Enantioselective Synthesis of (+)-SJ733, a Clinical Candidate for Malaria

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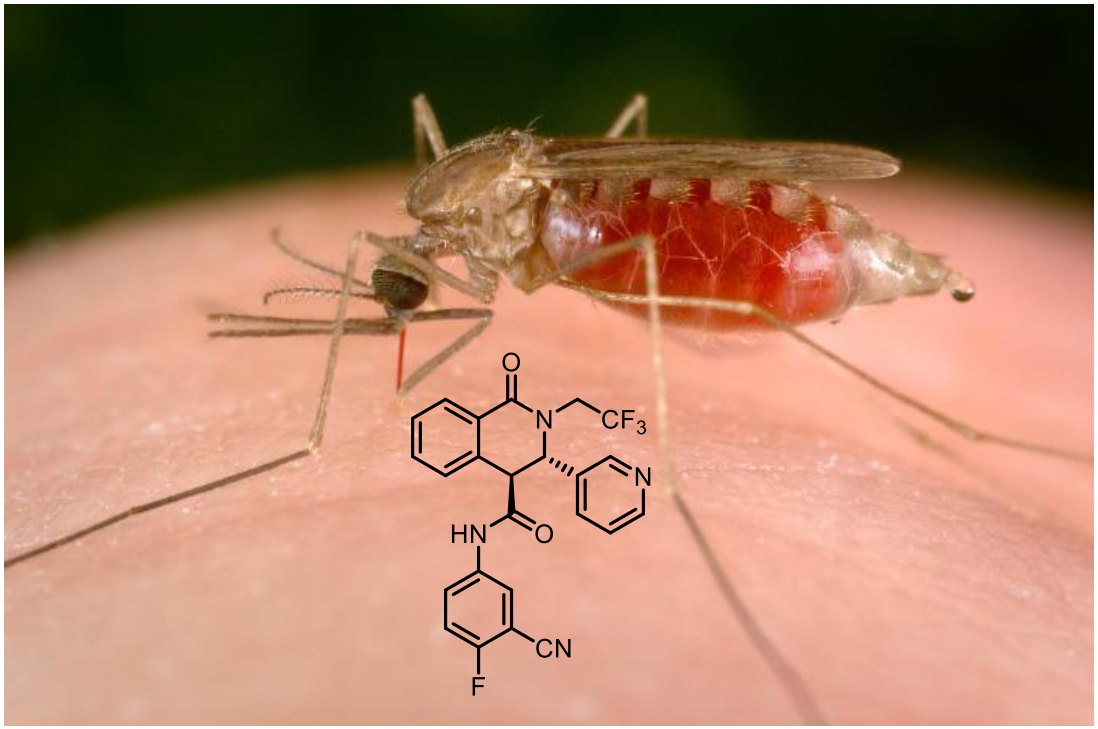


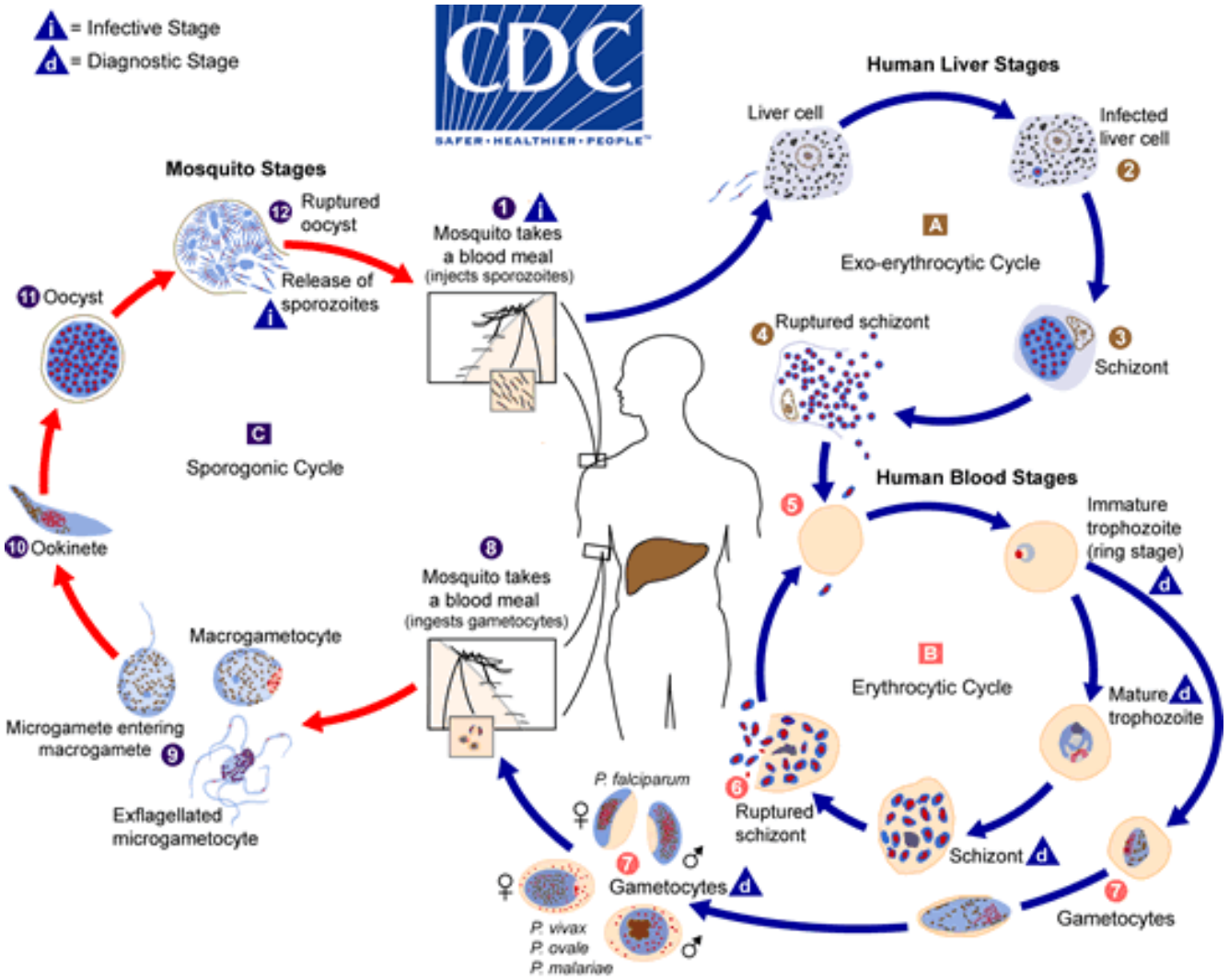
[1]

[1] http://wwwnc.cdc.gov/travel/images/anopheles-mosquito.jpg

Malaria: What everybody should know about it

- Tropical disease caused by a protozoan parasite of the genus *Plasmodium*
- Five species can infect humans: *Plasmodium falciparum* (Malaria *tropica*), *Plasmodium vivax* (Malaria *tertiana*), *Plasmodium ovale* (Malaria *tertiana*), *Plasmodium malariae* (Malaria *quartana*) and *Plasmodium knowlesi* (Malaria *quotidiana*)
- Disease transmission takes place *via* the bite of female mosquitoes of the species *Anopheles* (blood transfusion, while birth if the placenta is injured)
- Notification requirement (general, not by name): § 7 Abs. 3 IfSG (Germany)
- Complicated life cycle which contains sexual and asexual states (sporozoite, merozoites, gametocytes, hypnozoites…) which is summarized schematically by the CDC (Centers for Disease Control and Prevention, US)
- Ronald Ross (GB) received the Nobel Prize for Physiology or Medicine in 1902 for his work on Malaria
- Tu Youyou (CHN) received the Nobel Prize for Physiology or Medicine in 2015 for her work on antimalarial drug Artemisinin

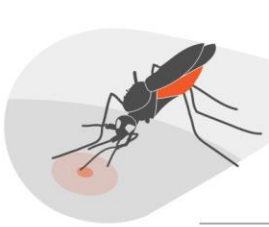
E. L. Flannery, A. K. Chatterjee, E. A. Winzeler, *Nat. Rev. Micro.* **2013**, *11*, 849-862.
For further information: http://www.who.int/malaria/en/



http://www.samaritanid.com/malariaCycle.gif

MALARIA FACTS

Malaria is a serious disease that is **PREVENTABLE** and **TREATABLE.**



Malaria is caused by *Plasmodium* parasites. Humans get infected via **mosquito bites.**

Pregnant women are at **HIGH RISK** of dying from complications of severe malaria.[3]

97 countries and territories had ongoing malaria transmission in 2015.[1]

3.2 billion people are at risk of malaria worldwide.[1]

a child dies from malaria in Sub-Saharan Africa.[4]

Each year, over **10,000** **travellers** are reported to become ill with malaria after returning home.[2]

MILD / MODERATE **SYMPTOMS** **SEVERE**

MEDICAL EMERGENCY

DO NOT IGNORE SYMPTOMS. Go straight to the doctor.

fever · sweating · headache · muscle aches · fatigue · shaking (rigors, chills) · vomiting · diarrhoea · fatal if not treated

EARLY DIAGNOSIS and prompt treatment prevent deaths

The 'ABCD' of Malaria Prevention

A — AWARENESS
Be **Aware** of the risk and the symptoms.

B — BITE PREVENTION
Avoid being **Bitten** by mosquitoes, especially between dusk and dawn.

