C-H Bond Functionalization via Hydride Transfer: Formation of α-Arylated Piperidines and 1,2,3,4-Tetrahydroisoquinolines via Stereoselective Intramolecular Amination of Benzylic C-H Bonds

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Supporting Information

Part A. Lewis Acid Screen:

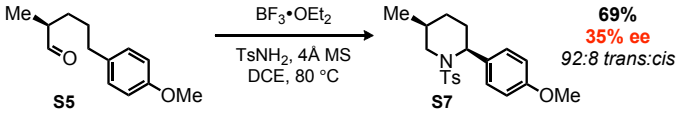
Table S1: The Effect of Various Metal Salts on Substrate **3**

entry	reagent	product **2** (%)	SM **3** (%)	imine **1** (%)
1	BF_3•OEt_2	86	0	0
2	TiF_4	82	0	0
3	$InCl_3$	40	32	27
4	$HfCl_4$	40	0	0
5	$In(OTf)_3$	31	34	33
6	$AuBr_3$	30	17	39
7	$PtCl_4$	27	2	0
8	$TiCl_4$	23	0	0
9	$Sc(OTf)_3$	0	25	75
10	$ScCl_3$	0	43	56
11	$Al(OTf)_3$	0	65	34
12	$Cu(OTf)_2$	0	73	26
13	$B(C_6F_5)_3$	0	77	22
14	$Ti(OEt)_4$	0	90	10
15	$Zn(OTf)_2$	0	99	0
16	$ZnCl_2$	0	99	0
17	$PtCl_2$	0	99	0
18	AuCl	0	83	0
19	$Hf(OTf)_4$	0	0	0
20	$AlCl_3$	0	0	0

All reactions were setup under an argon atmosphere employing 2 equivalents of reagent in DCE at 0.05 M concentration to substrate **3** and heated in a reaction block at 80 °C. Yields were determined by ^{1}H NMR relative to 1,2,4,5-tetrachlorobenzene, which was used as an internal standard.

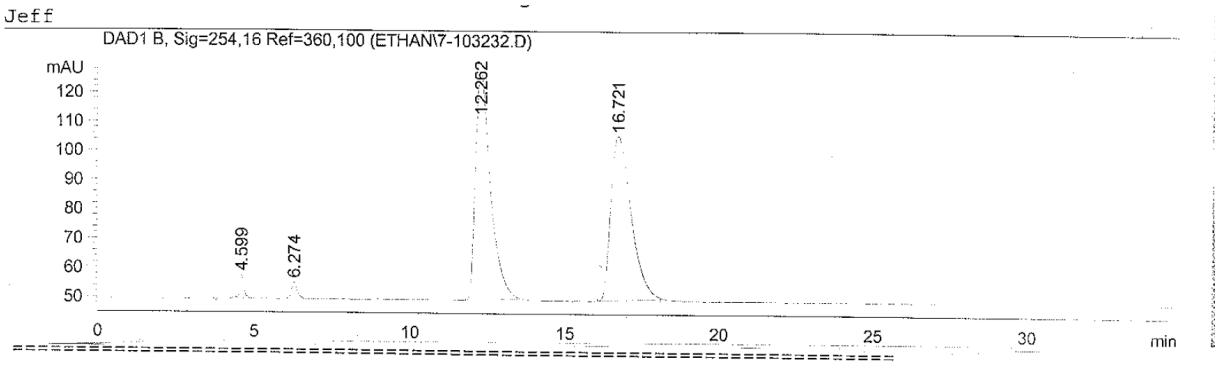
Part B. Discussion of the Reactivity of Chiral Substrate S5:

B.1 Results of the HT-amination of chiral substrate **S5**



Enantiomeric excess analysis was carried out by HPLC using a Chiracel OD Column No. OD00CE-1G001 from Daicel Chemical Industries, LTD. 97 % Hexanes, 3% Isopropanol were used with a flow rate of 1 mL/min.

