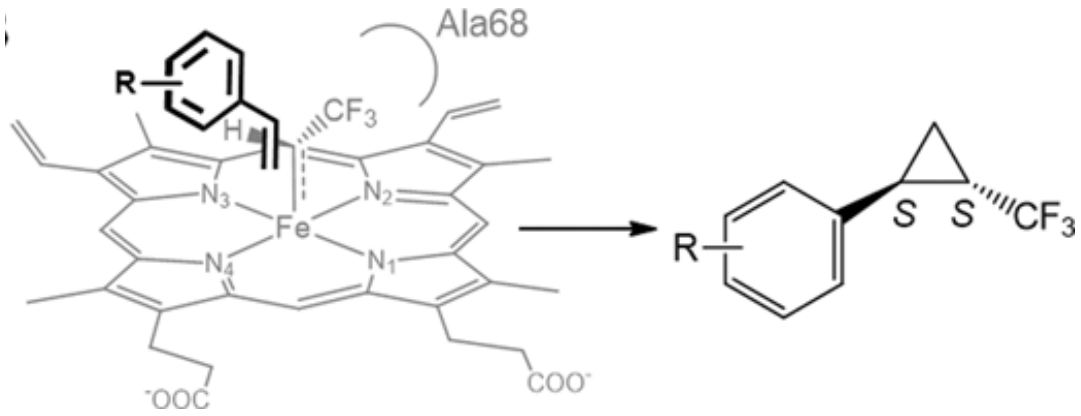
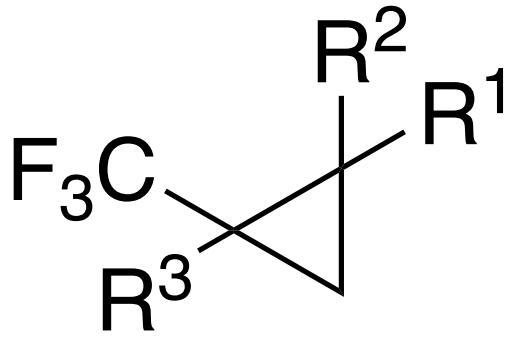
Highly Diastereo- and Enantioselective Synthesis of Trifluoromethyl-Substituted Cyclopropanes via Myoglobin-Catalyzed Transfer of Trifluoromethylcarbene



Antonio Tinoco, Viktoria Steck, Vikas Tyagi, and Rudi Fasan
J. Am. Chem Soc. 2017, **139**, 5293

Trifluoromethyl cyclopropane derivatives

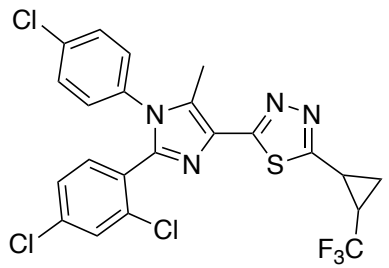
Conformational Rigidity – important feature in biologically active compounds.



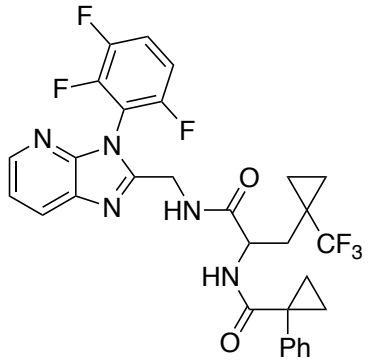
-CF_3 analogues impart important biological activity

1) Increase electrophilicity and decrease nucleophilicity of neighbouring functional groups
2) Modifies lipophilicity
3) Increase metaboloc stability

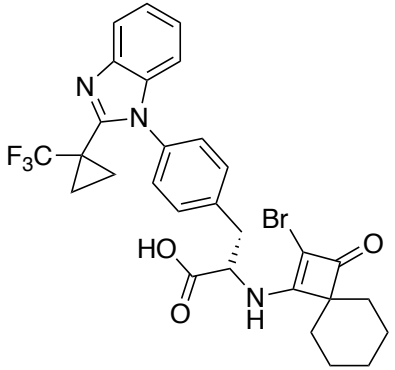
Trifluoromethylated cyclopropane is considered to be a bioisostere of fluorinated tert-butyl group



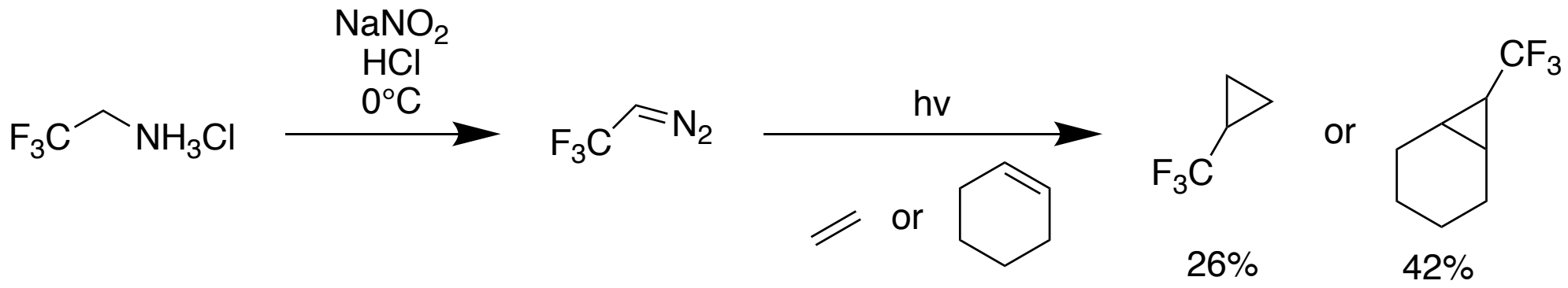
cannabinoid CB_1 receptor antagonist
IC_{50} = 33.5 nM