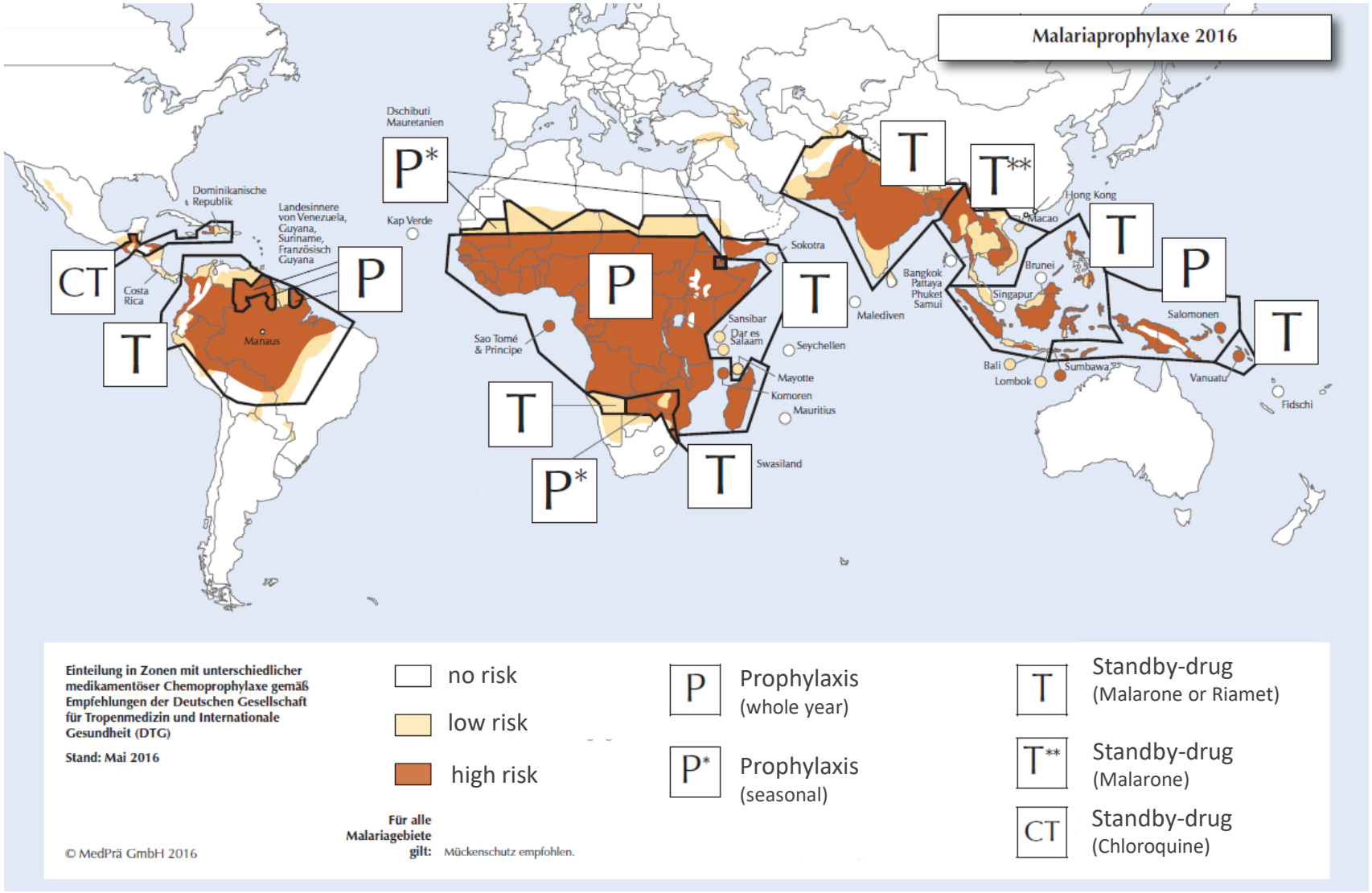
C — CHEMOPROPHYLAXIS
If presecribed for you, use **Chemoprophylaxis** (antimalarial medication) to prevent infection.

D — DIAGNOSIS
Immediately seek **Diagnosis** and treatment if a fever develops one week or more after being in a malarial area. *(up to one year after departure)*

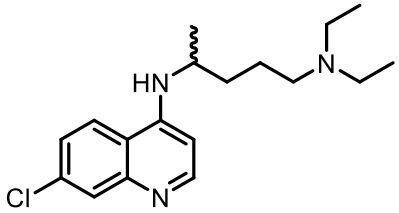
Sources
1. World Health Organization, *Malaria Fact Sheet*, January 2016
2. World Health Organization, *International Travel and Health*, Malaria 2015 update
3. World Health Organization, *10 Facts on Malaria*, November 2015
4. World Health Organization, *World Malaria Report 2015*

INTERNATIONAL SOS

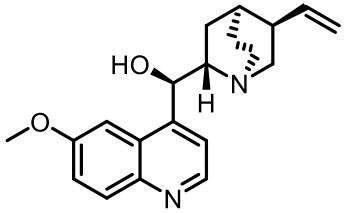
https://www.internationalsos.com/~/media/corporate/files/images/infographics/malaria-infographic-2016.jpg



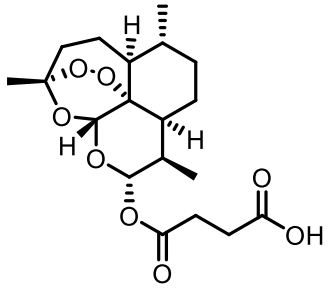
https://www.handbuch-reisemedizin.de/files/gen/DTG-Malaria.pdf



