Electronic Supplementary Material (ESI) for RSC Advances

Electronic Supplementary Information

Improved synthesis of Tadalafil using dimethylcarbonate and ionic liquids.

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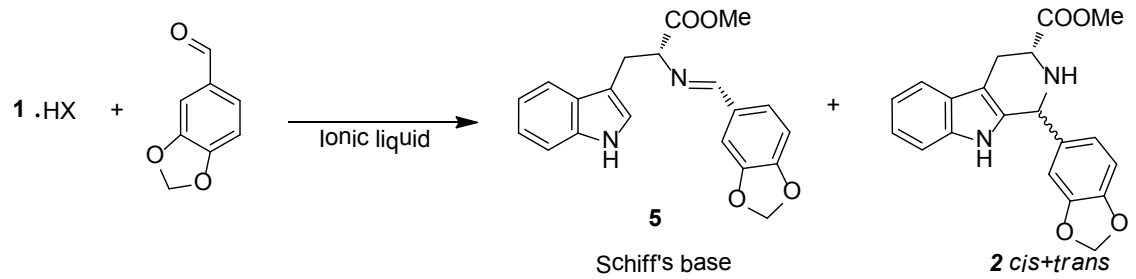
Pictet-Spengler reaction in ionic liquids

The reaction of tryptophan methyl ester with benzo[*d*][1,3]dioxole-5-carbaldehyde was studied using different ionic liquids as solvents (scheme S1).



Scheme S1. Pictet-Spengler reaction in ionic liquids between Tryptophan methyl ester and benzo[*d*][1,3]dioxole-5-carbaldehyde yield the Schiff base as an intermediate and the *cis* and *trans* adducts as products.

A series of reaction were carried out varying tryptophan salt anion, acid catalyst, reaction temperature and times and the solvent (Table S1).

Reactions were monitored by ^{1}H-NMR spectra of the mixture in deuterated chloroform after neutralisation with aqueous Na_2CO_3. At the end of the selected reaction time, mixtures were analysed using ^{1}H-NMR spectroscopy. Conversion and selectivity towards Pictet-Spengler adducts (*cis* and *trans*) were evaluated by integration of the CH_2 signals of the benzo[*d*][1,3]dioxole-5-carbaldehyde residue of compounds **2** ***cis*****, 2** ***trans*** and **5** against the same signal of benzo[*d*][1,3]dioxole-5-carbaldehyde (see Figure S12).[1]

For every reaction we took in consideration the conversion, the selectivity towards the Pictet-Spengler adduct and lastly the diastereoselctivity as *cis* to *trans* ratio. Results are summarised in Table 1.

The reaction was always very slow at room temperature, while at higher temperature (> 80° C), the formation of the desired product in moderate to good yields was achieved in reasonable reaction time (< 24 hours). However at high temperature no diastereoselection was observed (Table S1, line 3-6), while at 20 °C, even if the conversion was quite low, interestingly the *cis:trans* ratio was 80:20 (Table S1, line 3-6). Therefore we tried to find the conditions in which reaction proceeded smoothly at room temperature or lower to preserve diastereoselectivity. Hence we thought to use trifluoroethanoic acid as a catalyst as reported in Table S1, line 10-18 (this organic acid is commonly used as a catalyst in this kind of reaction[2]).

Table S1. The reaction of tryptophan methyl ester with benzo[*d*][1,3]dioxole-5-carbaldehyde in different ionic liquids[a]

#	HX	Ionic liquid	Cat	T(°C)	Time (h)	Conv. (%NMR)	Schiff base (%NMR)	cis+trans (%NMR)	cis/trans (NMR)
1	HCl	$[C_4dmim][NTf_2]$	none	20	22	<5	-	-	-
2				60	5	10	-	10	60/40
3				80	24	>80	-	>80	50/50
4				100	6	>80	-	>80	50/50
5		$[C_2mim][HSO_4]$	none	80	2	60	-	60	60/40
6				80	6	70	-	70	60/40
7		$[C_2mim][TFA]$	none	20	2	40	40	-	-
8	TFA	$[C_2mim]TFA$	none	20	5	15	13	2	80/20
9				20	23	21	13	5	80/20
10	None	$[C_4dmim][NTf_2]$	TFA[b]	20	2	90	90	-	-
11			TFA[c]	20	2	25	17	8	80/20
12				20	10	30	10	20	80/20
13				20	32	45	13	33	80/20
14				20	288	>80	-	>80	80/20
15			TFA[d]	20	2	20	10	10	80/20
16				20	18	50	10	40	70/30
17				20	65	>80	-	>80	60/40
18				20	96	>80	-	>80	60/40

[a]All reaction were carried out as follows; in a 2 mL vial 1.00 mmol of the appropriate tryptophan methyl ester salt, 1.25 g of the selected ionic liquid and 165 mg (1.1 mmol) of benzo[*d*][1,3]dioxole-5-carbaldehyde were added.using 1.25 g of ionic liquid as the solvent. The molar ratio tryptophan methyl ester: benzo[*d*][1,3]dioxole-5-carbaldehyde was 1.1.

[b]TFA:tryptophan methyl ester molar ratio was 0.10. [c]TFA:tryptophan methyl ester molar ratio was 2.0.