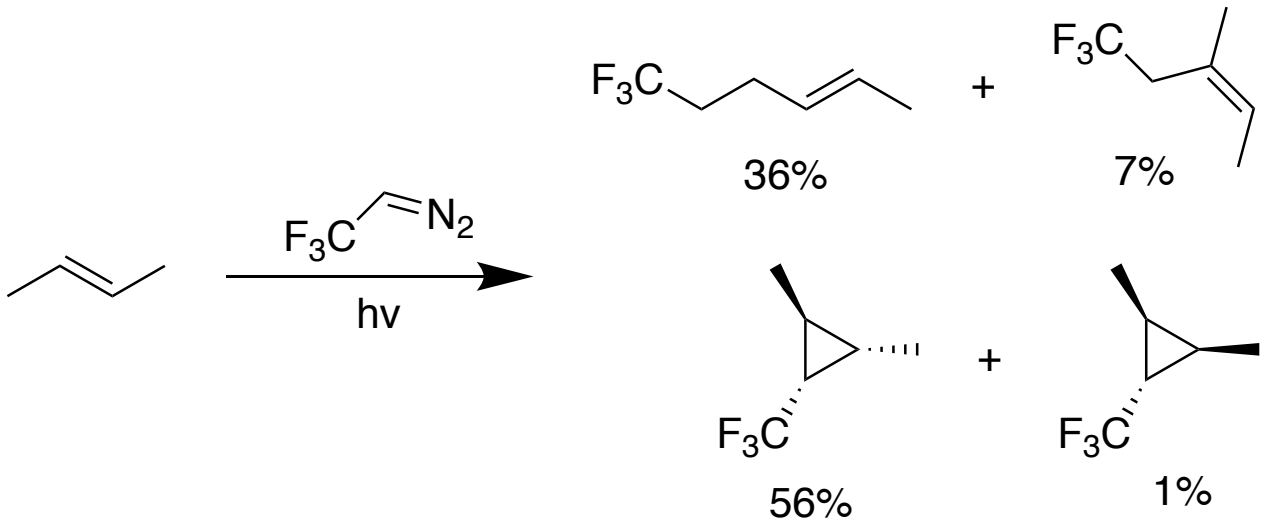


$hNa_V1.7$ channel blocker
IC_{50} = 182 nM

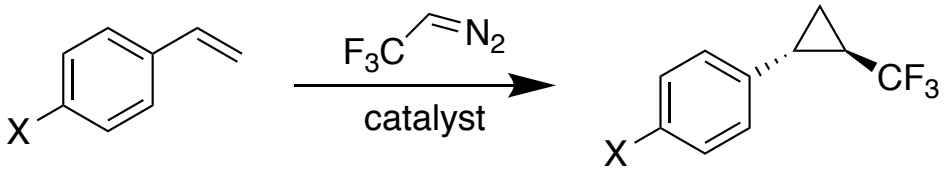


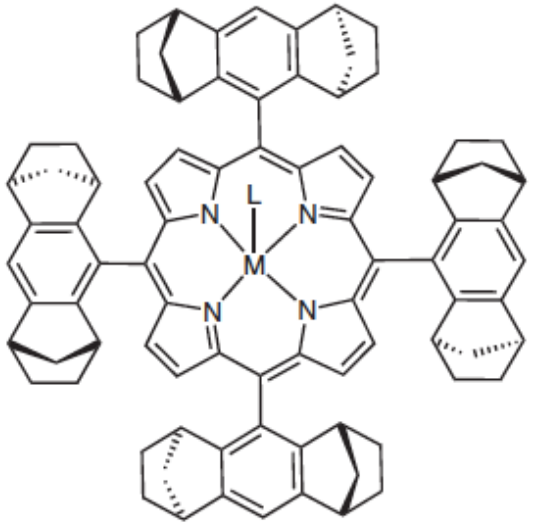
VLA-4 integrin antagonist
IC_{50} = 2 nM