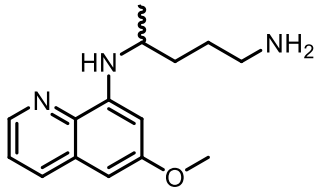
Chloroquine



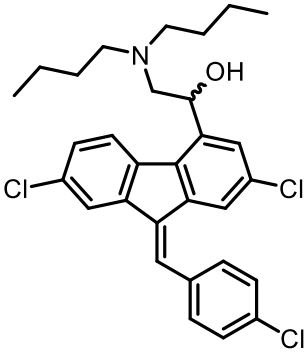
Quinine



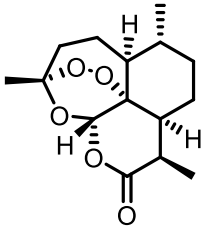
Artesunate



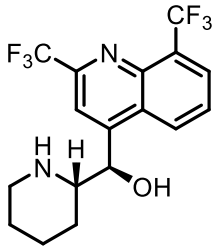
Primaquine



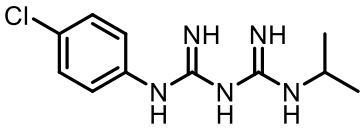
Lumefantrine



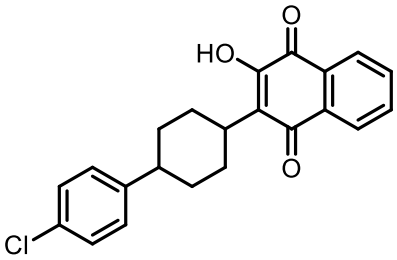
Artemisinin



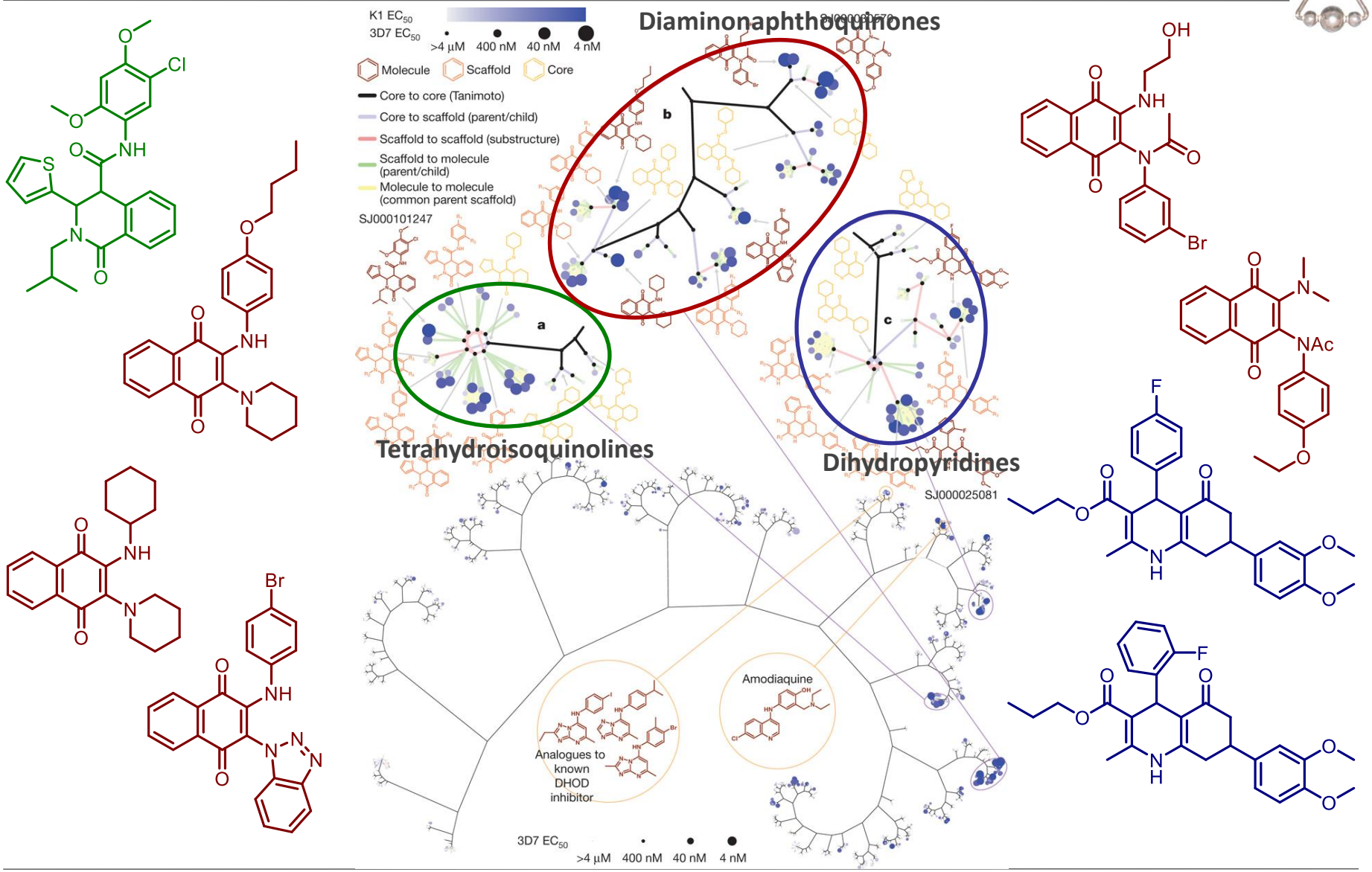
Mefloquine



Proguanil



Atovaquone



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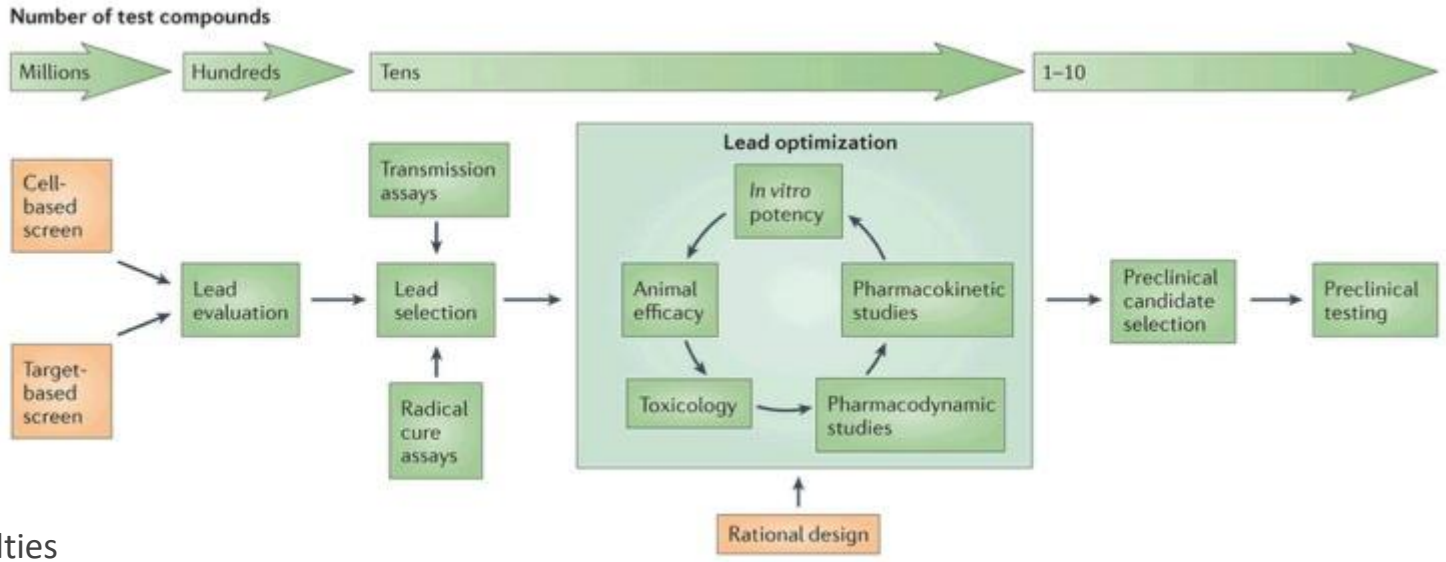


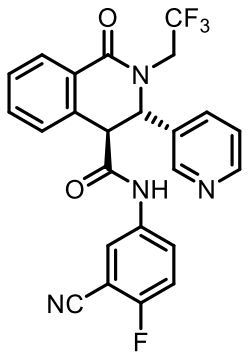
Difficulties

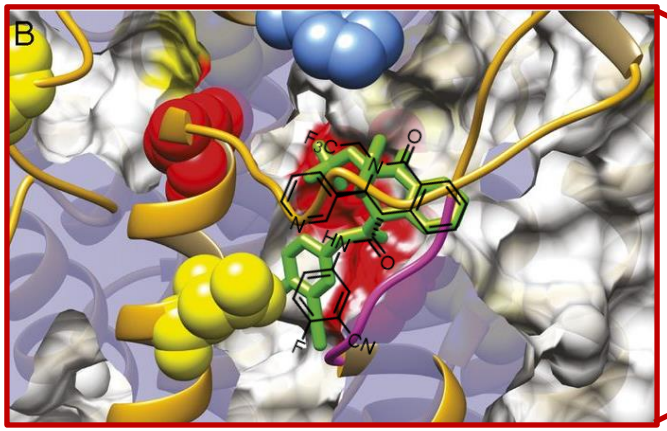
- Resistance of *Plasmodium falciparum* against many antimalarial drugs
- Lack of publicly accessible antimalarial chemotypes with differing modes of action
- Pressure of time, lack of vaccine up to now
- Target identification
- Lipinski's rule of five (not more than 5 hydrogen bond donors, not more than 10 hydrogen bond acceptors, molecular mass less than 500 u and octanol-water partition coefficient log P ≤ 5)

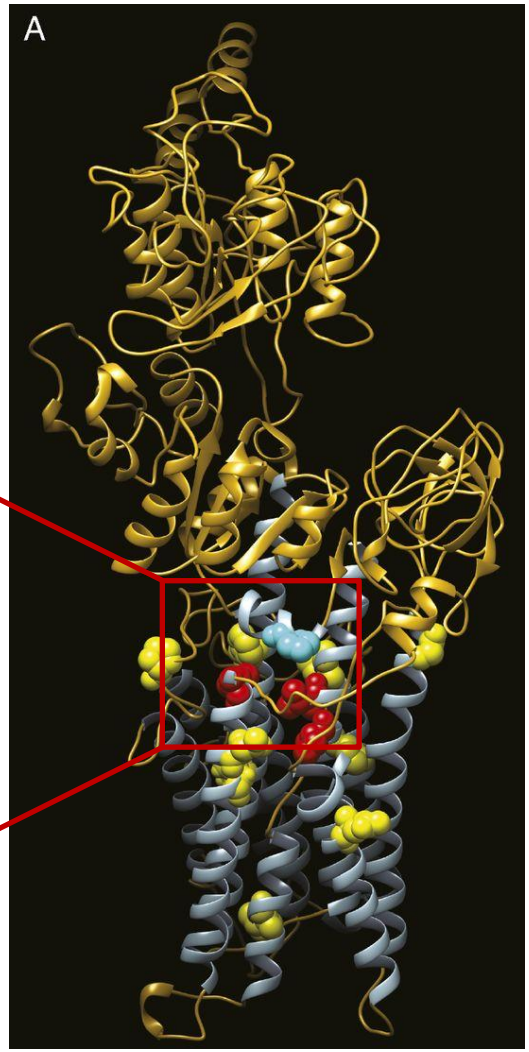
E. L. Flannery, A. K. Chatterjee, E. A. Winzeler, *Nat. Rev. Micro.* **2013**, *11*, 849-862; B. Munos, *Nat. Rev. Drug Discov.* **2006**, *5*, 723-729; C. A. Lipinski, F. Lombardo, B. W. Dominy, P. J. Feeney, *Adv. Drug Del. Rev.* **2001**, *46*, 3-26; J. N. Burrows, R. Hooft van Huijsduijnen, J. J. Möhrle, C. Oeuvray, T. N. Wells, *Malar. J.* **2013**, *12*, 187; K. C. Arnab, K. S. Y. Bryan, *Curr. Top. Med. Chem.* **2012**, *12*, 473-483.

(+)-SJ733, a Clinical Candidate

- Targets *Plasmodium* cation-transporting ATPase, ATP4
- High oral bioavailability
- High safety margin



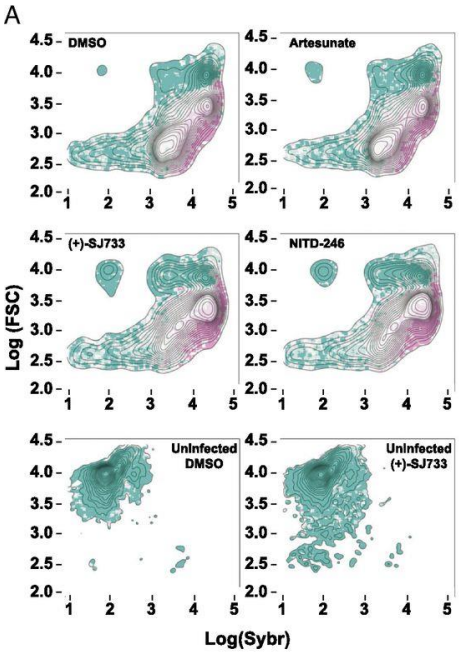


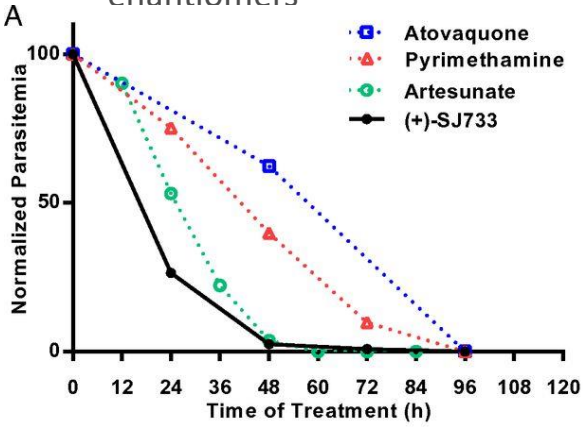


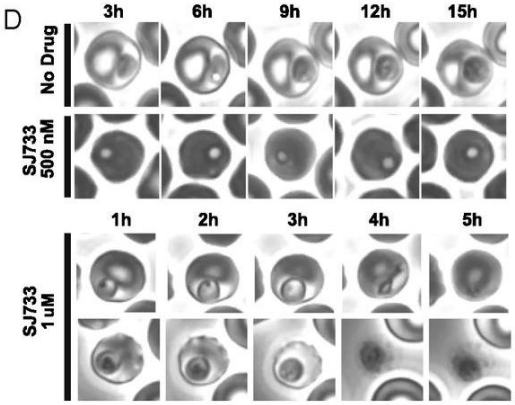
M. B. Jiménez-Díaz *et al. Proc. Natl. Acad. Sci.* **2014**, *111*, E5455-E5462.