Chromatogram obtained for racemic standard (compound **19**)



Area Percent Report

Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Sample Amount : 20.00000 [ng/ul] (not used in calc.)

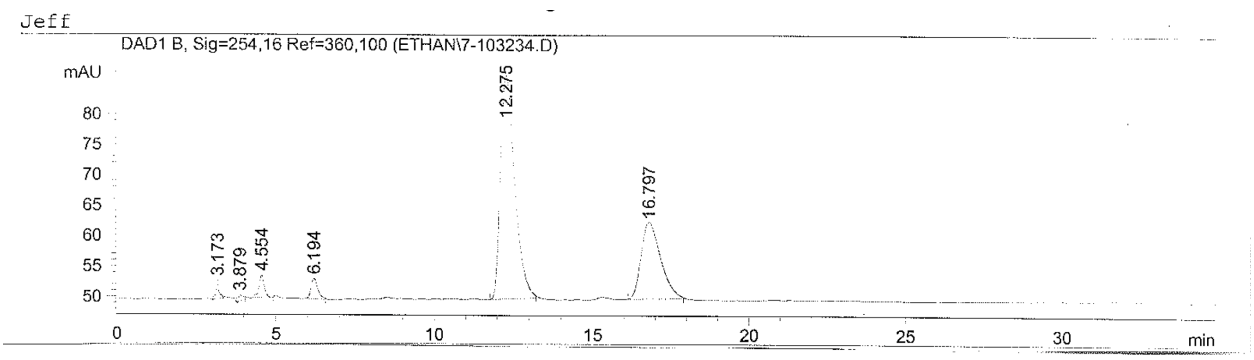
Signal 1: DAD1 B, Sig=254,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %	
1	4.599	VB	0.1310	70.19636	7.95279	1.3159	
2	6.274	BB	0.1913	72.44825	5.66007	1.3581	
3	12.262	BB	0.5030	2612.51147	77.95828	48.9740	•
4	16.721	BB	0.7140	2579.32520	56.13780	48.3519	•

Totals : 5334.48128 147.70894

Results obtained with enhanced integrator!

Chromatogram obtained for compound **S7**

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=====================================================================
                    Area Percent Report
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Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Sample Amount         :     20.00000  [ng/ul]    (not used in calc.)

Signal 1: DAD1 B, Sig=254,16 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]       [min]    [mAU*s]     [mAU]      %
----|-------|----|-------|----------|----------|--------|
   1   3.173 PB    0.0862   19.88968    3.12586   1.0962
   2   3.879 PB    0.1162    9.29710    1.10399   0.5124
   3   4.554 BB    0.1802   44.38266    3.69423   2.4462
   4   6.194 BB    0.2244   50.22655    3.39892   2.7683
   5  12.275 BB    0.4767 1142.86926   36.76376  62.9904
   6  16.797 BB    0.6461  547.69031   12.57604  30.1865