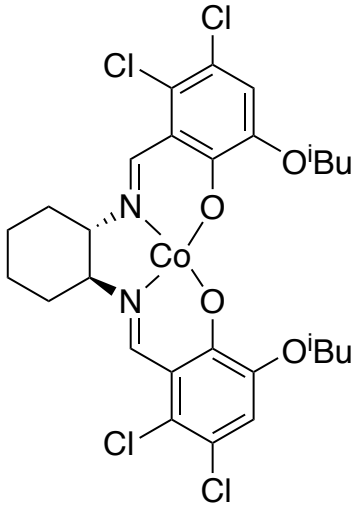


J. Chem. Soc. C. **1967**, 1450





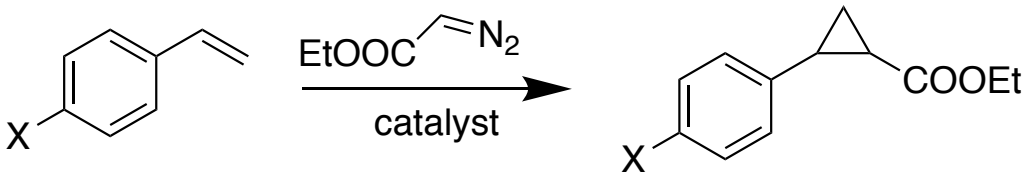
ML = FeCl
de 88-94%
ee 17-61%



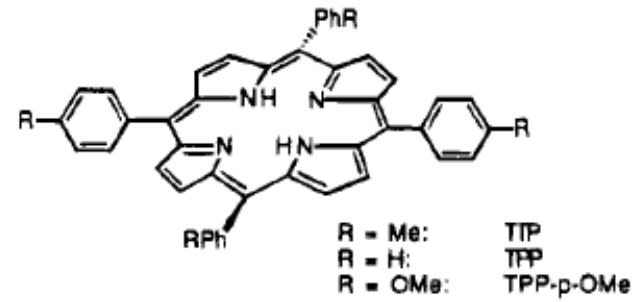
dr 180:1
ee upto 92%

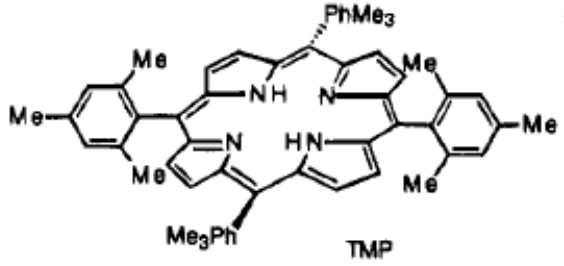
Synthesis 2006, 2006, 1701
Angew. Chem. Int. Ed. 2011, **50**, 1101

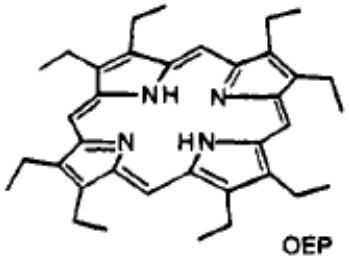
Metal porphyrin catalysed cyclopropanations