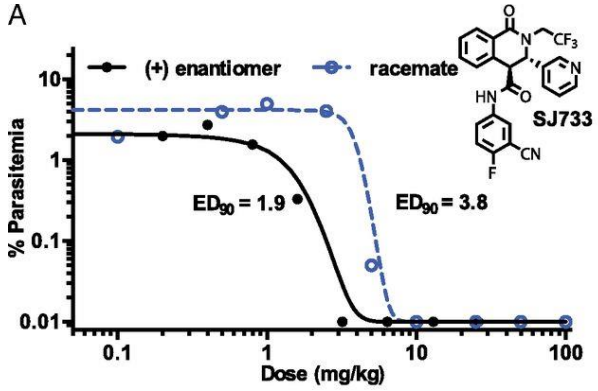
(+)-SJ733, a Clinical Candidate

- Transmission blocking activity
- Rapid clearance of parasites
- Multiple effects exclusively on the infected cell: increase of [Na^+], increase membrane rigidity, externalization of phosphatidylserine (PS), eryptosis or senescence
- Mutations that confer resistance to (+)-SJ733 carry a high fitness cost
- Synthesis in 5 steps, including a separation of the enantiomers



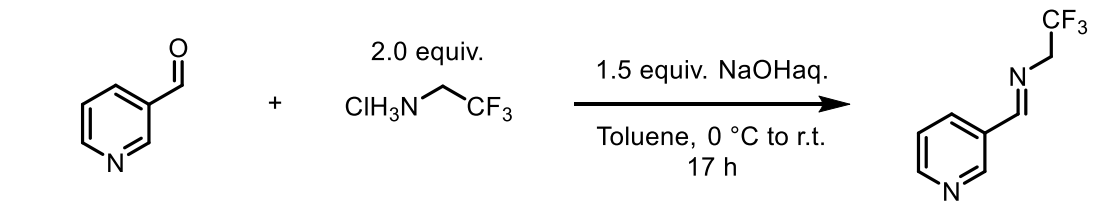




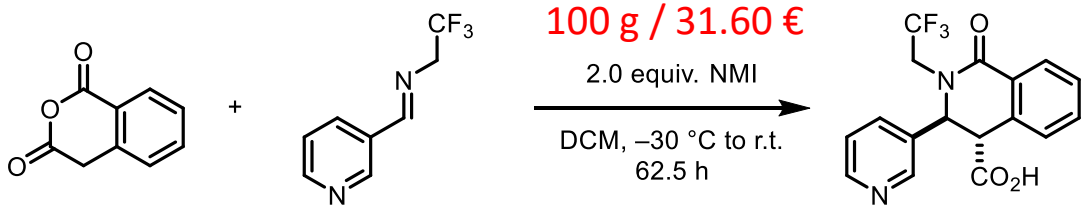


M. B. Jiménez-Díaz, D. Ebert, Y. Salinas, (…), R. K. Guy, *Proc. Natl. Acad. Sci.* **2014**, *111*, E5455-E5462.

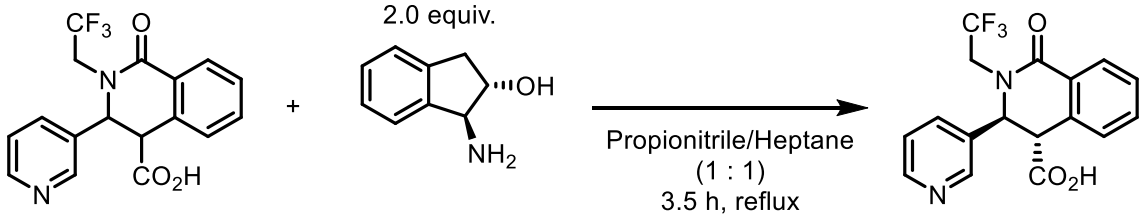
Synthetic Protocol from the Literature



25 g / 21.90 € 10 g / 146.00 € 94%



5 g / 52.70 € 84%



1 g / 36.80 € 36%

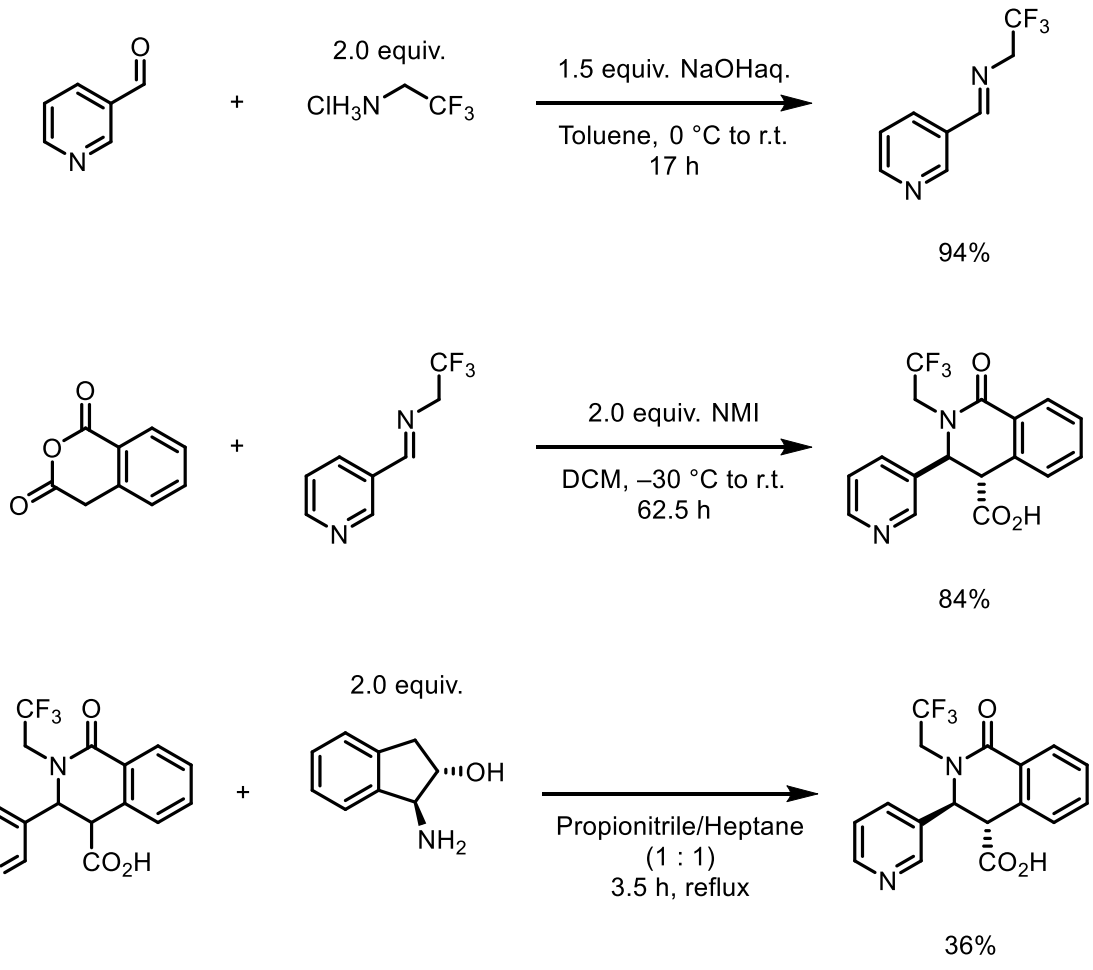
→ Overall yield (3 steps) 28%

J. Liu, Z. Wang, A. Levin, T. J. Emge, P. R. Rablen, D. M. Floyd, S. Knapp, *J. Org. Chem.* **2014**, *79*, 7593-7599.

*Costs for chemicals Sigma Aldrich (15.11.2016)

Oversimplified Calculation

10.0 mmol



→ 1 g / 144.35 €*
(resolution: 87.22 €)

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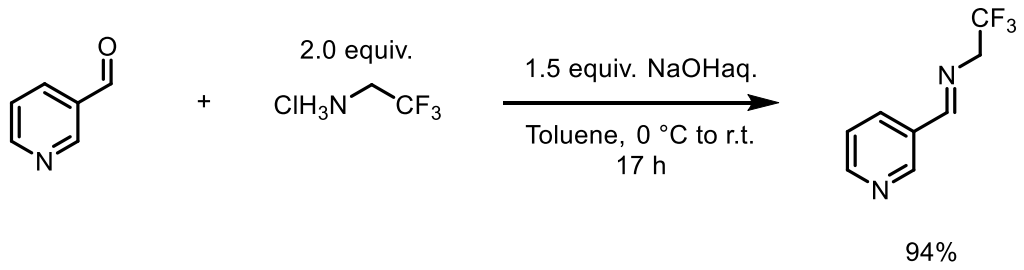
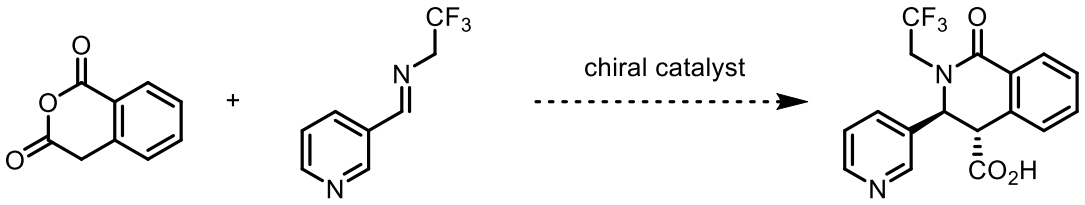
*Costs for chemicals Sigma Aldrich (15.11.2016)

