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Asymmetric Catalysis

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Kinetic Resolution of Tertiary Alcohols: Highly Enantioselective Access to 3-Hydroxy-3-Substituted Oxindoles**

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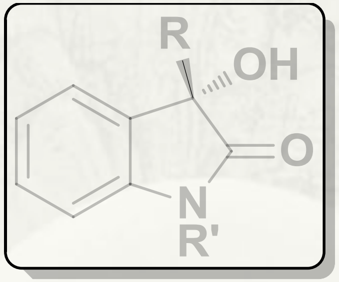
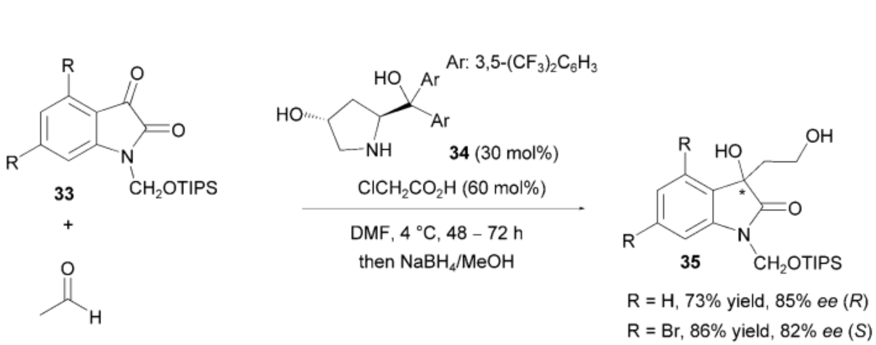
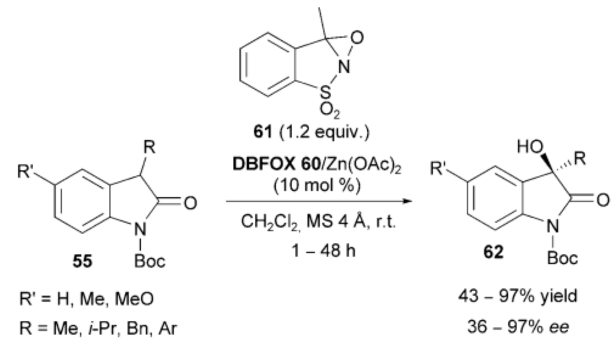


Angew.Chem.Int.Ed. **2013**, *52*,1–5

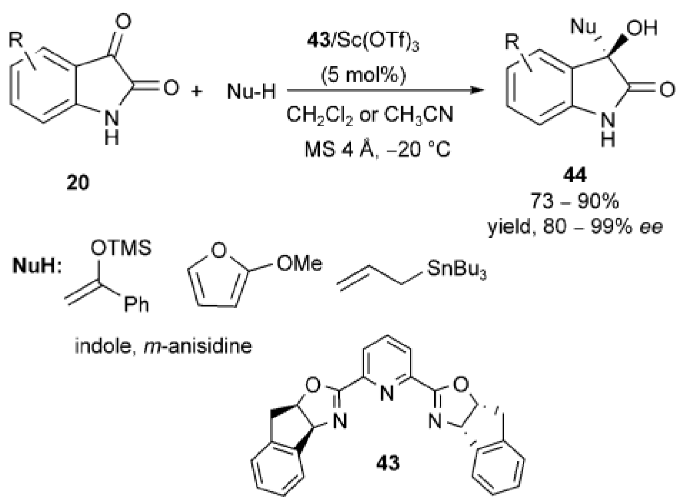
Existing methods of getting asymmetric 3-hydroxy-3-substituted oxindoles



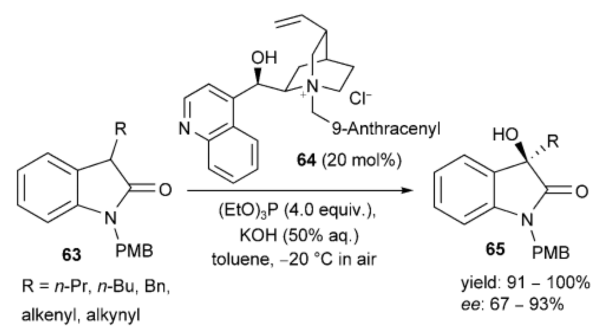
Org.Lett. **2009**, 3854–3857.