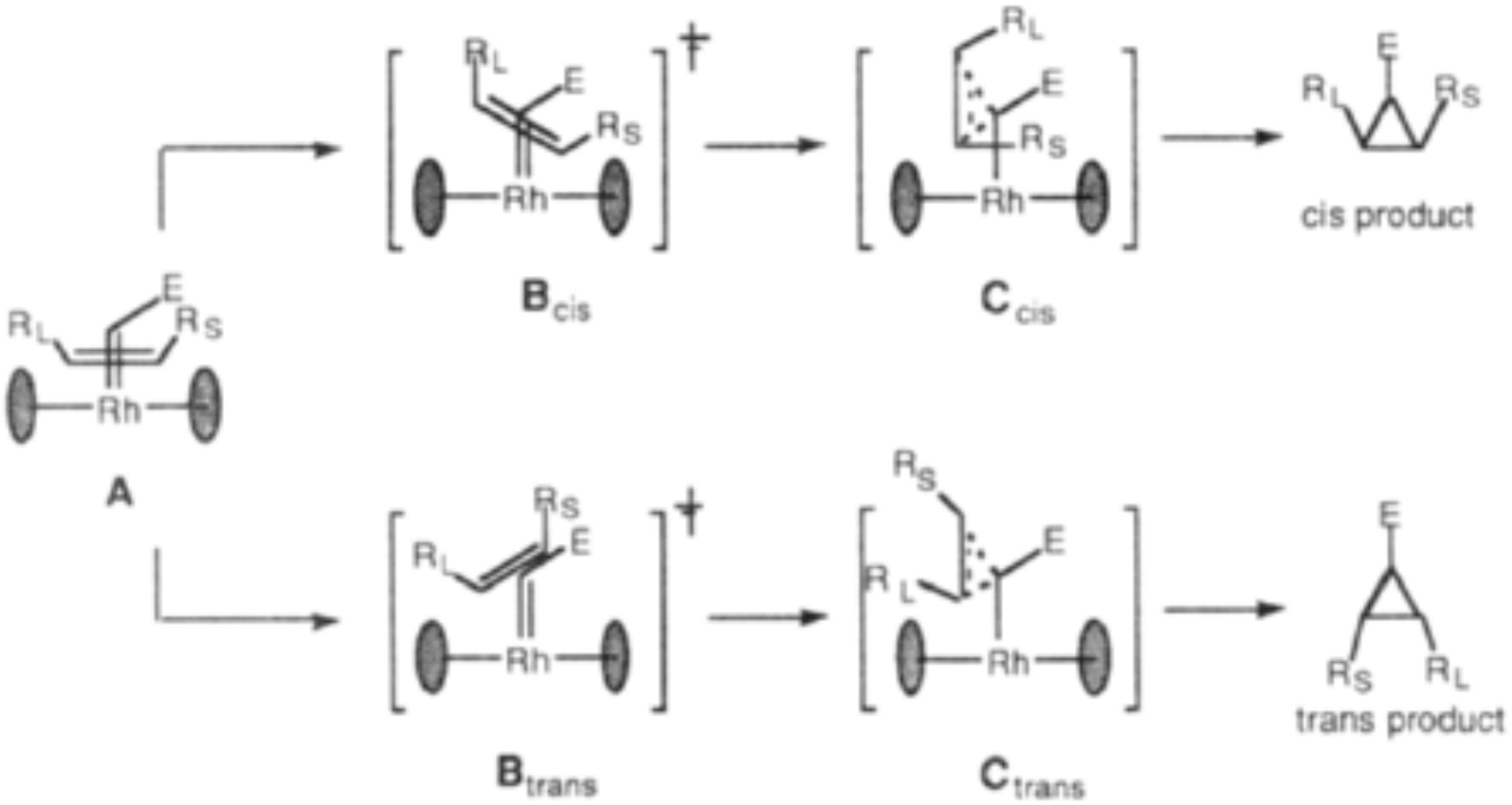
Rh - cis
Fe - trans



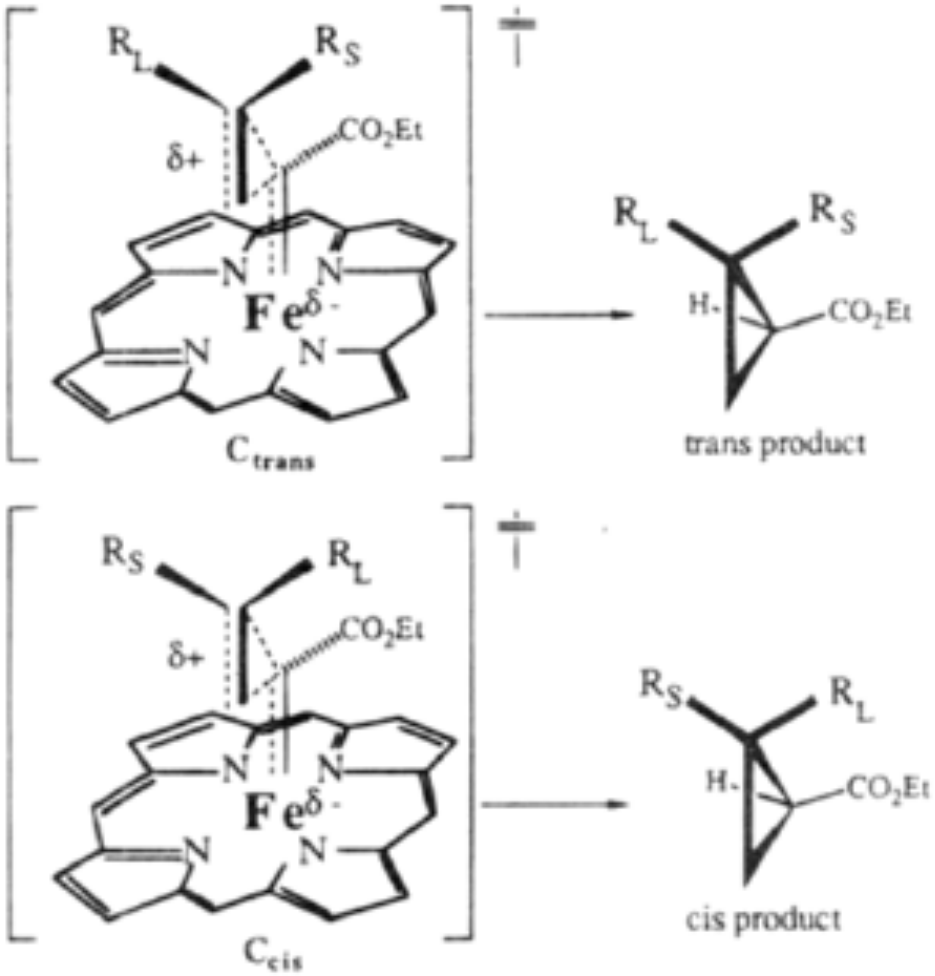




Tetrahedron Lett. 1980, 21, 3489
J. Am. Chem. Soc. 1995, 117, 9194 – 9199

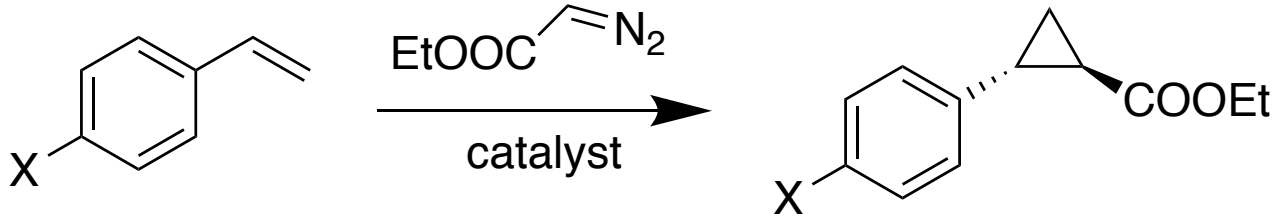