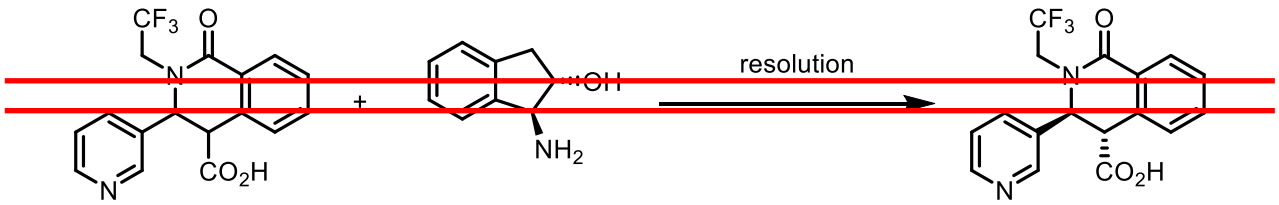
Oversimplified Calculation

3.62 mmol





→ 1 g / 20.45 €*



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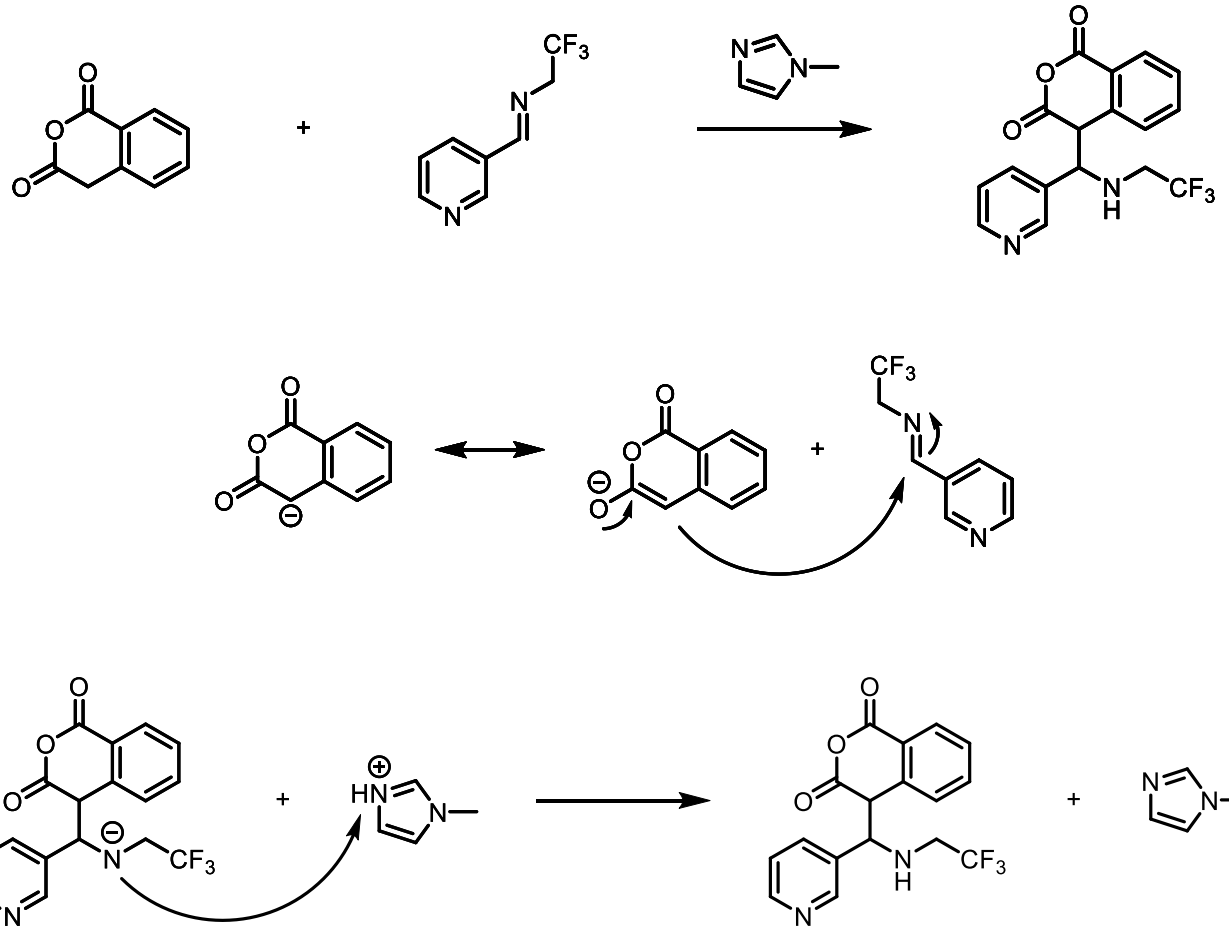

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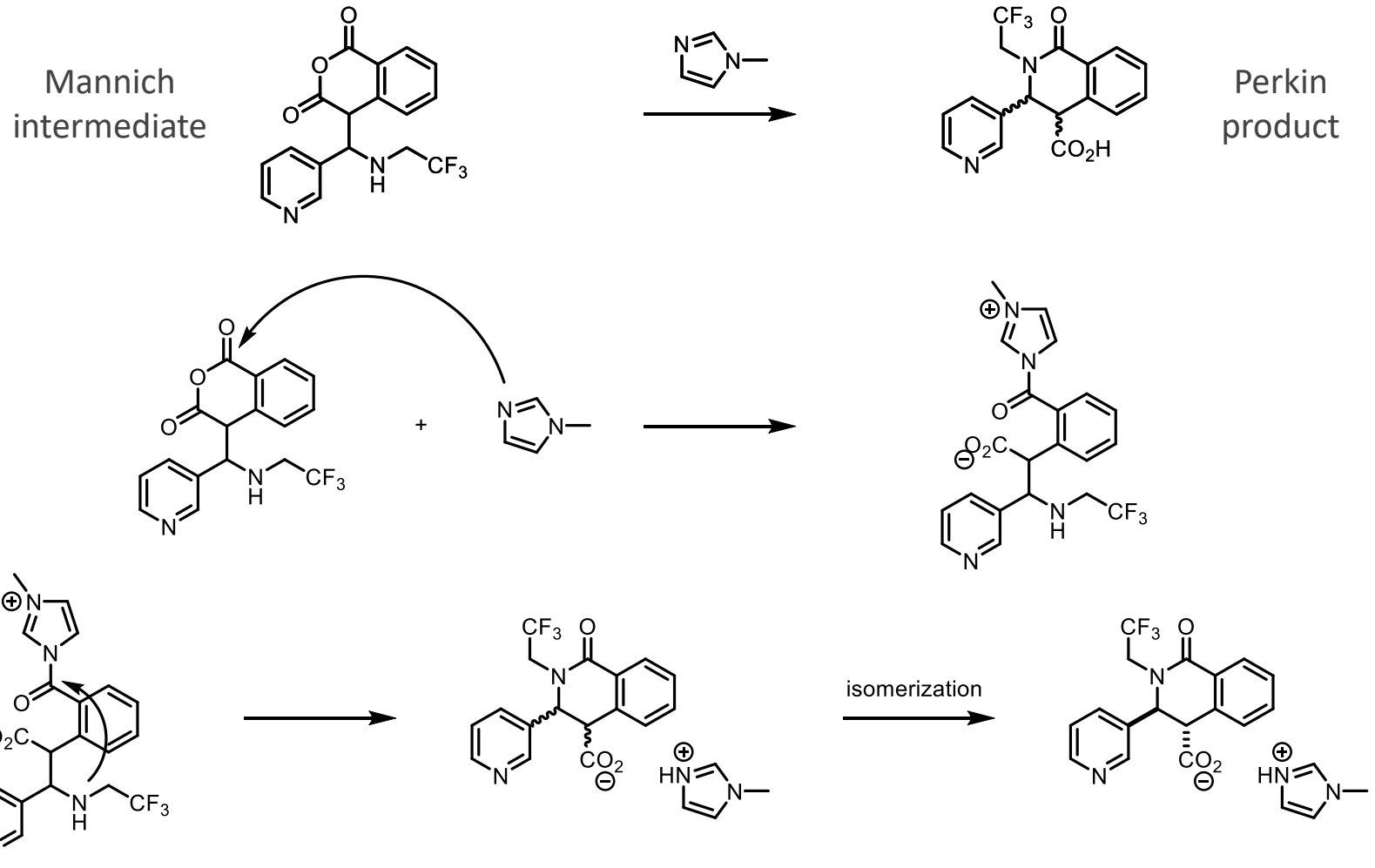