J.Am.Chem.Soc. **2006**, 16488–16489

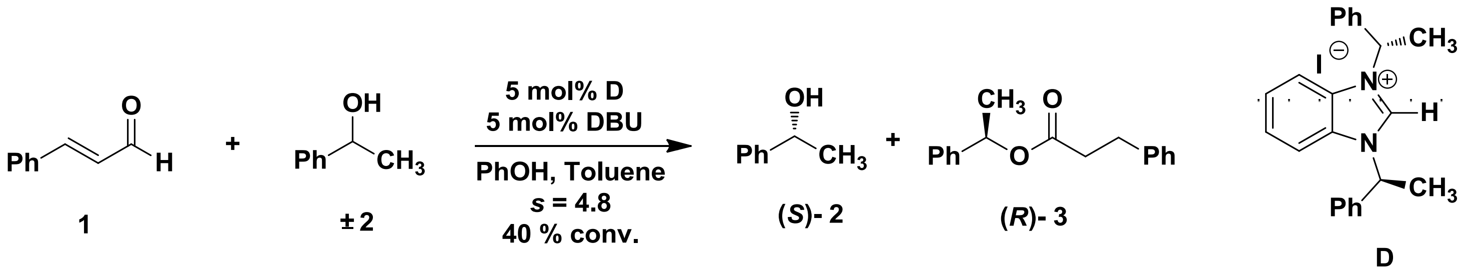


Angew.Chem.Int.Ed. **2010,** *49*,744-747.

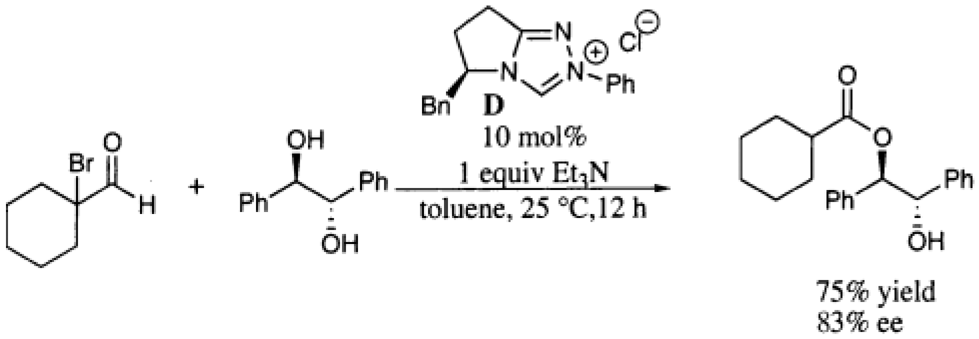


Org.Lett. **2008**, 1593–1595

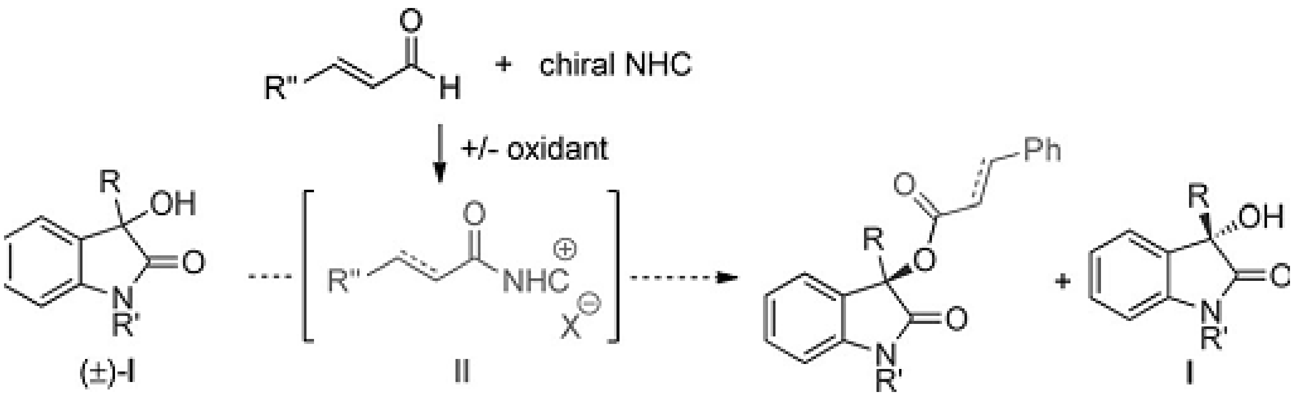
Chiral NHCs as catalyst induce asymmetric induction of secondary alcohols