Totals :                  1814.35556   60.66280

 Results obtained with enhanced integrator!
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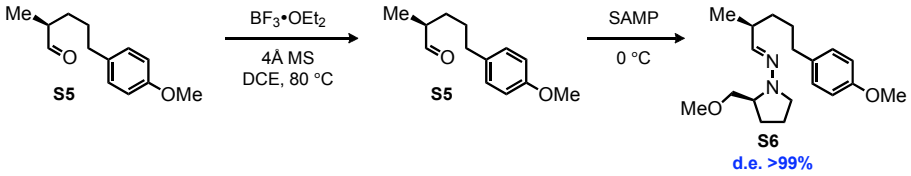
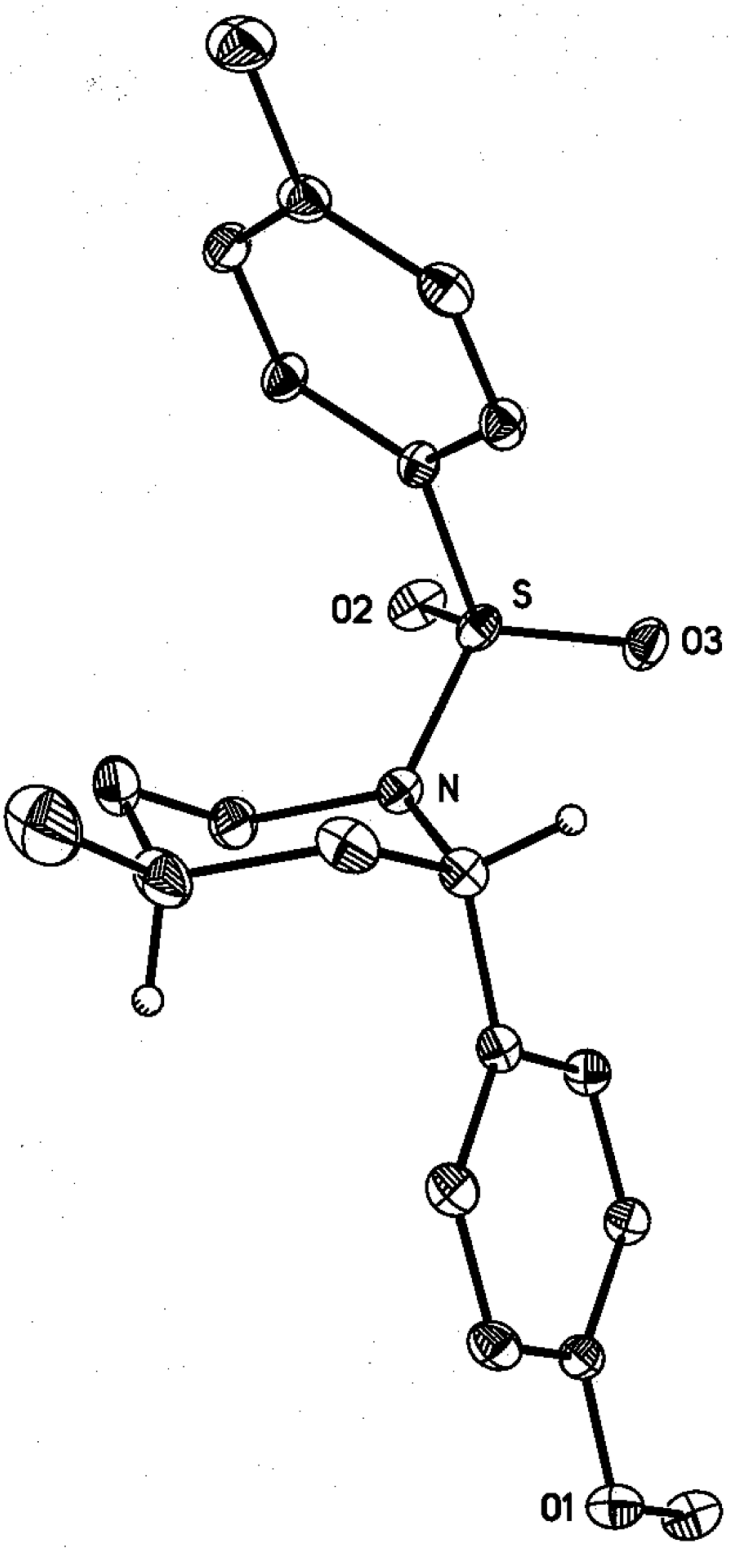
B.2 Rationale for the HT-amination results of **S5**