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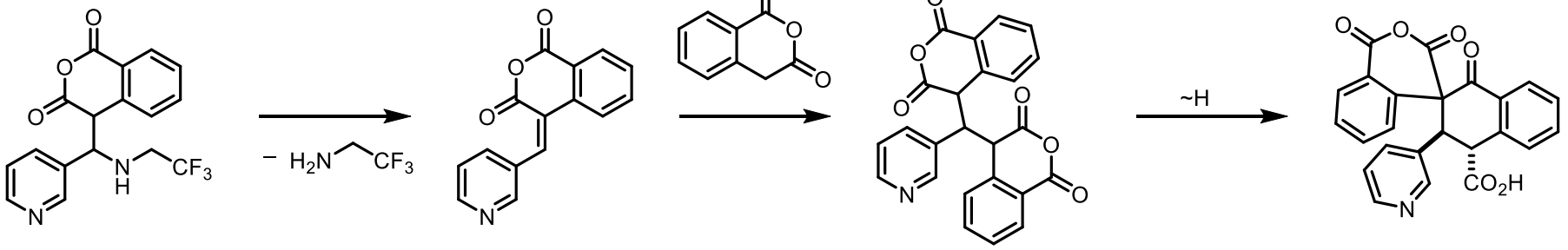
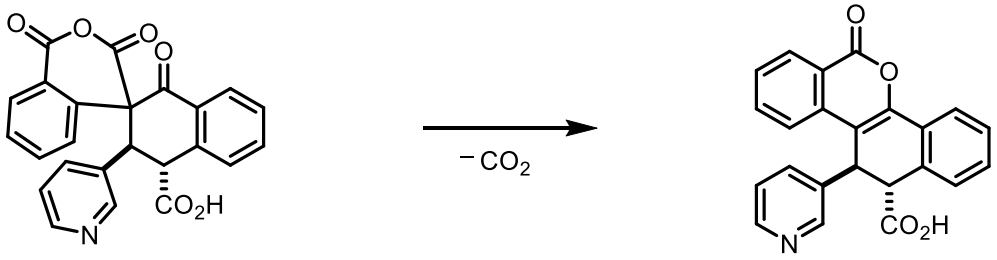


Mannich intermediate

Knoevenagel product

„two-to-one“ adduct

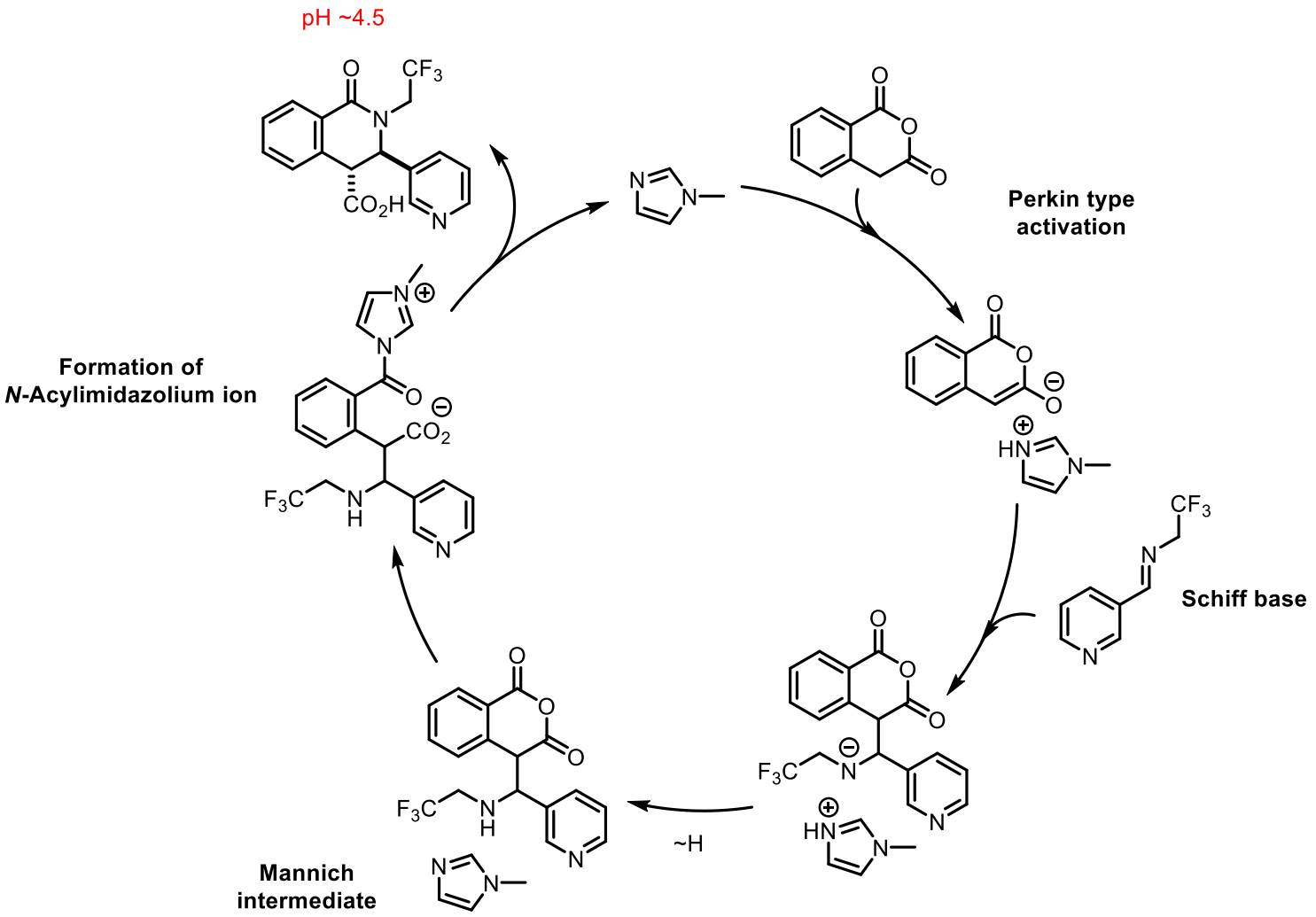
C-acylation product



spiro anhydride

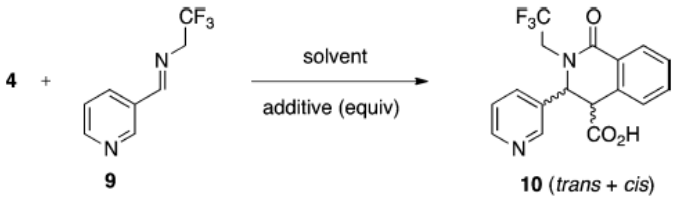
decarboxylation product

J. Liu, Z. Wang, A. Levin, T. J. Emge, P. R. Rablen, D. M. Floyd, S. Knapp, *J. Org. Chem.* **2014**, *79*, 7593-7599.



W. H. Perkin, *J. Chem. Soc.* **1868**, *21*, 181-186; W. H. Perkin, *J. Chem. Soc.* **1877**, *31*, 388-427; C. Mannich, W. Krösche, *Arch. Pharm.* **1912**, *250*, 647-667; B. Neises, W. Steglich, *Angew. Chem. Int. Ed.* **1978**, *17*, 522-524.

Table 1. Effect of Additives and Solvent on the Apparent Yield of 1-Oxo-2-(2,2,2-trifluoroethyl)-3-(3-pyridyl)-1,2,3,4-tetrahydroisoquinoline-4-carboxylic Acids 10



base (equiv)	pK_a[a]	solvent	NMR yield (*trans*:*cis*)
no base		$CHCl_3$	47% (2.2:1)
pyridine (1.0)	5.2	〃	45% (1:1)
DABCO (1.0)	8.8	〃	[b]
2,4,6-collidine (1.0)	7.6	〃	[b]
N,*N*-diethylaniline (1.0)	6.6	〃	[b]
N-methylmorpholine (1.0)	7.4	〃	[b]
4-(dimethylamino)pyridine (1.0)	9.2	〃	55%
4-(dimethylamino)pyridine (1.0)	〃	CH_3CN	[b]
4-(4-morpholino)pyridine (1.0)	8.0	$CHCl_3$	47%
4(1-pyrrolidino)pyridine (1.0)	9.6	〃	36%
HOAc (1.0)	4.8	〃	50% (4:1)
N-methylimidazole, NMI (1.0)	7.0		63%
NMI (1.5)	〃	〃	68%
NMI (0.5)	〃	〃	65%
NMI (2.0)	〃	〃	78%
NMI (5.0)	〃	〃	53%
NMI (neat)	〃	〃	[b]
NMI (1.0)	〃	toluene	[b]
NMI (1.0)	〃	CH_2Cl_2	66%
NMI (1.0)	〃	14 other solvents[c]	[b]

[a]Approximate pK_a of conjugate acid. [b]Poor yield and/or messy reaction mixture. [c]Solvents tried: methyl acetate, ethyl acetate, isopropyl acetate, isobutyl acetate, *n*-butyl acetate, ethyl lactate, dimethyl carbonate, diethyl carbonate, tetrahydrofuran, acetone, *tert*-butanol, acetonitrile, propionitrile, and diethoxymethane.