[d]TFA:tryptophan methyl ester molar ratio was 5:1

^{1}H and ^{13}C NMR Spectra

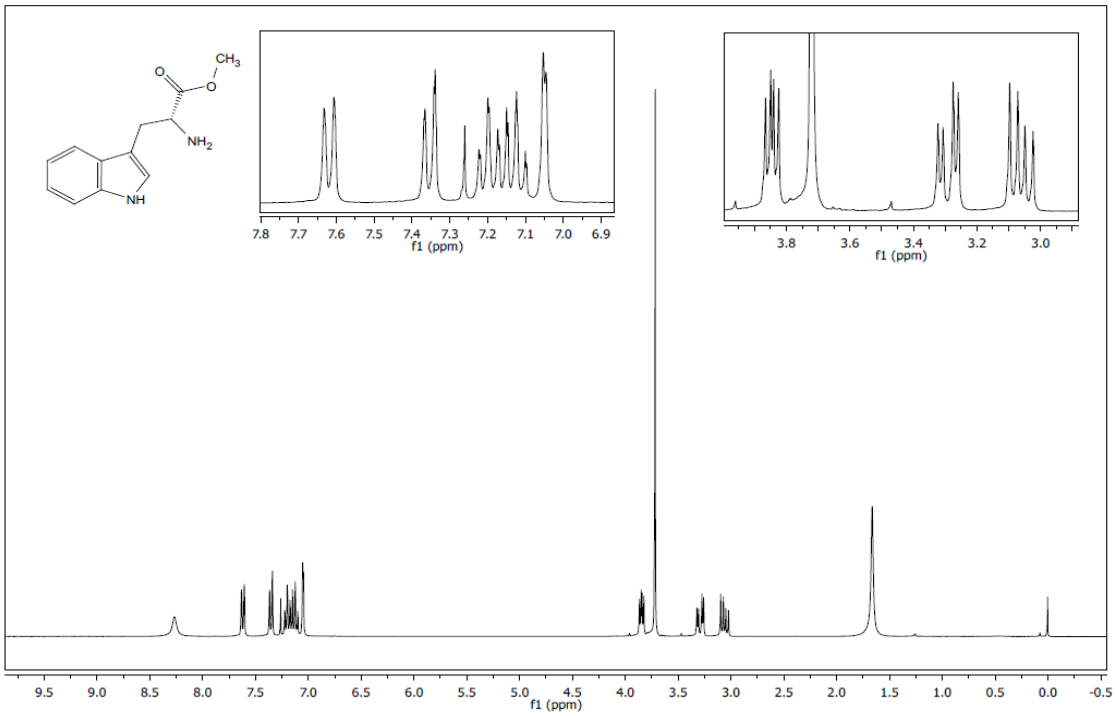


Figure S1 ^{1}H NMR ($CDCl_3$, 300 MHz) spectrum of compound **1**.

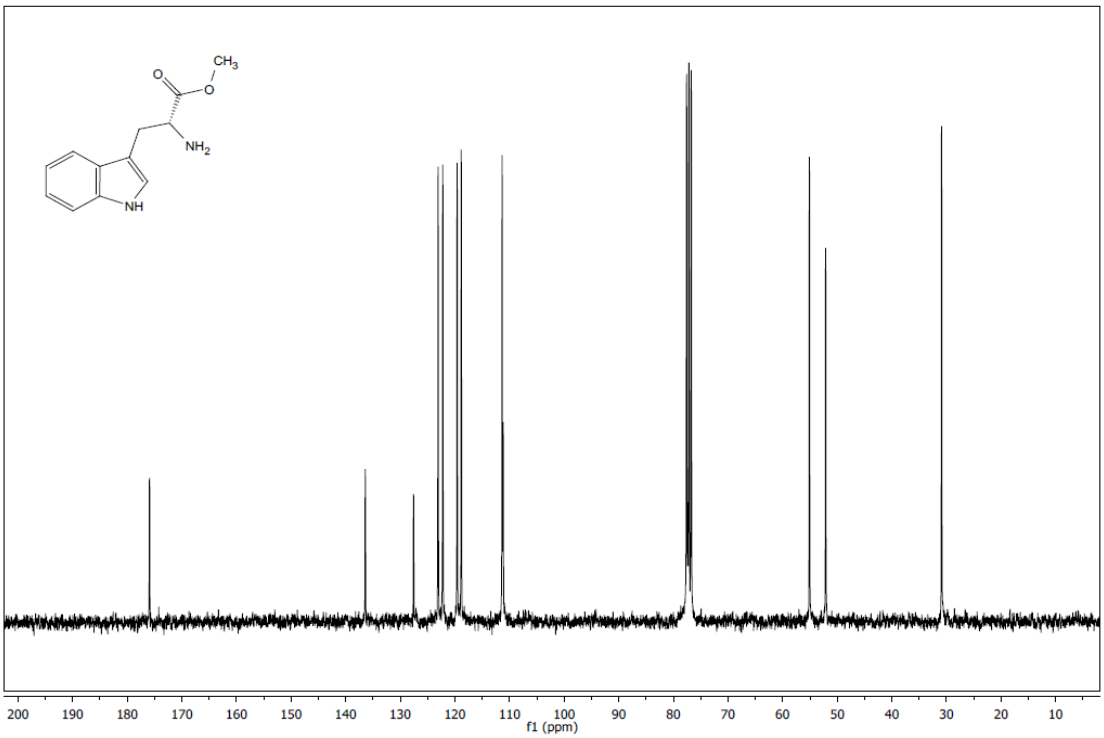


Figure S2. ^{13}C NMR ($CDCl_3$, 75 MHz) spectrum of compound **1**.

