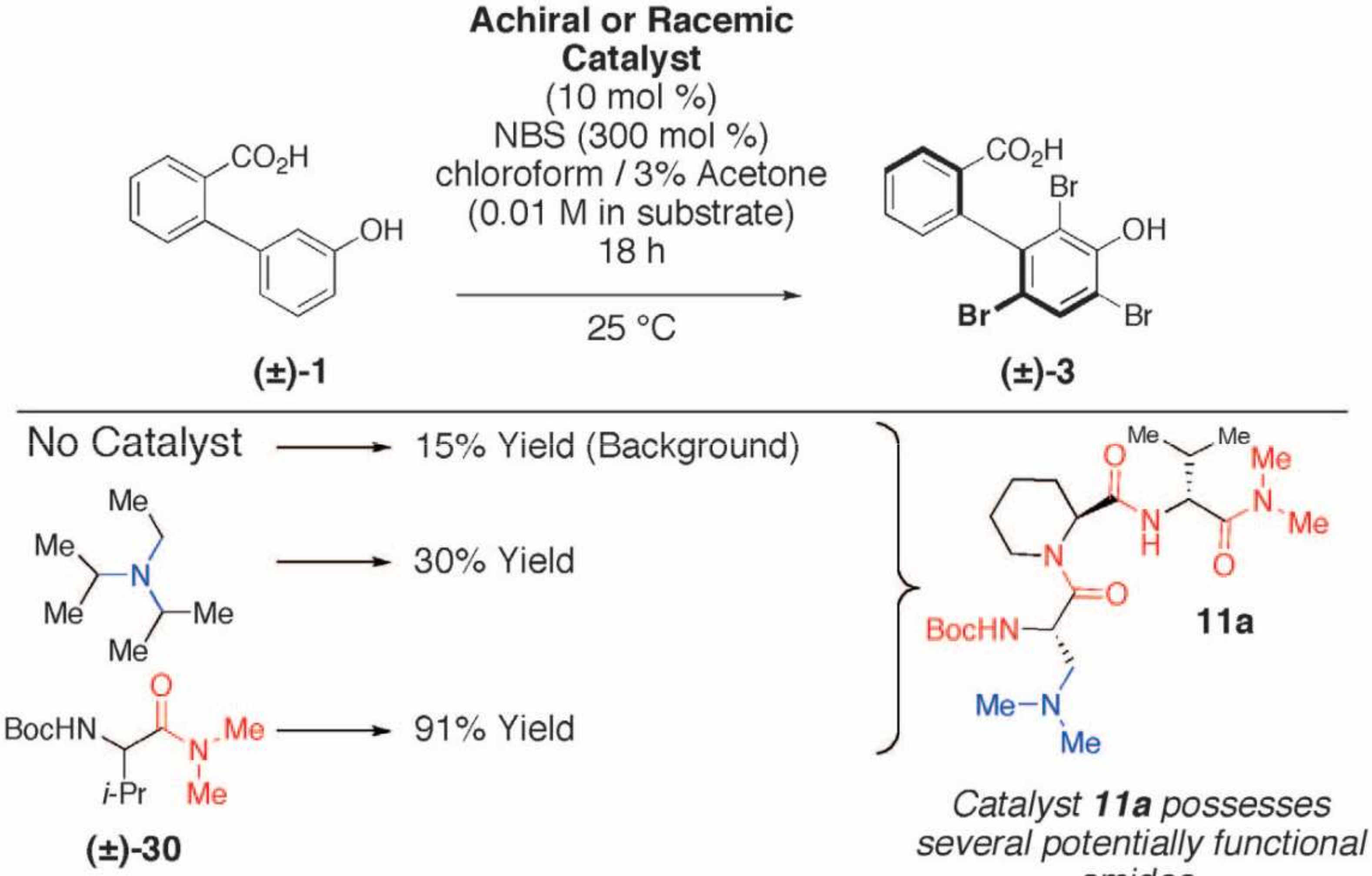


Substrate scope…

Entry	Racemic Starting Material	Product	Yield (%)	E.r.
1	 (±)-1d	 3d	80	97.0:3.0
2	 (±)-12	 13	85	97.0:3.0
3	 (±)-14	 15	75	96.5:3.5
4	 (±)-16	 17	70	96.0:4.0
5	 (±)-18	 19	80	94.0:6.0
6	 (±)-20	 21	70	97.0:3.0
7	 (±)-22	 23	65	96.5:3.5
8	 (±)-24	 25	85	87.0:13.0
9	 (±)-26	 27	77*	85.0:15.0
10	 (±)-28	 29	70	95.0:5.0