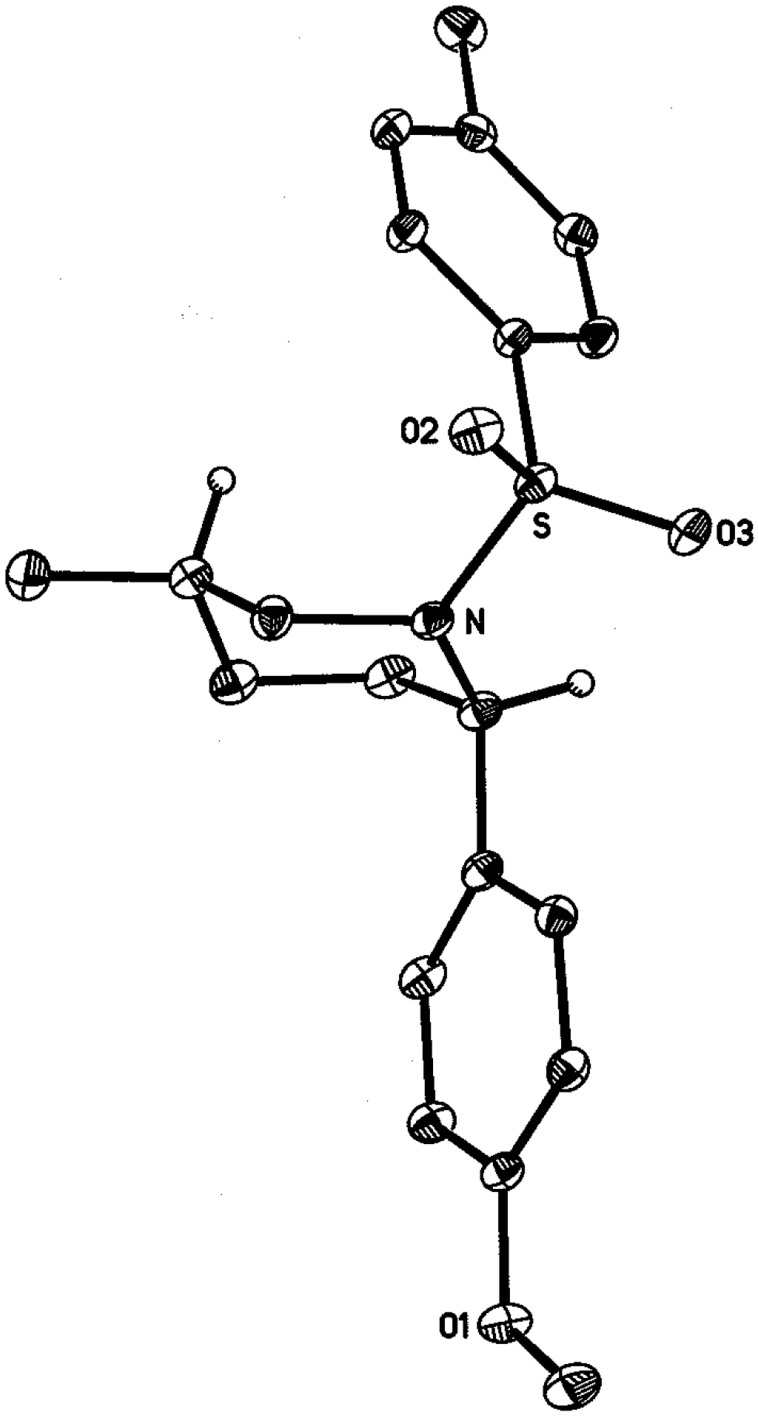
Substrate **S5** was subjected to the standard reaction conditions without the addition of toluenesulfonamide. After stirring for 2 hr at 80 °C the reaction was worked-up according to the general HT-amination procedure. The resulting crude aldehyde was converted to hydrazone **S6** as previously described. The resulting product was analyzed by ^{1}H NMR and was found to have a diastereomeric ratio of >99:1. This result indicated that under the reaction conditions the aldehyde does not undergo tautomerization by the action of BF_3•OEt_2. Given this observation we propose that the epimierization of the α-substituent occurs following formation of the intermediate imine, which likely proceeds through reversible imine-enamine tautomerization.