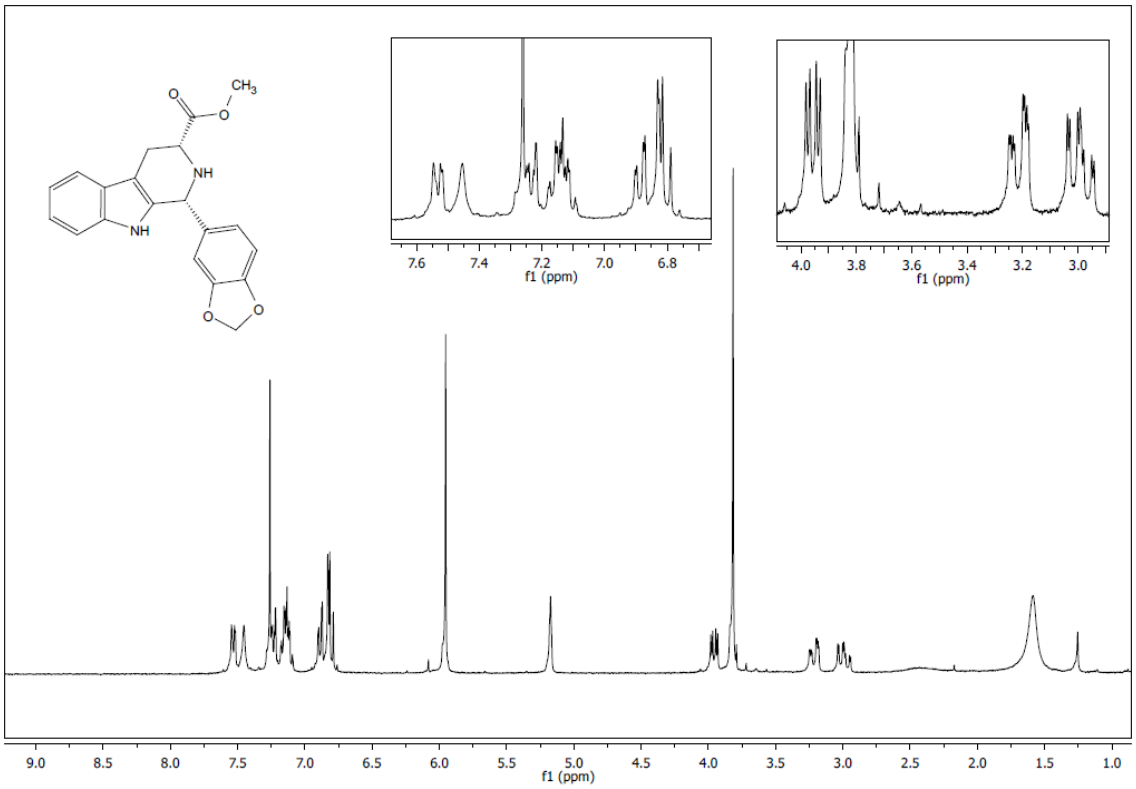


Figure S3. ^{1}H NMR ($CDCl_3$, 300 MHz) spectrum of compound **2*cis***.

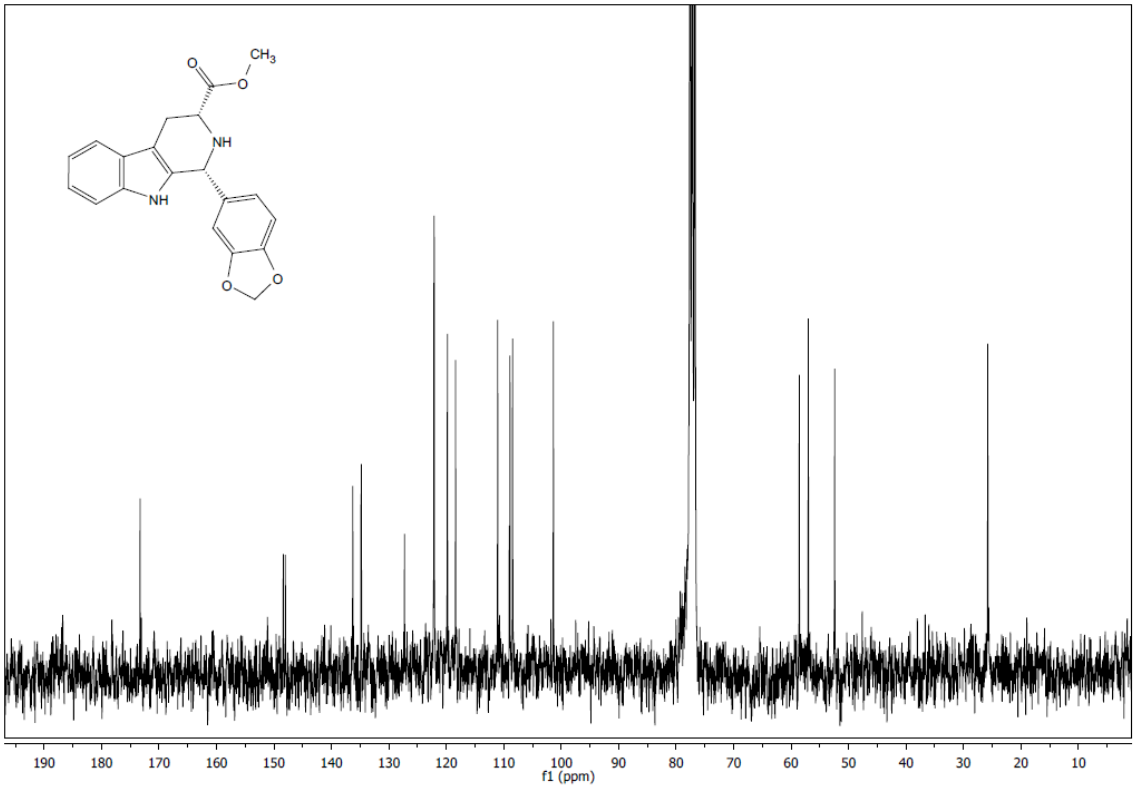


Figure S4. ^{13}C NMR ($CDCl_3$, 75 MHz) spectrum of compound **2*cis***.