Org.Lett. **2005**, *7*,905–908

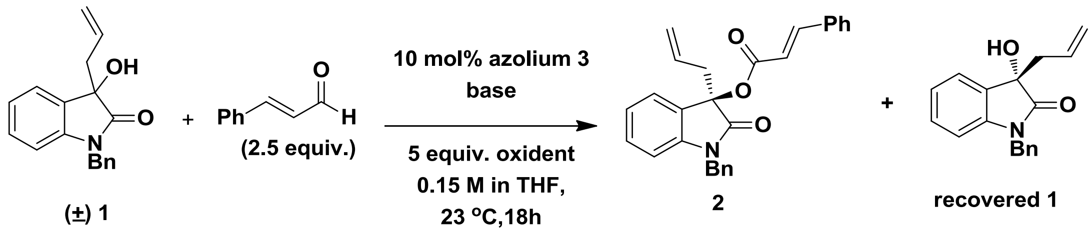


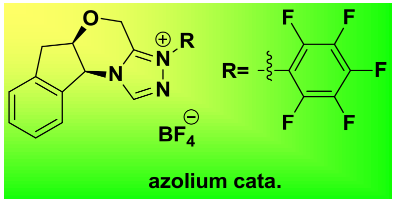
J.Am.Chem.Soc. **2004**, *126*,9518–9519



Kinetic resolution of 3-hydroxy-3-substituted oxindoles by NHC-catalyzed esterification

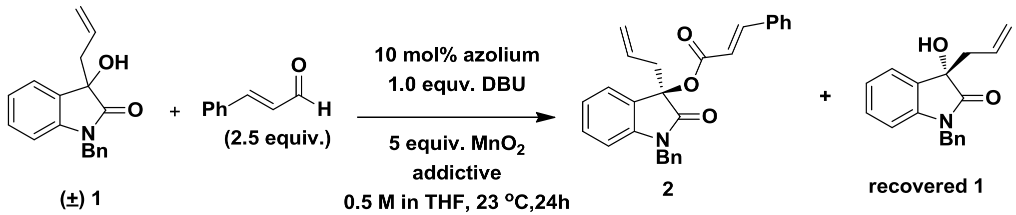
Optimum condition





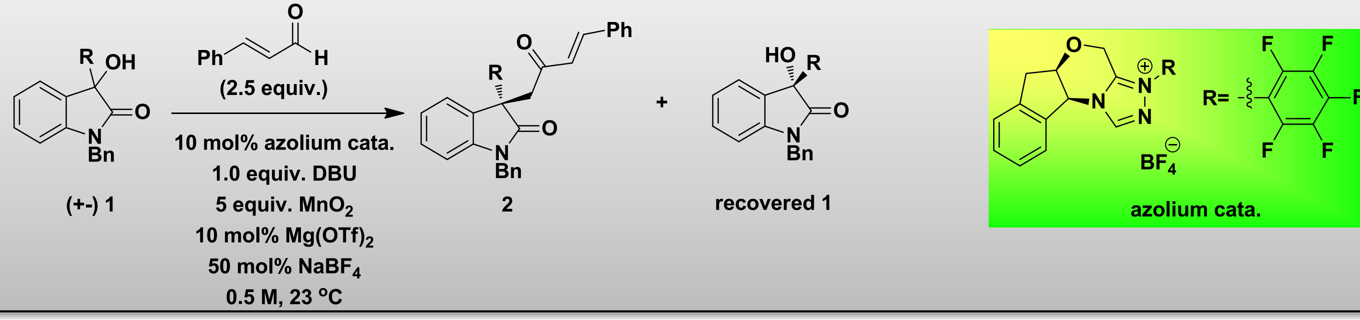
Entry	Azolium	Base	Oxidant	ee $_{2a}$[a]	ee$_{1a}$[a,b]	Conv.[c]	S[c]
2	3	1.0equiv.DBU	MnO_2	88	63	42	30