Part C. X-ray Data for Products 11, 19 and 39:



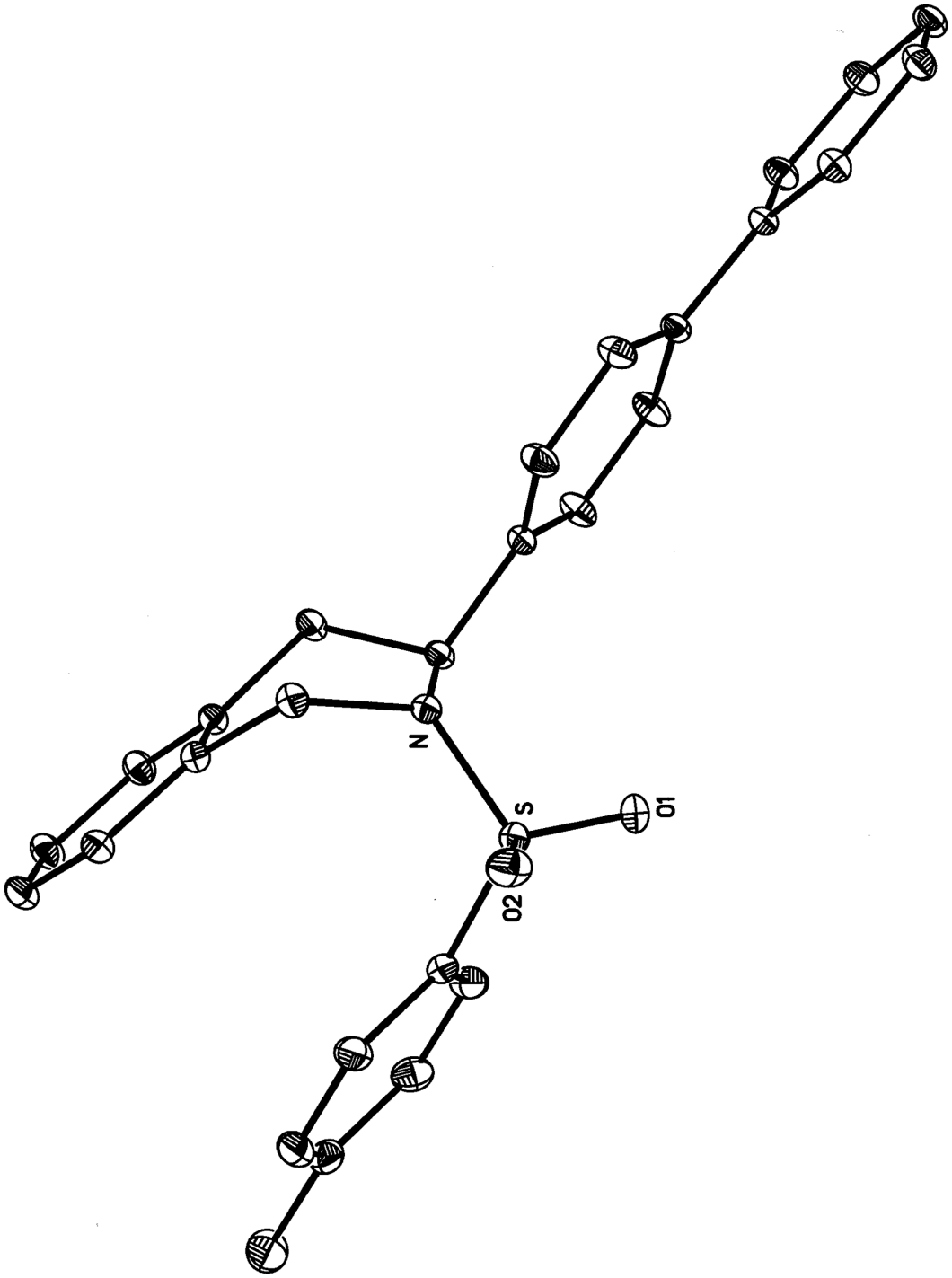
ORTEP of compound 11

Compound	**11**
Empirical formula	$C_{20}H_{25}NO_3S$
Formula weight	359.47 g/mol
Temperature	150(2) K
Wavelength	0.71073 Å
Crystal system	monoclinic
Space group	$P2_1/n$
Unit cell dimensions	*a* = 12.8046(7) Å alpha = 90°
	b = 10.1185(5) Å beta = 105.4920(10) °
	c = 15.2099(8) Å gamma = 90°
Volume, Z	1899.05(17) $Å^3$, 4
Density (calculated)	1.257 Mg/m^3
Absorption coefficient	0.188 mm^{-1}
F (000)	768
Crystal size	0.45 x 0.40 x 0.30 mm
Θ range for data collection	1.85 to 31.00°
Limiting indicies	$-18 \le h \le 18$, $-14 \le k \le 14$, $-22 \le l \le 22$
Reflections collected	30712
Independent reflections	6072 (R_{int} = 0.0245)
Completeness to Θ = 31.00°	100.0%
Absorption correction	EMPIRICAL
Max. and min. transmission	0.9456 and 0.9200
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	6072 / 0 / 229
Goodness-of-fit on F^2	1.027
Final R indices [I>2σ(I)]	R1 = 0.0401, wR2 = 0.1090
R indicies (all data)	R1 = 0.0507, wR2 = 0.1186
Largest diff. peak and hole	0.447 and -0.434 $eÅ^{-3}$



ORTEP of compound 19

Compound	**19**
Empirical formula	$C_{20}H_{25}NO_3S$
Formula weight	359.47 g/mol
Temperature	200(2) K
Wavelength	0.71073 Å
Crystal system	monoclinic
Space group	$P2_1/n$
Unit cell dimensions	*a* = 13.6482(7) Å alpha = 90°
	b = 10.2749(5) Å beta = 103.1450(10) °
	c = 13.7082(7) Å gamma = 90°
Volume, Z	1871.98(16) $Å^3$, 4
Density (calculated)	1.257 Mg/m^3
Absorption coefficient	0.191 mm^{-1}
F (000)	768
Crystal size	0.31 x 0.25 x 0.25 mm