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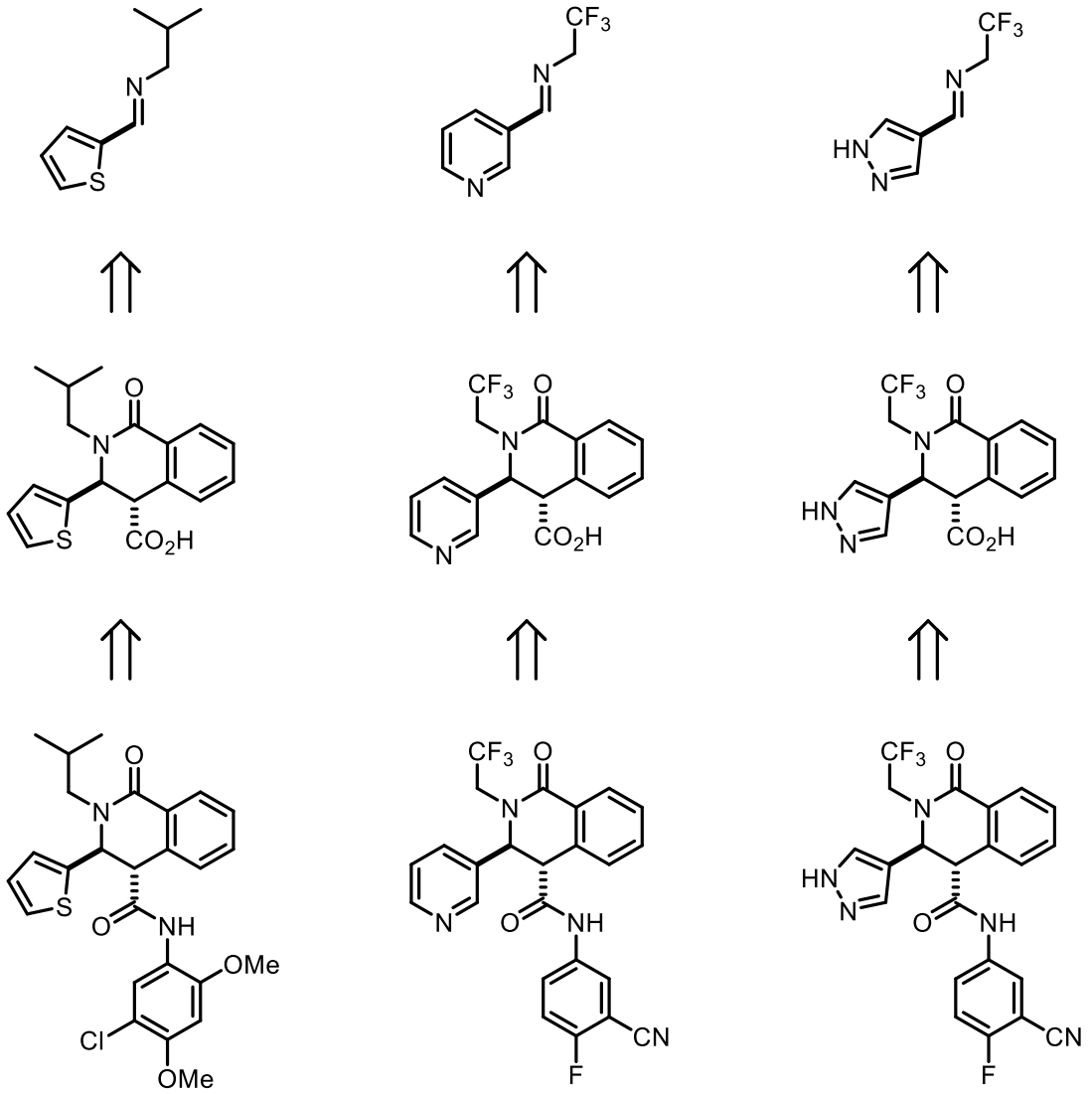
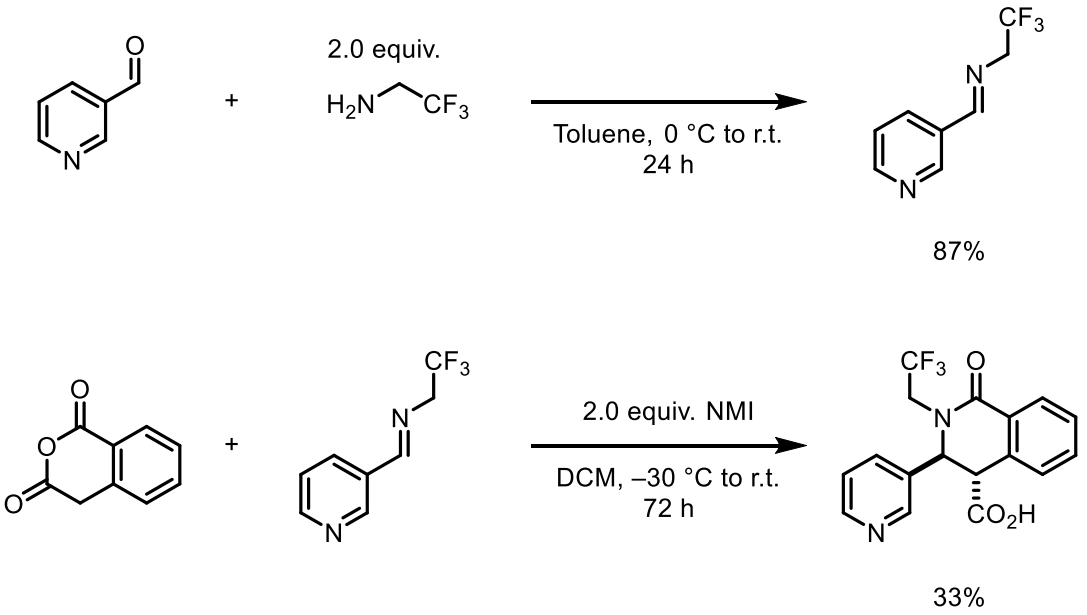
Access to Chiral Tetrahydroisoquinolines

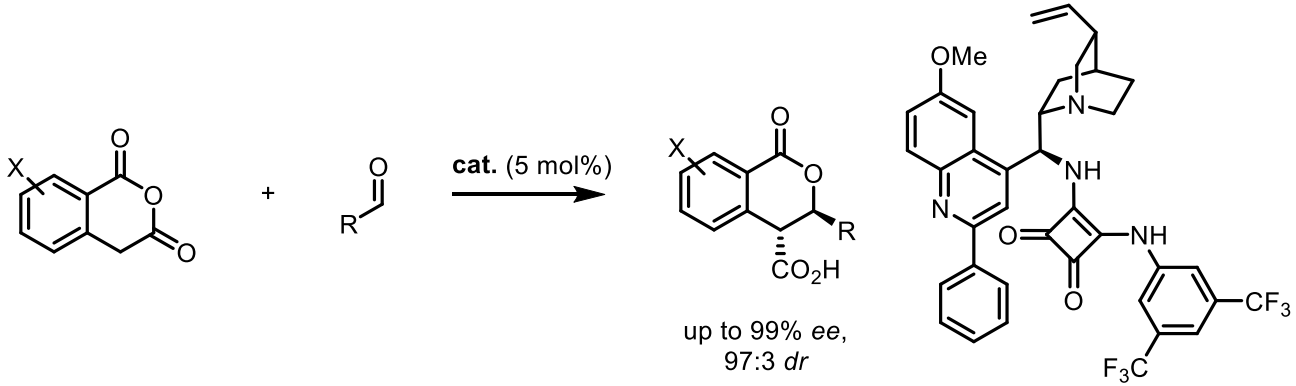


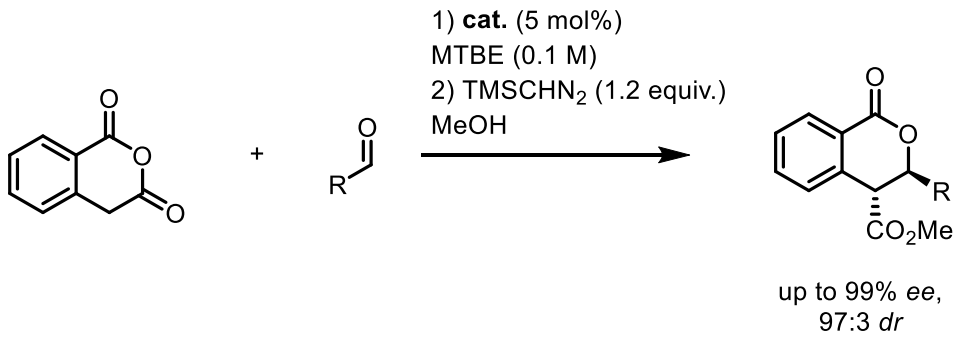
J. Liu, Z. Wang, A. Levin, T. J. Emge, P. R. Rablen, D. M. Floyd, S. Knapp, *J. Org. Chem.* **2014**, *79*, 7593-7599.

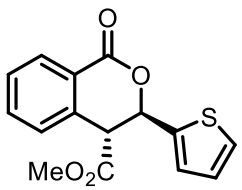


- NMR

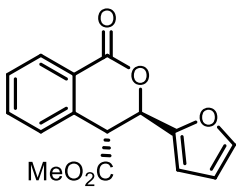
- Separation of the enantiomers *via* chiral HPLC
  Chiralpak IB 1,0 mL min^{-1} *n*-Hexane 76.25% : TBME 15.0% : IPA 8.75% : TFA 0.0375%
  Ret. Time [min]: 14.40 and 18.19