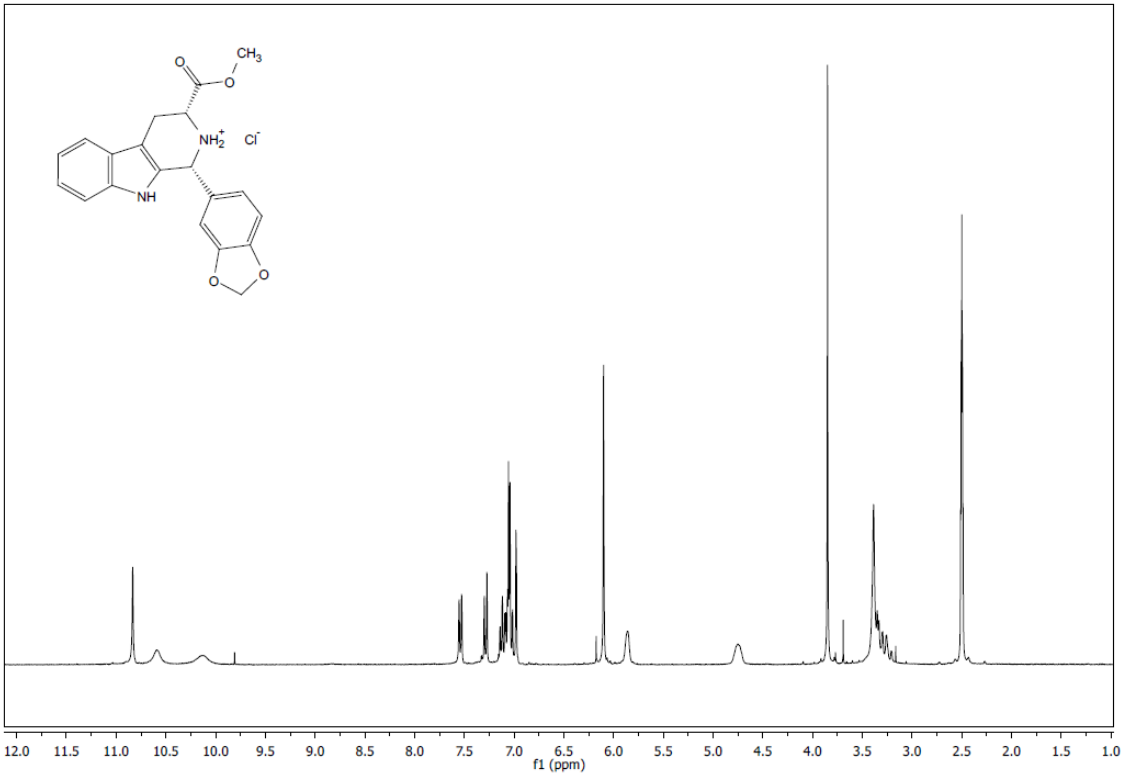


Figure S5. ^{1}H NMR (DMSO-d_6, 300 MHz) spectrum of compound **2*cis*·HCl**.

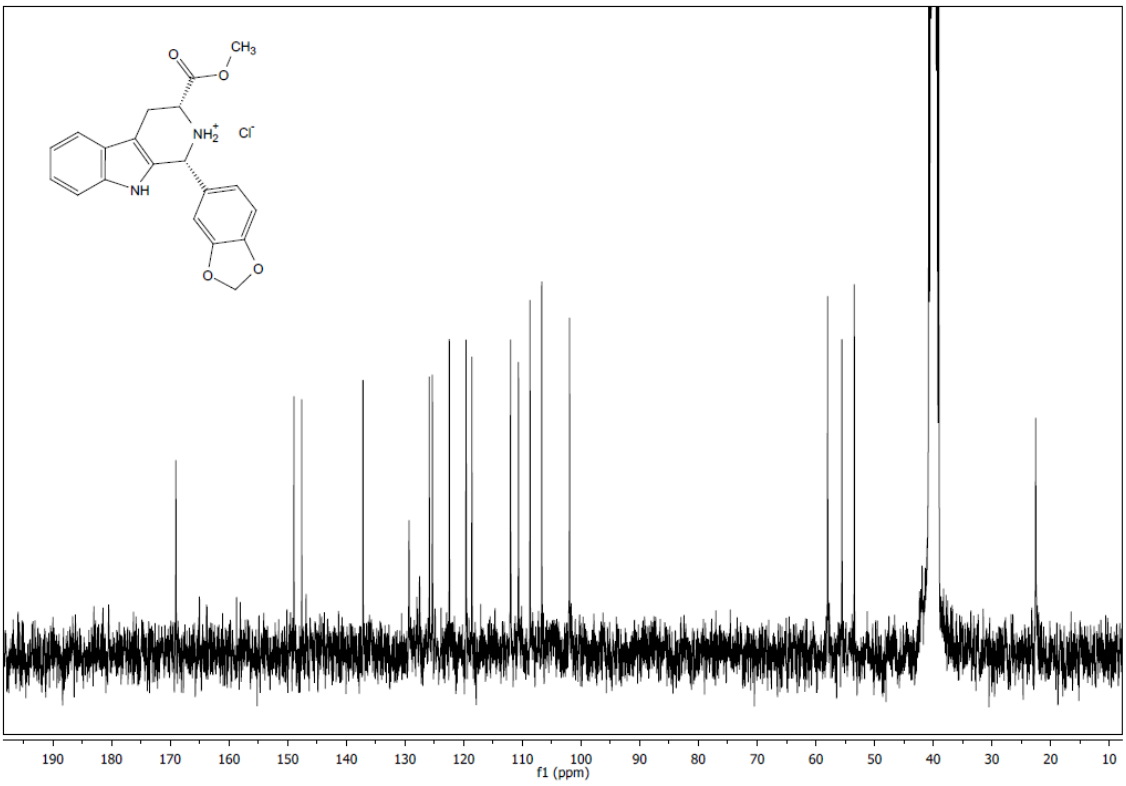


Figure S6. ^{13}C NMR (DMSO-d_6, 75 MHz) spectrum of compound **2*cis*·HCl**.

