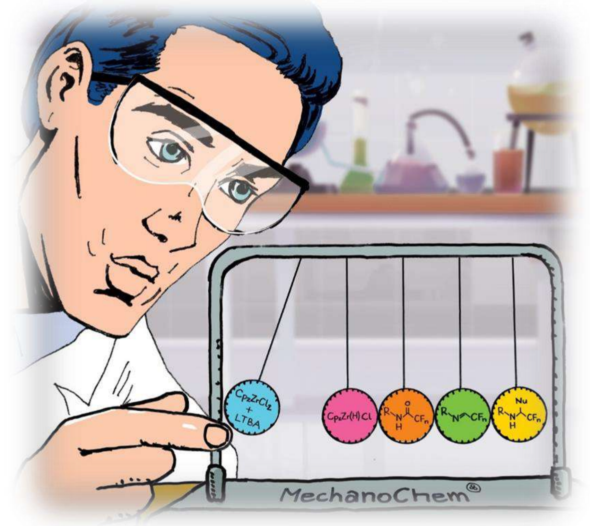

From flask to mill: reductive functionalization of fluoroacetamides as a case study for transferring solvent-based reactions to the solid state

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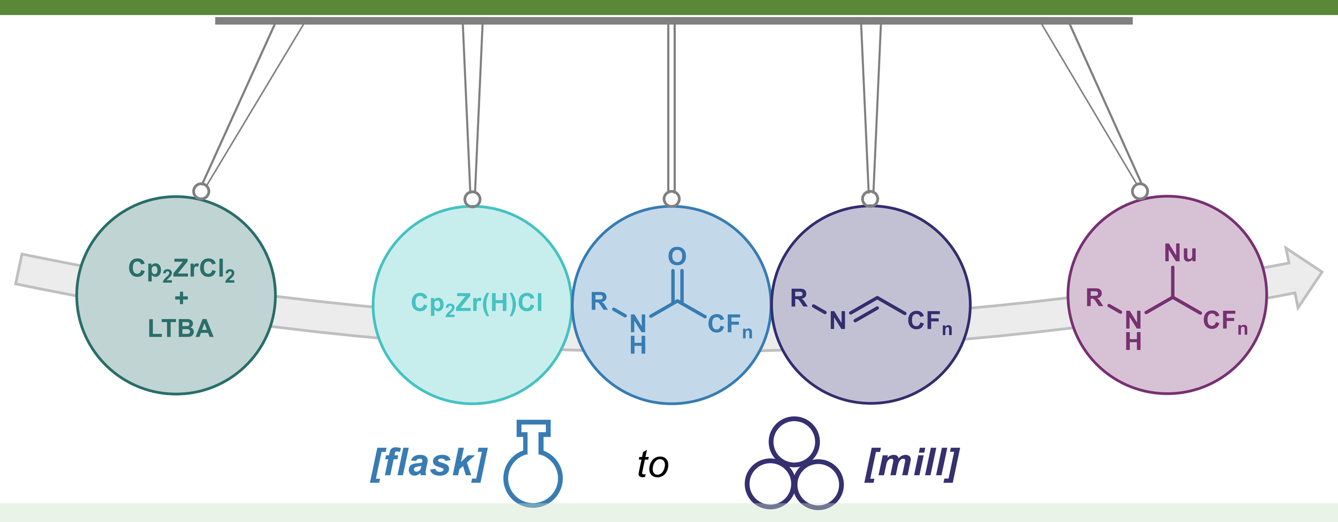
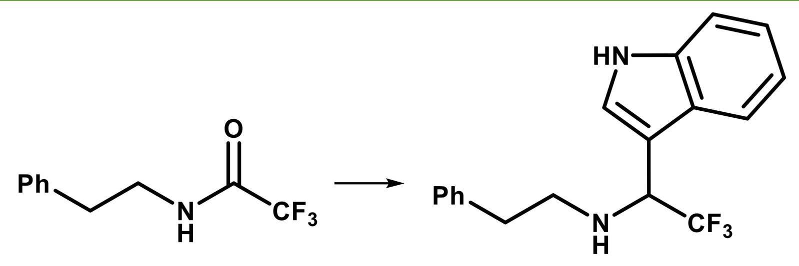
From flask to mill



- mechanochemical Schwartz's reagent generation
- no chromatography
- three-steps one-jar
- more green

The step-by-step adaptation of a solution-based methodology for the reductive functionalization of fluoroacteamides to a ball-milling conditions was developed. The solid-state, two-steps one-jar strategy based on the partial reduction of amides by an in situ mechanochemically generated zirconocene chloride hydride (Schwartz's reagent) and tandem nucleophilic addition of indole to afford high-value functionalized fluorinated amines. In addition, the sustainable approach was complemented by operationally simple purification by an acidic resin.

