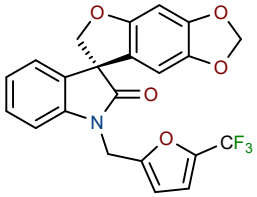
TV-45070

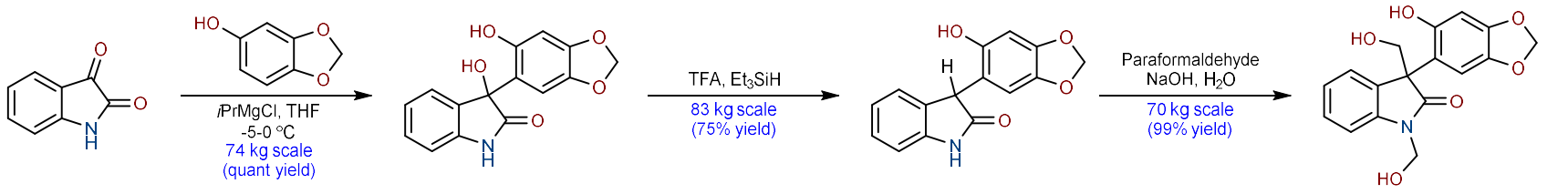


(S)-TV-45070

- A novel analgesic developed by Xenon Pharmaceuticals (formerly in partnership with Teva Pharmaceutical, 2012-2018)
- An antagonist of the $Na_v1.7$ sodium ion channel protein
- Currently in Phase II trials for Postherpetic neuralgia (PHN)
- Have potential therapeutic value for chronic pain caused by alterations in $Na_v1.7$ or corresponding encoding gene SCN9A

Sclafani, J. A, *Org. Process Res. Dev.* **2017**, *21, 1616*. https://doi.org/10.1021/acs.oprd.7b00237

First-generation process route



- Large-scale chromatography to purify the crude racemic compound required
- Significant losses due to late stage resolution
- Genotoxic bromomethylfuran used in late stage

Cardieux, J. J. U.S. Patent 8,445,696, May 21, 2013.

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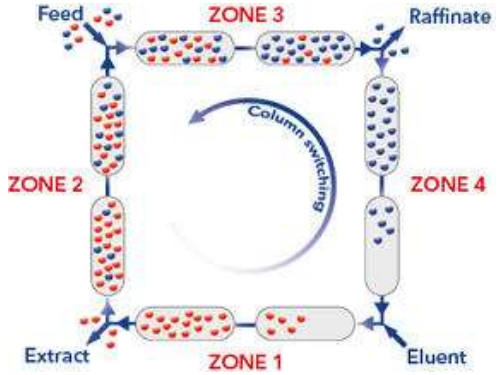
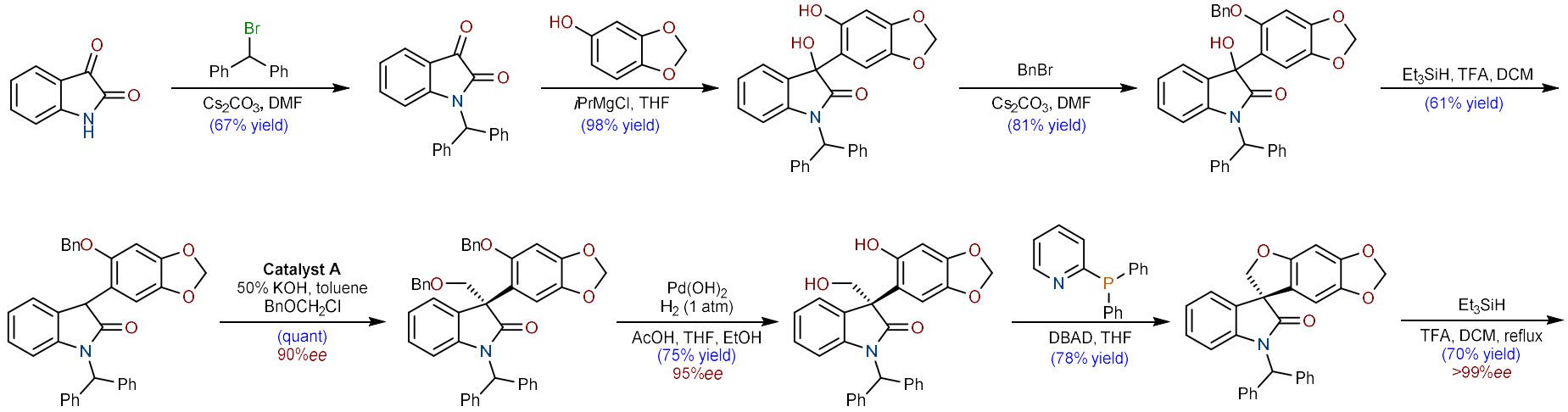
Simulated moving bed (SMB) chromatography



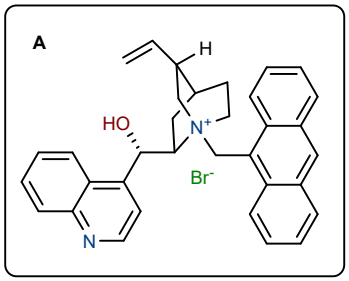
- The liquid phase is in motion and the solid phase moves in counter-current mode to the liquid phase.
- The feed (component A+B) is injected in the middle of the demonstrated SMB column.
- The liquid phase transports component A (blue), which is led out of the system in the raffinate as a pure substance.
- The solid phase transports component B (red), which is guided out as an extract.
- Contrary to the traditional chromatographic separation in a single column, the entire column bed is efficiently used.