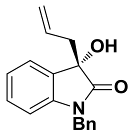
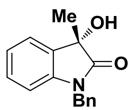
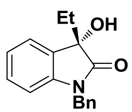
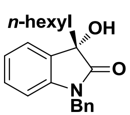
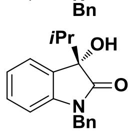
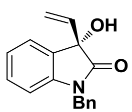
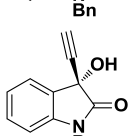
[a] Determined by HPLC, [b]The absolute configuration of the recovered 1a was assigned by comparison of the mesured optical rotation of with the reported value [c]Conversions and selectivity values were calculated by the methods of Kagan and Fiaud, Conv.=$ee_1/(ee_1+ee_2)$, S=$\ln[(l\text{-Conv.})(1\text{-}ee_1)]/\ln[(1\text{-Conv.})(1+ee_1)]$, [d]DIPEA=diisopropylethylamine

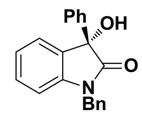
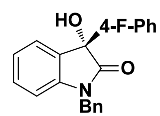
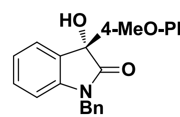
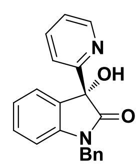


Entry	Lewis acid	$NaBF_4$	ee $_{2a}$[a]	ee$_{1a}$[a,b]	Conv.[c]	S[c]
4	10mol $Mg(OTf)_2$	50mol%	88	98	53	70

Scope of the kinetic resolution of 3-hydroxy-3-substituted oxindoles

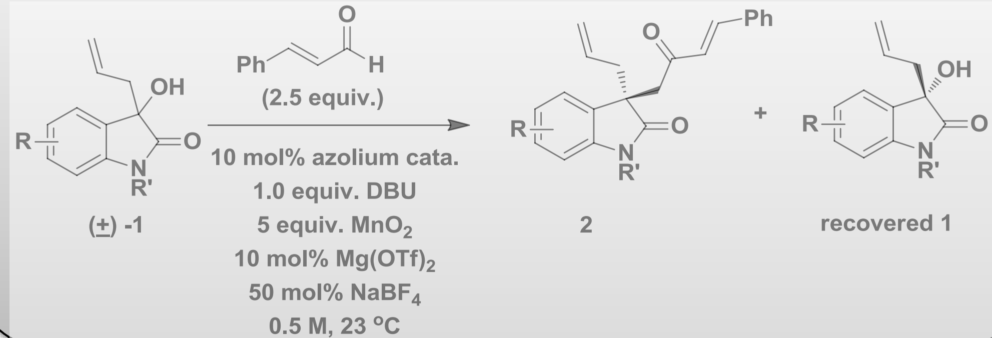


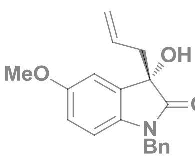
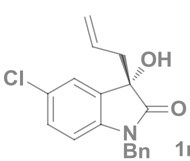
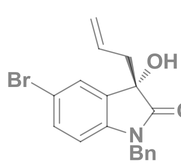
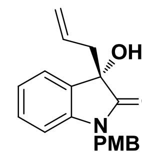
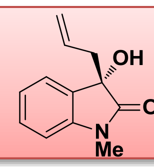
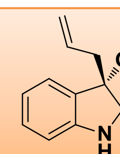
Entry	Recovered 1	t (h); conversion (%)	Yield 2 (%); ee_2 (%)	Yield 2 (%); ee_2 (%)	S
1		24; 53	52; 87	45; 98	70
2[b]		24; 55	52; 80	39; 99	46
3[b]		24; 56	53; 78	40; 99	41
4		24; 46	43; 92	52; 80	59
5		24; 27	24; 95	69; 35	56
6		36; 57	53; 72	42; 98	27
7		24; 63	59; 58	35; 99	18