J. Am. Chem. Soc. 1995, 117, 9194 – 9199



J. Am. Chem. Soc. 1995, 117, 9194 – 9199

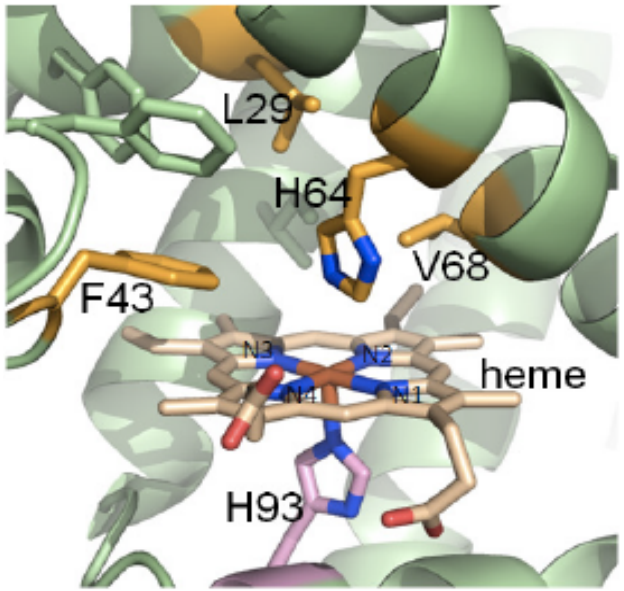
Engineered Myoglobin catalysts

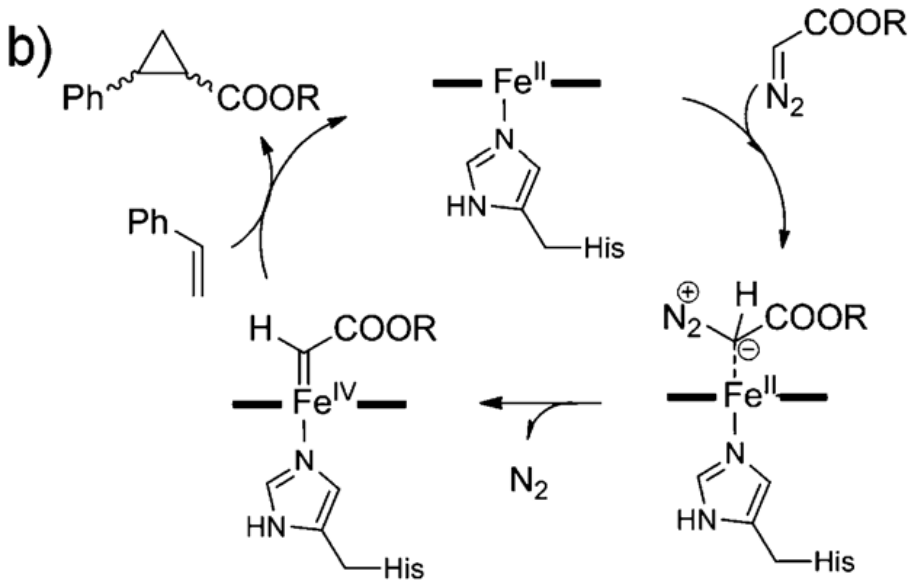


Mb(H64V,V68A)