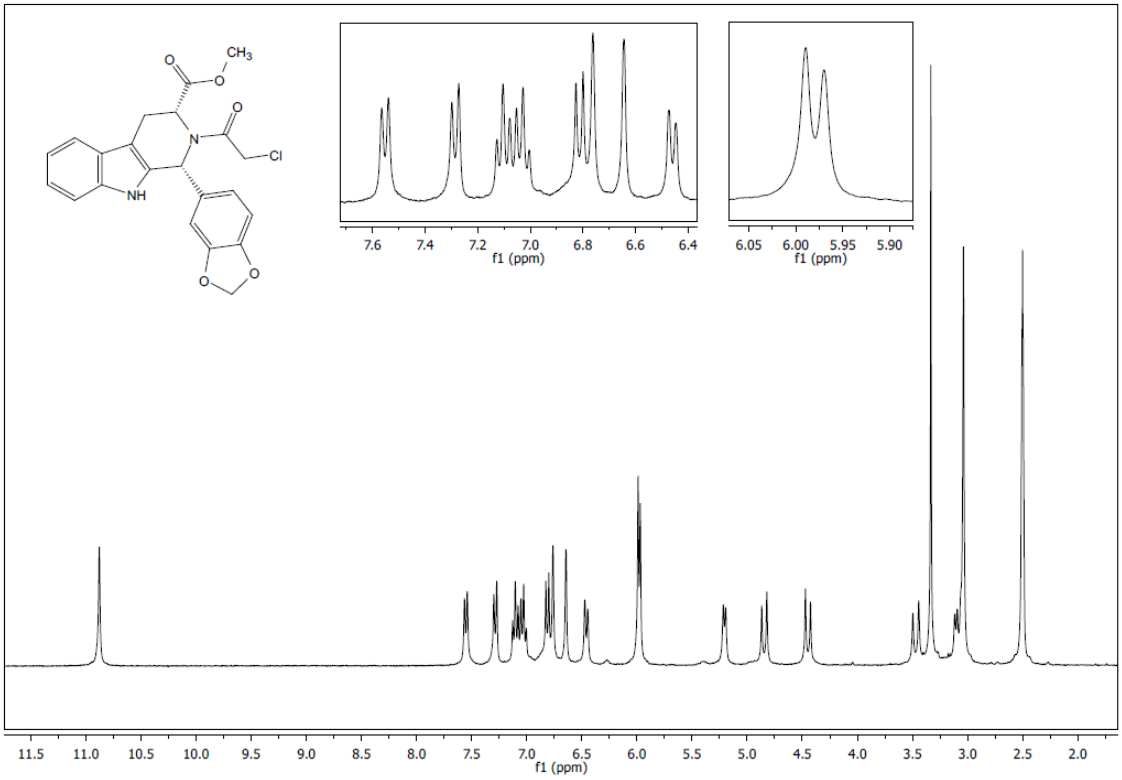


Figure S7. ^{1}H NMR (DMSO-d_6, 300 MHz) spectrum of compound **3**.

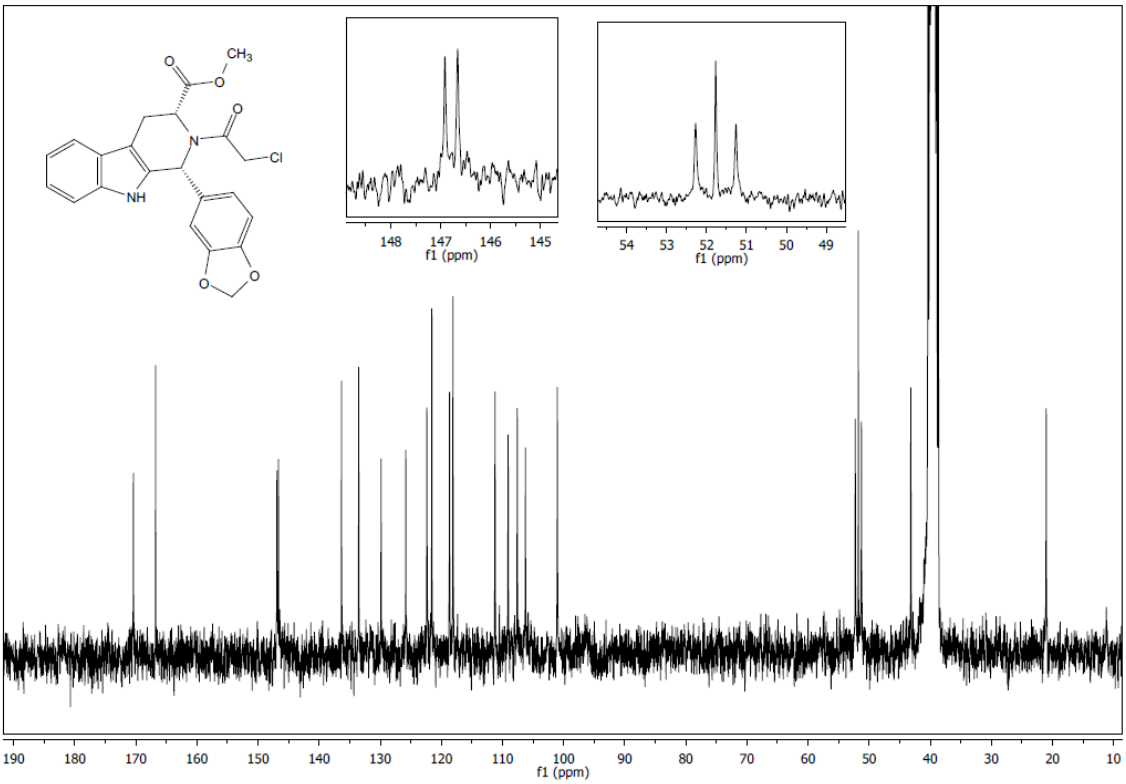


Figure S8. ^{13}C NMR (DMSO-d_6, 75 MHz) spectrum of compound **3**.