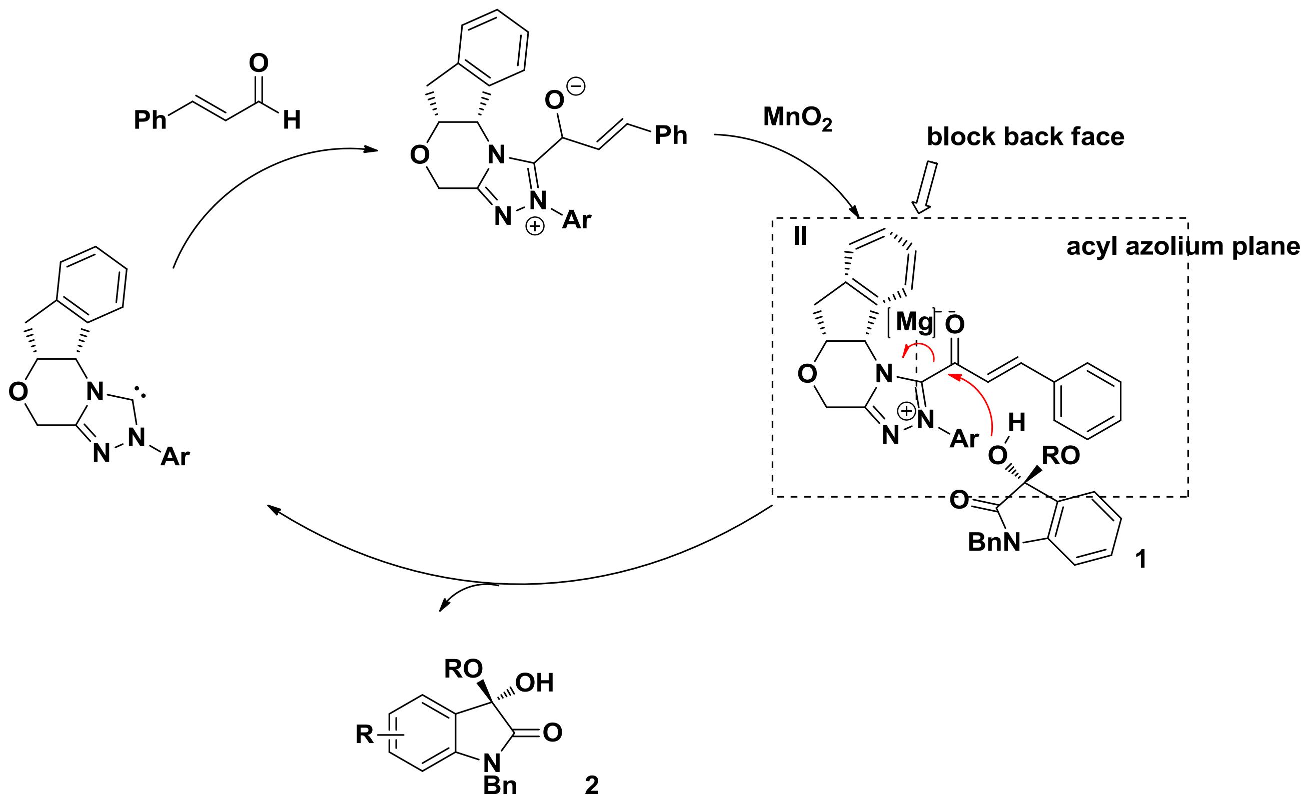
Entry	Recovered 1	t (h); conversion (%)	Yield 2 (%); ee_2 (%)	Yield 2 (%); ee_2 (%)	S
8[b]		48; 60	57; 64	32; 98	20
9		36; 39	34; 86	52; 55	23
10[b]		36; 53	53; 80	44; 92	29
11		48; 34	30; 83	60; 43	16

[a] Unless stated otherwise, all reactions were carried out in THF for the period of time as indicated. All reagents were used as received from commercial supplier without purification. Conversions and selectivity values were calculated by the methods of Kagan and Fiaud : Conv.=$ee_1/(ee_1+ee_2)$, S=ln[(l-Conv.)(1-ee_1)]/ln[(1-Conv.)(1+ee_1)]. [b] Reactions were run in CH_3CN.

Scope of the kinetic resolution of 3-hydroxy-3-substituted oxindoles



Entry	recovered 1	t [h]; Conversation [%]	$Yield_2$ [%] ee_2 [%]	$Yield_1$ [%] ee_1 [%]	S
1	 1l	72;52	51;91	46;98	78
2	 1m	72;52	51;83	45;92	34
3	 1n	72;54	52;81	44;95	35
4	 1o	55;52	50;89	47;97	68
5	 1p	55;28	24;80	70;31	12
6	 1q	55;29	26;85	67;35	17



Proposed reaction pathway

Conclusion:

- It is the first time for asymmetric induction of tertiary alcohols using NHC catalysis

- The substrate scope of this catalytic system turned out to be remarkably broad

- Oxindole structure is important for this system to work, such as 1-methyl-1-indanol lacking the amide moiety showed no reactivity under similar conditions.

- Futher studies are needed to expand the scope of this catalyst and explain the function of $NaBF_4$

Thanks for your attention!