Lieres, E. *Comput. Chem. Eng.* **2018**, *111,* 183. https://doi.org/10.1016/j.compchemeng.2017.12.022

First-generation asymmetric route



(S)-TV-45070

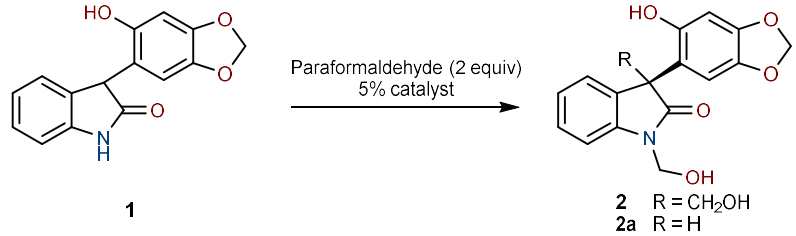


- Several protecting groups used
- Genotoxic bromomethylfuran used in late stage

- Enrichment of ee comparable to the earlier SMB process
- Use of phosphine facilitates the purification step

Sun, S. U.S. Patent 9,487,535, Nov 08, 2016..

Asymmetric aldol reaction with unprotected phenol 1



1

2 R = CH_2OH
2a R = H

catalyst	temp (°C)	time (h)	**1** (A%)	**2a** (A%)	**2** (A%)	impurities (A%)	*ee* of **2** (%)
$(DHQ)_2PHAL$	20	22	0.9	36	61	2.1	43
$(DHQ)_2PHAL$	0	64	5.4	41	7	46.6	46
$(DHQ)_2Pyr$	20	18	2.3	52	25	20.7	51
$(DHQ)_2Pyr$	0	64	0.7	34	9	64.4	25

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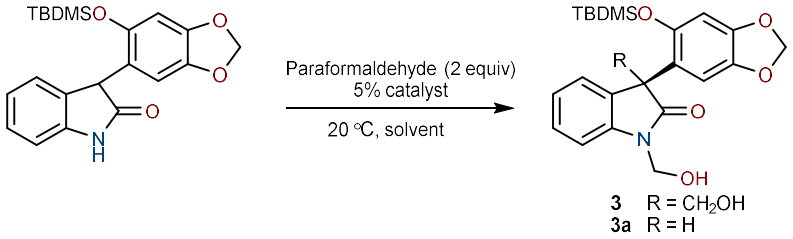
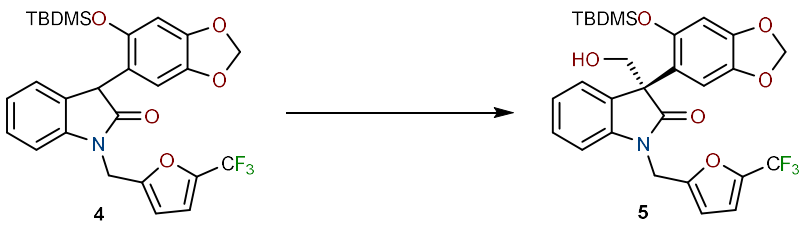
Asymmetric aldol reaction with protected phenol intermediate



catalyst	solvent	time (h)	**3** (A%)	**3a** (A%)	*ee* of **3** (%)
$(DHQ)_2PHAL$	CH_2Cl_2	113	30	62	27
$(DHQ)_2PHN$	CH_2Cl_2	90	41	47	27
$(DHQ)_2PHN$	THF	90	35	56	13
B	CH_2Cl_2	18	87	9	33
B	THF	18	77	13	32
B	toluene	18	91	3.9	10
B	CH_3CN	18	92	3.2	25
C	toluene	21	92.7	3.2	17
C	THF	21	71.5	25.9	30
C	CH_2Cl_2	18	82	7.1	35



catalyst	solvent	time (h)	**4** (A%)	**5** (A%)	*ee* of **5** (%)
C	CH_3CN	18	30	70	45
C	CH_3CN*	18	28	72	50
C	**heptane**	**18**	**5**	**95**	**73**
C	heptane*	18	29	71	54
B	heptane	18	2	98	58
B	CH_3CN	18	2.7	97.3	36
B	THF	40	18	82	41
B	toluene	18	32	68	54

*Performed using 30 mL/g versus 10 mL/g

Optimized plant synthesis