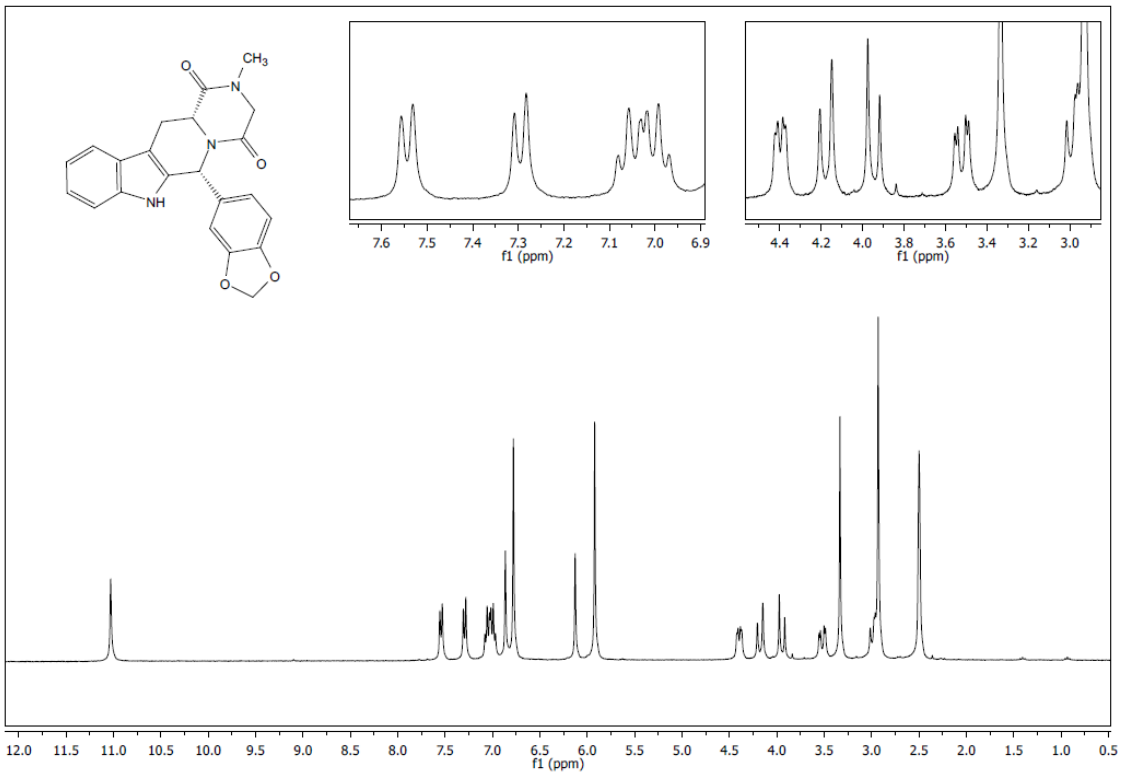


Figure S9. ^{1}H NMR (DMSO-d_6, 300 MHz) spectrum of compound **4**.

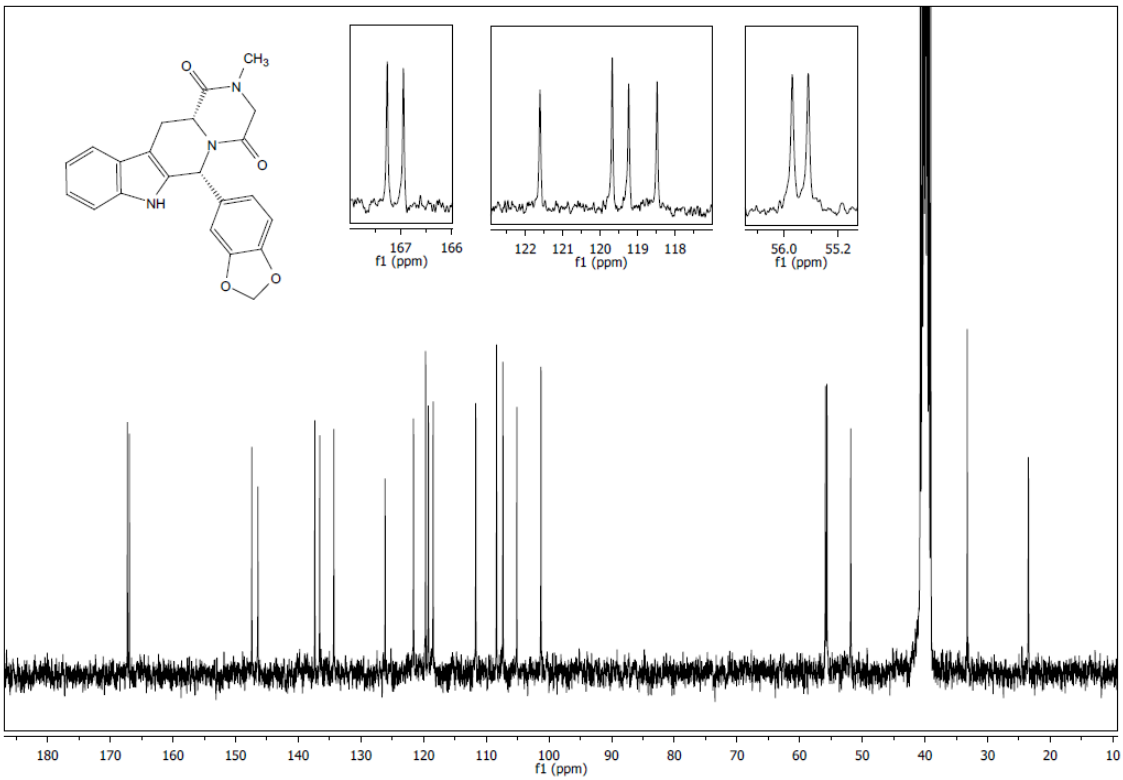


Figure S10. ^{13}C NMR (DMSO-d_6, 75 MHz) spectrum of compound **4**.