Θ range for data collection	1.90 to 30.57°
Limiting indicies	$-19 \le h \le 19$, $-14 \le k \le 14$, $-19 \le l \le 19$
Reflections collected	29321
Independent reflections	5757 (R_{int} = 0.0299)
Completeness to Θ = 31.00°	99.9%
Absorption correction	EMPIRICAL
Max. and min. transmission	0.9538 and 0.9431
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	5757 / 0 / 229
Goodness-of-fit on F^2	1.035
Final R indices [I>2σ(I)]	R1 = 0.0482, wR2 = 0.1264
R indicies (all data)	R1 = 0.0655, wR2 = 0.1391
Largest diff. peak and hole	0.599 and -0.460 $eÅ^{-3}$



ORTEP of compound 39

Compound	**39**
Empirical formula	$C_{28}H_{25}NO_2S$
Formula weight	439.55 g/mol
Temperature	125(2) K
Wavelength	0.71073 Å
Crystal system	monoclinic
Space group	C2/c
Unit cell dimensions	*a* = 27.9292(15) Å alpha = 90°
	b = 8.1522(4) Å beta = 92.9860(10) °
	c = 19.4546(10) Å gamma = 90°
Volume, Z	4423.5(4) $Å^3$, 8
Density (calculated)	1.320 Mg/m^3
Absorption coefficient	0.173 mm^{-1}
F (000)	1856
Crystal size	0.43 x 0.40 x 0.10 mm
Θ range for data collection	1.46 to 30.50°
Limiting indicies	$-39 \le h \le 39$, $-11 \le k \le 11$, $-27 \le l \le 27$
Reflections collected	34522
Independent reflections	6754 (R_{int} = 0.0222)
Completeness to Θ = 31.00°	99.9%
Absorption correction	EMPIRICAL
Max. and min. transmission	0.9829 and 0.9295
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	6754 / 0 / 290
Goodness-of-fit on F^2	1.042
Final R indices [I>2σ(I)]	R1 = 0.0402, wR2 = 0.1050
R indicies (all data)	R1 = 0.0471, wR2 = 0.1118
Largest diff. peak and hole	0.575 and -0.298 $eÅ^{-3}$