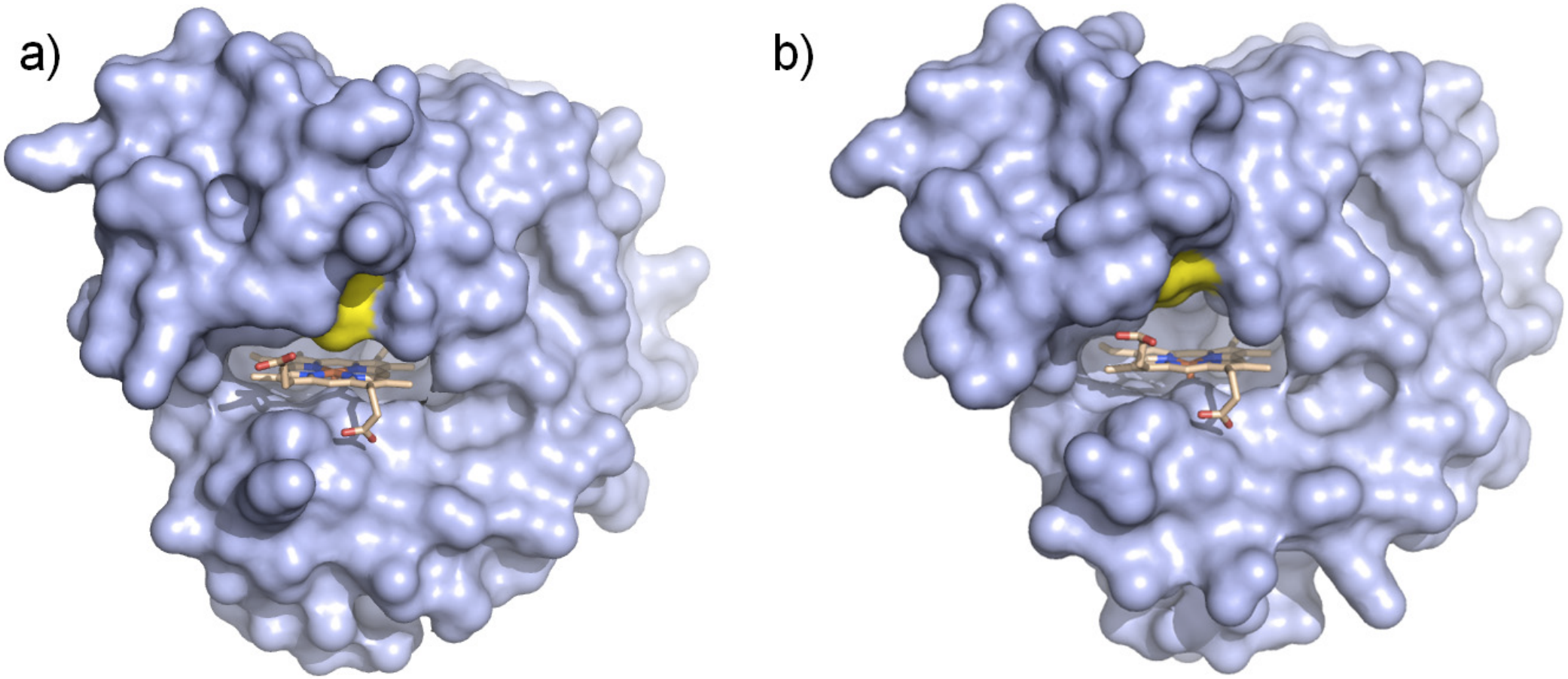
de 97 - 99.9%

ee 96 - 99.9%

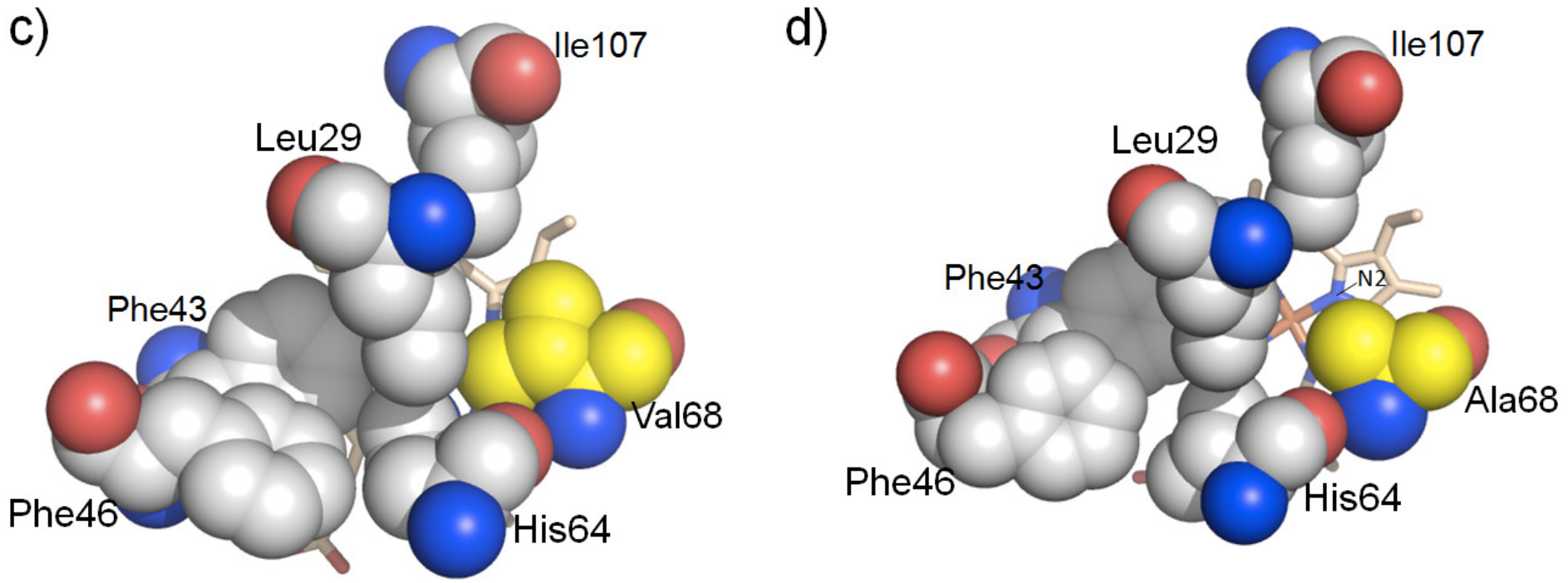


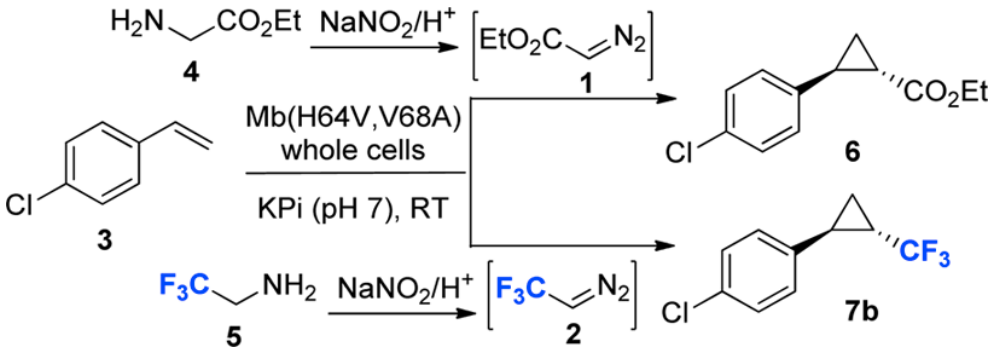


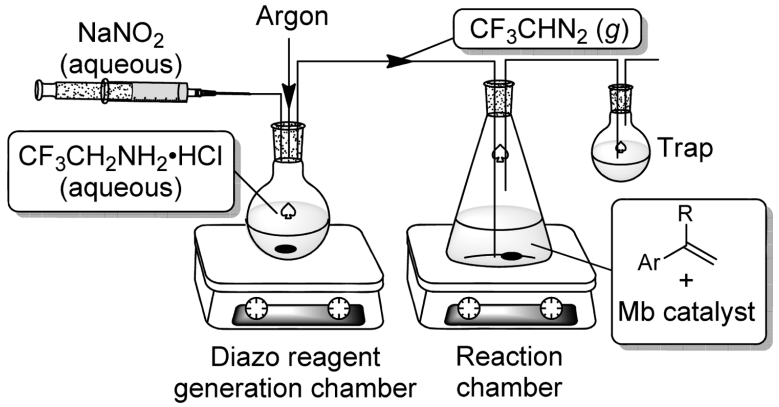
Angew. Chem. Int. Ed. 2015, **54**, 1744



Angew. Chem. Int. Ed. 2015, **54**, 1744

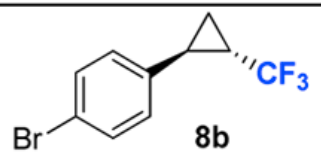
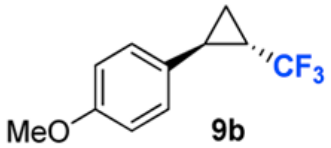
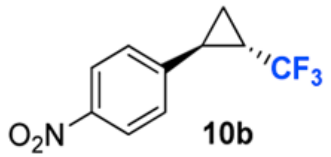
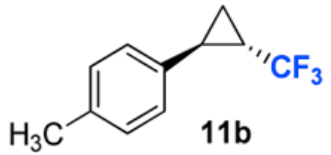
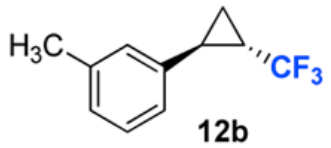
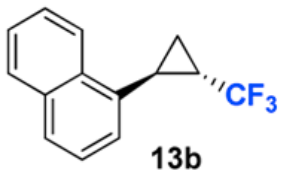
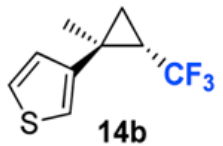

c)
Ile107
Leu29
Phe43
Val68
Phe46
His64
d)
Ile107
Leu29
Phe43
N2
Ala68
Phe46
His64