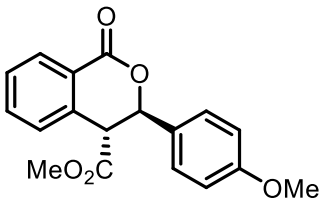




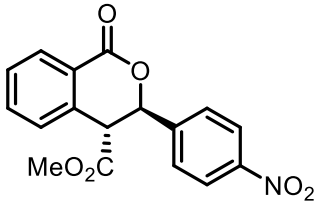
84%, 94:6 d.r., 97% *ee*



90%, 93:7 d.r., 97% *ee*



78%, 90:10 d.r., 91% *ee*



84%, 93:7 d.r., 96% *ee*

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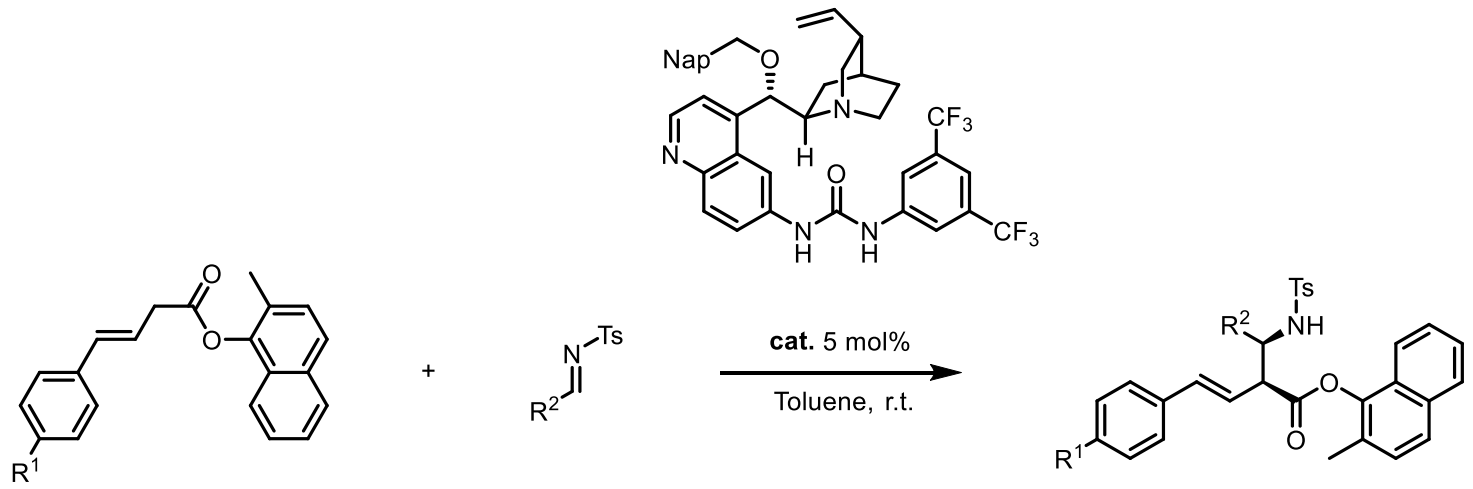
Outlook



up to 96:4 d.r., up to 97% *ee*

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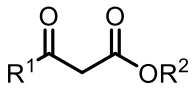
Outlook



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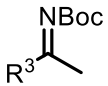
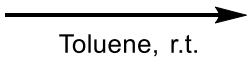
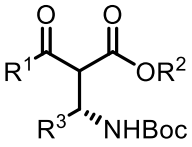
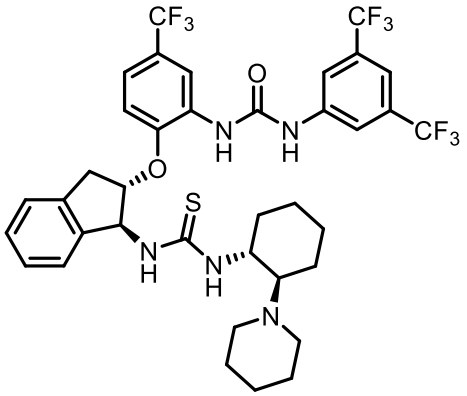




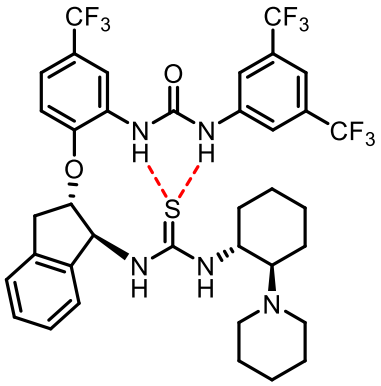




R^1 = aliphatic, aromatic
R^2 = Me, Et, Bn

R^3 = aliphatic, (hetero)aromatic

up to 99% yield, up to 98% *ee*



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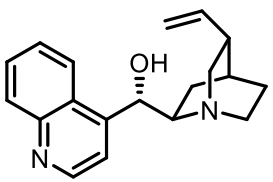
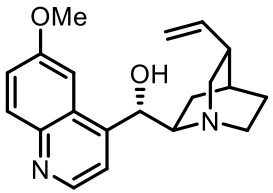
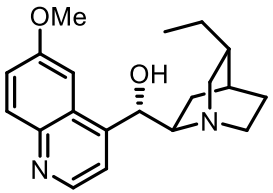
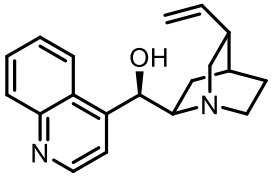
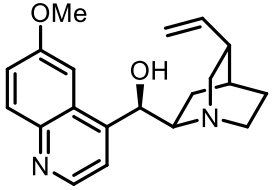
Outlook

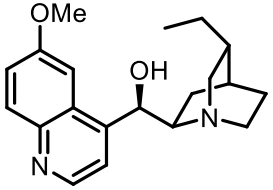


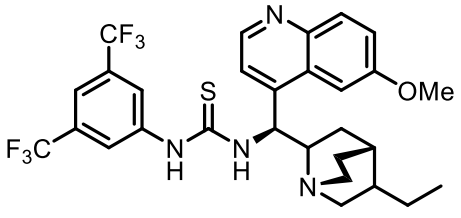


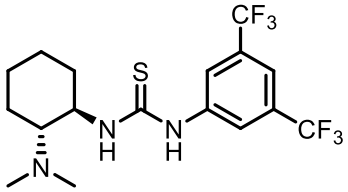


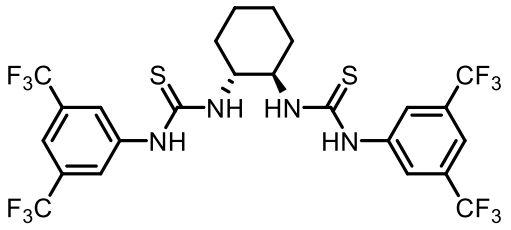












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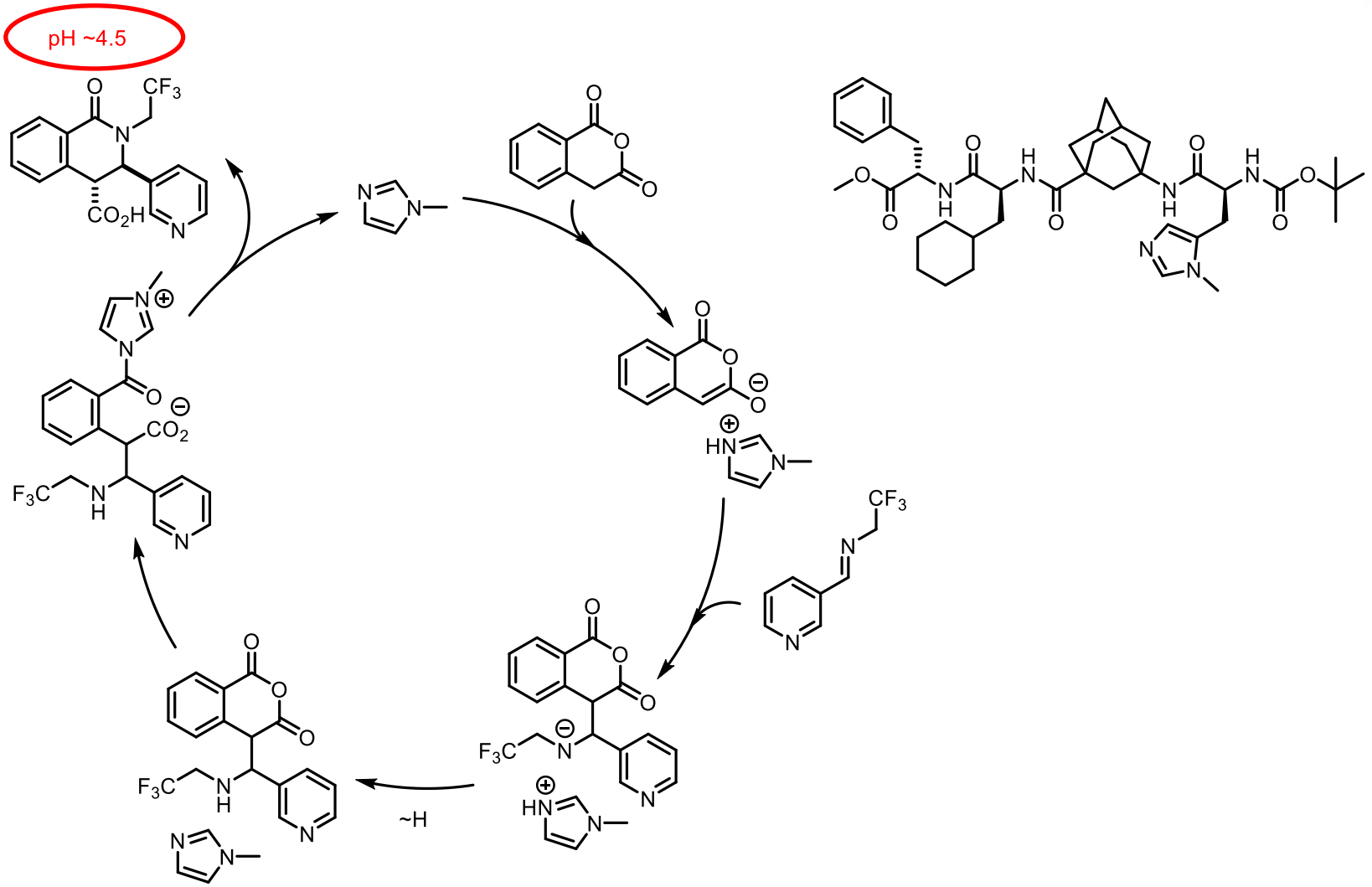

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- Dr. Heike Hausmann, Steffen Wagner, Stefan and Anika Bernhardt
- PRS-Group

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