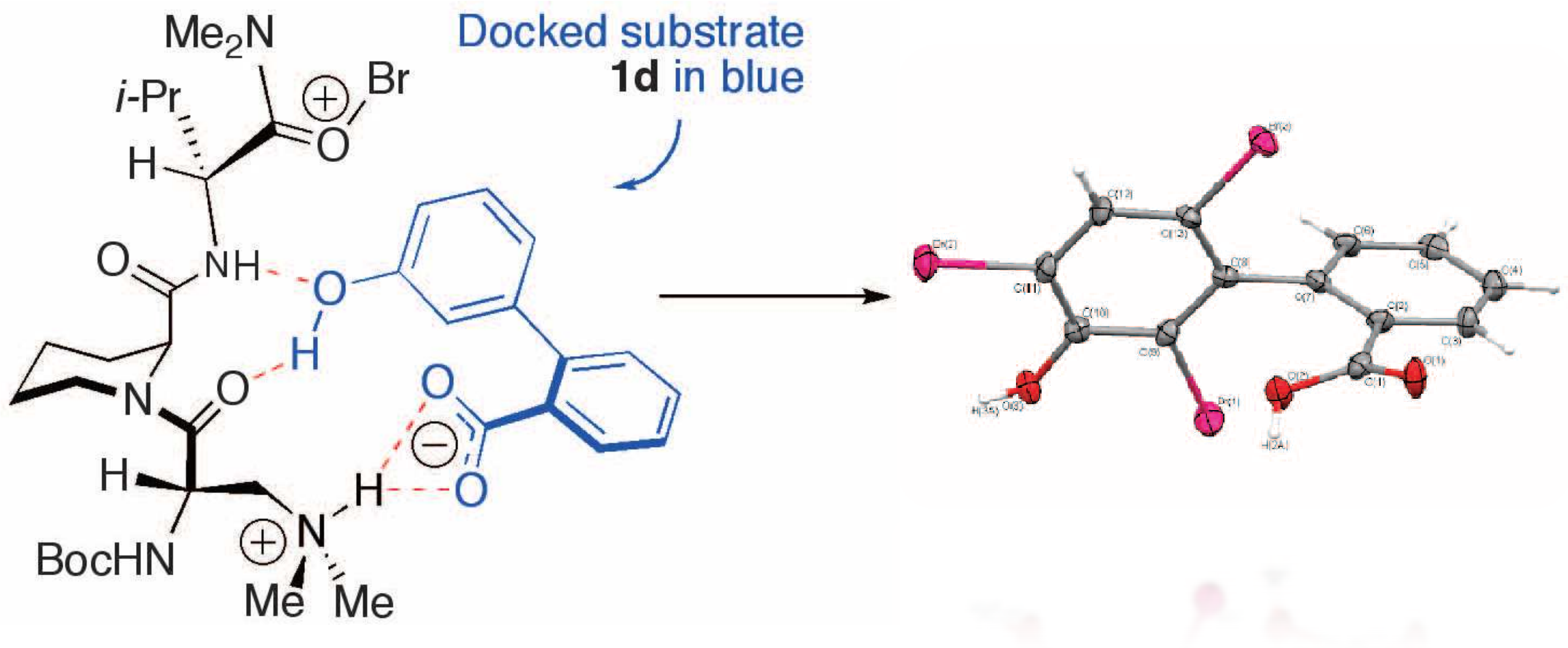
* 400 mol % of NBP.

Mechanistic rationale



*Catalyst **11a** possesses several potentially functional amides.*

Proposed intermediate..



Synthesis of optically enriched biaryls using enantioselective catalysts may enable improved access to the atropisomeric materials. This approach may also stimulate research involving interconverting axially chiral compounds.