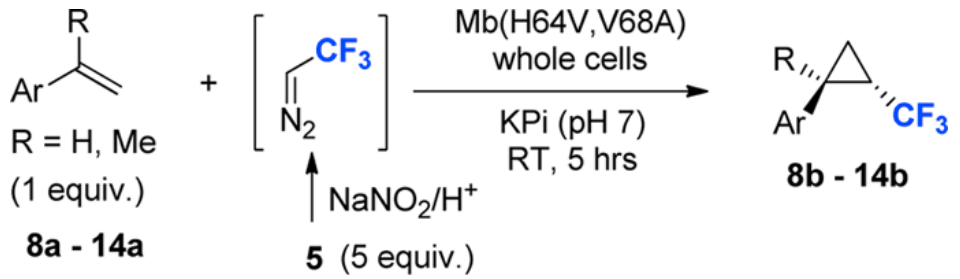


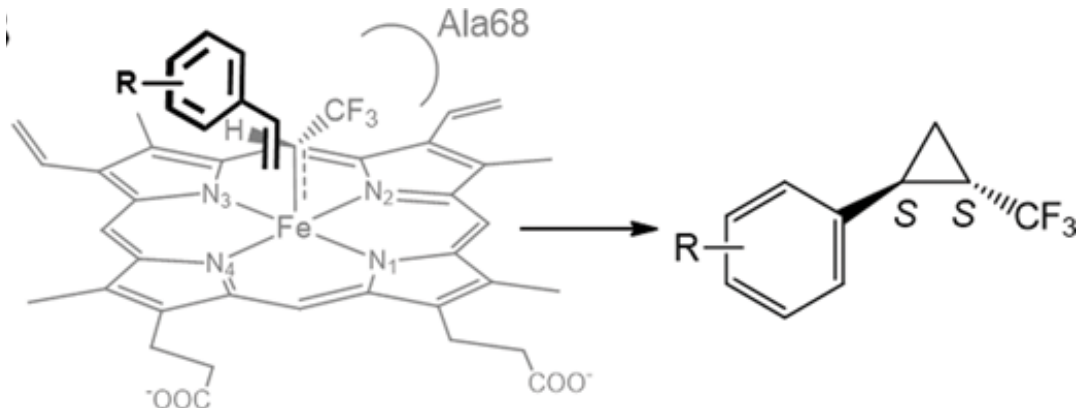


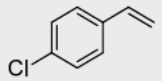
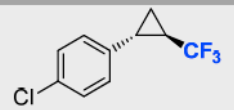
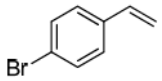
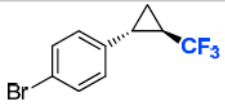
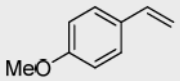
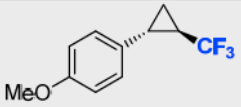
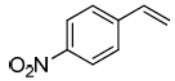
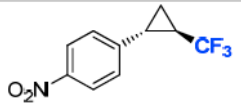
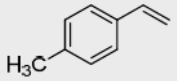
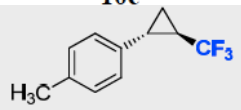
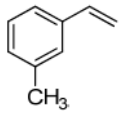
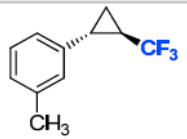
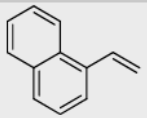
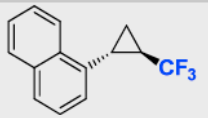
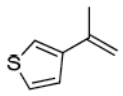
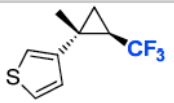
entry	catal.	prod.	equiv 4 or 5[b]	yield[c]	TON	% *de*	% *ee*
1	protein	6	2	4%	180	99.9	99.8
2	cells[d]	6	2	47%	560	97.2	99.9
3	cells	6	5	80%	365	99.9	99.8
4	cells	6	10	75%	340	98.5	99.9
5	cells	6	10	>99%[e]	500	99.9	99.9
6	protein	7b	5	22%	1110	98.5	99.9
7	cells	7b	5	92% (67%)	520	99.9	99.9

Mb Variant	*p*-methoxy-styrene + EDA [a]		*p*-methoxy-styrene + DTE [b]		|Δ(%*de*)|	|Δ(%*ee*)|
	% *de* (trans)	% *ee* (1*S*,2*S*)	% *de* (trans)	% *ee* (1*S*,2*S*)		
WT	79	13	70	4	9	9
Mb(H64V)	91	26	>99	65	8	39
Mb(V68A)	97	86	>99	98	2	12
Mb(H64V,V68A)	>99	99	>99	99.5	0	0.5
Mb(H64V,V68S)	98	84	97	83	1	1
Mb(H64V,V68G)	93	99	>99	98	6	1
Mb(H64V,I107W)	93	77	93	30	0	47

Entry	Product	OD_{600}	Yield [b]	% *de*	% *ee*
1	 **8b**	80	69% (68%)	99.9	99.9
2	 **9b**	80	92% (76%)	99.9	99.9
3	 **10b**	80	54% (43%)	99.9	99.9
4	 **11b**	40 80	85% 88% (78%)	96 96 [c]	31 97 [c]
5	 **12b**	40 80	76% >99% (82%)	99.8 99.9 [c]	28 99.9 [c]
6	 **13b**	80	70% (58%)	99.9	92
7	 **14b**	40	>99% (71%)	99.9	99.9





Entry	Substrate	Product	Mb variant	% *de* (trans)	% *ee* (1*R*,2*R*)
1	 **7a**	 **7c**	Mb(H64V,V68L,L29T) = RR2	99.9	83
2	 **8a**	 **8c**	Mb(H64V,V68L,L29T) = RR2	99.9	80
3	 **9a**	 **9c**	Mb(H64V,V68L,L29T) = RR2	98	91
4	 **10a**	 **10c**	Mb(H64V,V68L,L29T) = RR2	99.9	65
5[a,b]	 **11a**	 **11c**	Mb(H64V,V68L,L29T) = RR2	99.9	85
6[a,b]	 **12a**	 **12c**	Mb(H64V,V68L,L29T) = RR2	99.9	88
7[a,c]	 **13a**	 **13c**	Mb(H64V,V68L,L29T) = RR2 Mb(H64V,V68L,L29T,I107L) = RR4	99.9 99.9	21 58
8[a,c]	 **14a**	 **14c**	Mb(H64V,V68L,L29T) = RR2	99.9	92

Conclusions

1) Developed a biocatalytic strategy for the asymmetric synthesis of trifluoromethyl substituted cyclopropane.

2) Applicable to a number vinylarene substrates and give high enantio- and diastereoselectivity.

3) Both enantiomers are accessible depending on the mutations of the myoglobin.

4) First study which demonstrates that a carbene other than α-diazoesters can be used for biocatalytic carbene transfer.