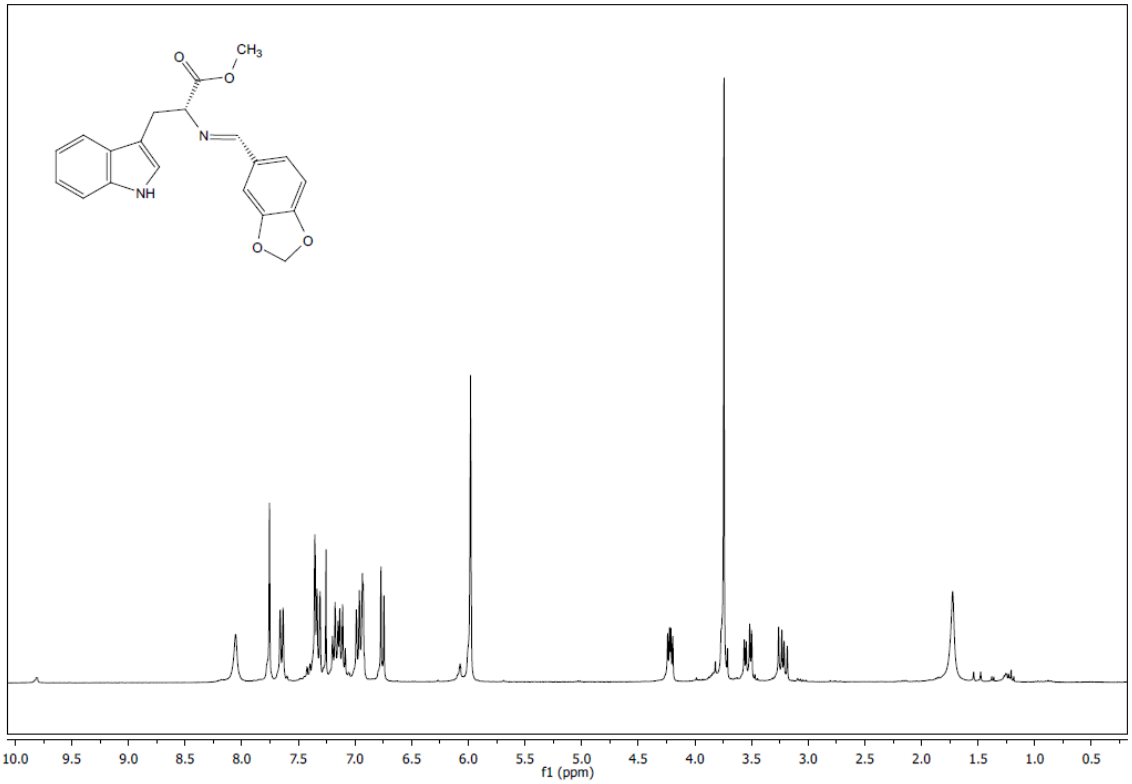


Figure S11. ^{1}H NMR ($CDCl_3$, 300 MHz) spectrum of the Schiff's base **5**.

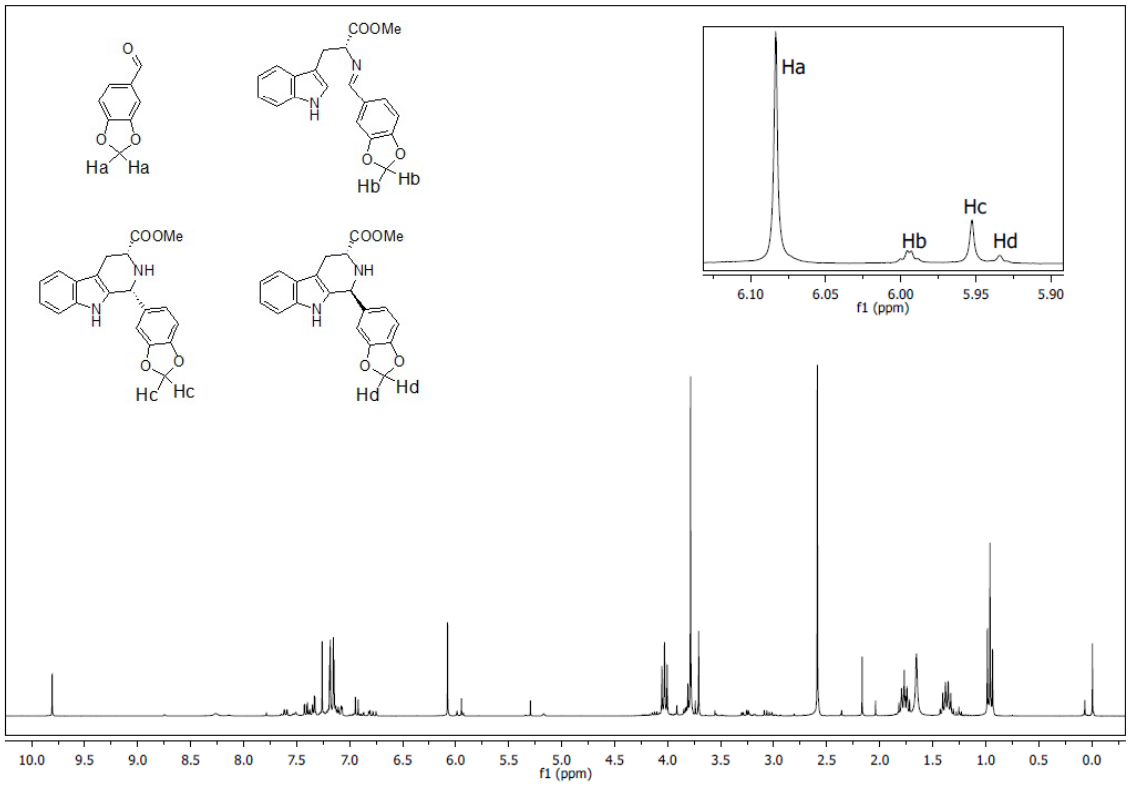


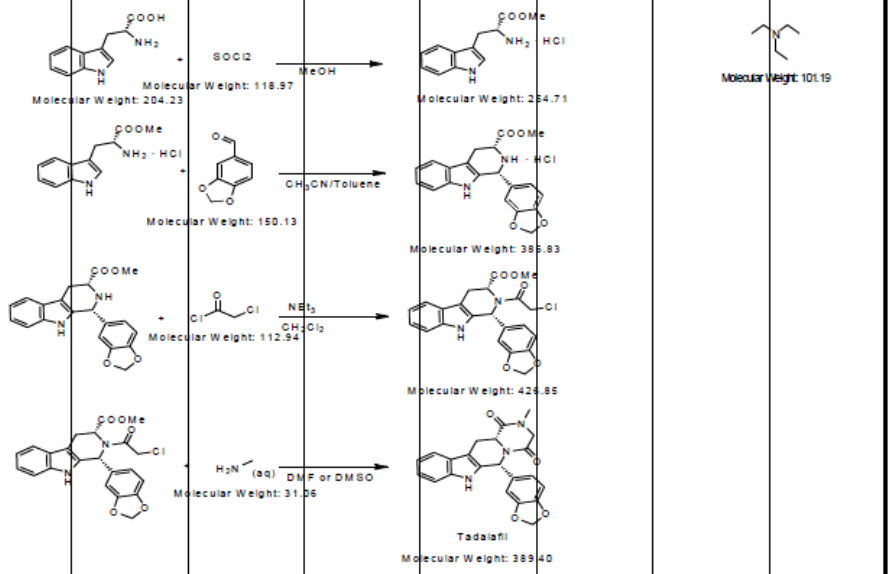
Figure S12. ^{1}H NMR ($CDCl_3$, 300 MHz) spectrum of the Pictect-Spengler reaction mixture in [C_4dmim][NTf_2]. Diagnostic signals whose integration was used to evaluate conversion and selectivity of the reaction are highlighted in the expansion box.1

Mass indices calculations

The spreadsheet developed by Andraos[3] was used for the calculation of the Mass Indeces and other green chemistry metrics (Figures 13-14). To perform the calculation each step was virtually scaled by the appropriate factor in order to simulate a process in which starting from 2.00 g of D-tryptophan all the obtained products were used in the following step.

REACTION METRICS FORM
REFERENCE:
DATE:
NAME OF TARGET PRODUCT:
REACTION CLASSIFICATION:

BALANCED CHEMICAL EQUATIONS:



PART 1: RAW MATERIALS USAGE

(A) REACTION STAGE:

(i) REAGENTS	SC	MW (g/mol)	Density (g/mL)	Volume (mL)	Moles	Mass (g)	Cost ($/g)	Cost ($)	
D tryptophan	1	204,13			0,009797678	2		0,000	12
thionylchloride	1	118,97	1,631	1,00	0,013709338	1,631		0,000	13
piperonal	1	150,13			0,011350163	1,704		0,000	
triethylamine	2	101,19			0,038818065	1,964		0,000	
chloroacetylchl	1	112,94			0,017965291	2,029		0,000	14
methylamine	1	31,06			0,082678686	2,568		0,000	15
								0,000	
TOTAL REAGENTS		718,42			Add lines 12 to 15	11,896		0,000	16

(ii) CATALYSTS / LIGANDS	MW (g/mol)	Density (g/mL)	Volume (mL)	Moles	Mass (g)	Cost ($/g)	Cost ($)	
							0,000	19
							0,000	20
							0,000	21
TOTAL CATALYSTS				Add lines 19 to 21	0		0,000	22

Figure S13. Spreadsheet (part 1) used to calculate the Green Chemistry Metrics relative to the developed processes for the preparation of Tadalafil.

(iii) SOLVENTS		Density (g/mL)	Volume (mL)		Mass (g)	Cost ($/g)	Cost ($)			
MeOH		0,791	32		25,312		0,000	25		
DMC		1,069	24		25,656		0,000	26		
C4dmim NTf2					26,96		0,000			
Water		1	3,852		3,852		0,000	27		
TOTAL SOLVENTS				Add lines 25 to 27	81,78		0,000	**28**		
Reaction Materials Subtotals				Add lines 16, 22, 28	93,676		0,000	31		
(B) WORK-UP STAGE:										
MATERIAL		Density (g/mL)	Volume (mL)		Mass (g)	Cost ($/g)	Cost ($)			
					0		0,000	35		
					0		0,000	36		
					0		0,000	37		
					0		0,000	38		
					0		0,000	39		
TOTAL WORK-UP MATERIALS				Add lines 35 to 39	0		0,000	**40**		
(C) PURIFICATION STAGE:										
MATERIAL		Density (g/mL)	Volume (mL)		Mass (g)	Cost ($/g)	Cost ($)			
					0		0,000	44		
					0		0,000	45		
					0		0,000	46		
					0		0,000	47		
TOTAL PURIFICATION MATERIALS				Add lines 44 to 47	0		0,000	**48**		RME
Post-reaction Materials Subtotals				Add lines 40, 48	0		0,000	50		
					Mass (g)	**Cost ($)**				
TOTAL INPUT MATERIALS				Add lines 31, 50	93,676	0,000	53			

		MW (g/mol)	**Moles**	**Yield**	**Mass (g)**	**Cost ($/g)**				
OUTPUT TARGET PRODUCT		389,4	0,007945557	0,810963303	3,094	0,000	56			
PART 2: GREEN METRICS ANALYSIS										
Limiting reagent:										
PARAMETER		VALUE								
Reaction Scale		0,009797678	moles		61					
E(mw)		0,844940935	MW byproducts/MW product		62					
AE		0,542022772	MW product/Σ MW reagents		63					
(i) Under reclaiming reaction solvents, catalysts, and byproducts, and all post-reaction materials										
Mass of waste (line 16 - 56)		8,802	g		66					
E(m)		2,844861021	g waste/g product		67					
RME		0,260087424	g product/Σ g inputs		68					
MI		3,844861021	Σ g inputs/g product		69					
SF		1,69004933			70					
Mass of excess reagents		4,857152207								
Wasted input costs ($)		0,000			72					
(ii) Under committing all reaction solvents, catalysts, and byproducts, and post-reaction materials to waste										
Mass of waste (line 53 - 56)		90,582	g		75					
E(m)		29,27666451	g waste/g product		76					
RME		0,033028737	g product/Σ g inputs		77					
MI		30,27666451	Σ g inputs/g product		78					
Wasted input costs ($)		0,000			79					
Check formula (RME)		0,033029			81					
(iii) Under reclaiming ...										
Mass of waste		12,654	g		84					
E(m)		4,090	g waste/g product		85					
RME		0,196	g product/Σ g inputs		86					
MI		5,090	Σ g inputs/g product		87					
Wasted input costs ($)					88					

Figure S14. Spreadsheet (part 2) used to calculate the Green Chemistry Metrics relative to the developed processes for the preparation of Tadalafil.

Notes and references

1 [1]H-NMR spectra of compounds **2*cis***, **2*trans*** and **5** are reported in literature. See a) J. D. Revell, N. Srinivasan and A. Ganesan, *Synlett*, 2004, **8**, 1428 - 1430; b) X. -X. Shi, S.L. Liu, W. Xu and Y.L. Xu, *Tetrahedron:Asymmetry,* 2008, **19**, 435–442.

2 B. Saha, S. Sharma, D. Sawant and B. Kundu, *TetrahedronLetters,* 2007, **48**, 1379–1383.

3 (a) J. Andraos and M. Sayed, M. *J. Chem. Educ*. 2007, **84**, 1004. (b) J. Andraos, *Org. Process Res. Dev.*, 2009, **13**, 161-185.