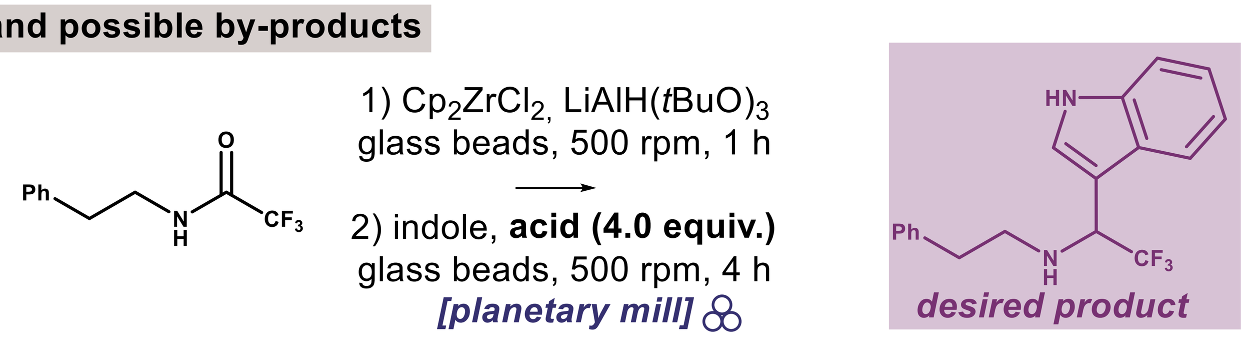
Methodology transfer

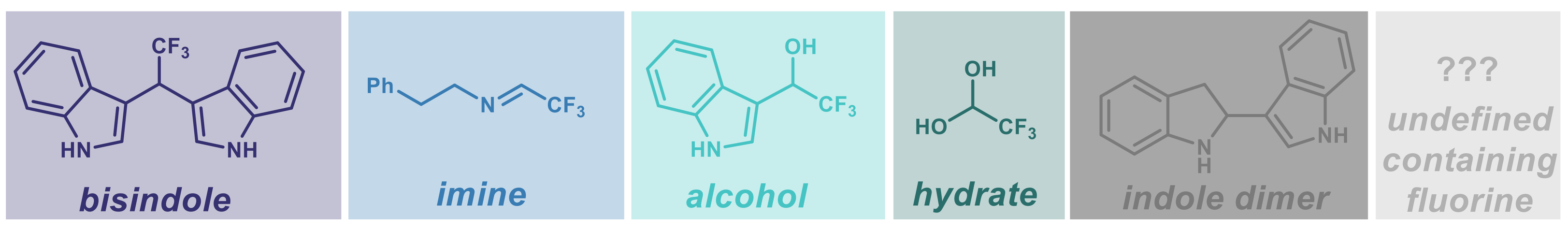


[flask]	**[mill]**
1) $Cp_2Zr(H)Cl$ THF, 45 min, rt 2) TFA, indole THF, 16 h, rt	1) Cp_2ZrCl_2, $LiAlH(tBuO)_3$ 500 rpm, 1 h 2) 4-nitrophenol, indole toluene (LAG) 500 rpm, 2 h

Adaption and optimization

reaction and possible by-products





influence of acid on products distribution

acid	indole dimer	product to fluorinated byproducts ratio	distribution of fluorinated products
none	no	1 : 1.55	39% / 14% / 11% / 8% / 25%
$Et_3N \cdot HCl$	no	1 : 4.15	19% / 12% / 14% / 43% / 12%
PhOH	no	1 : 0.43	70% / 17%
NH_4Cl	no	1 : 3.50	22% / 7% / 16% / 11% / 35% / 8%
H_3BO_3	no	1 : 0.84	54% / 7% / 28%
4-nitrophenol	**no**	**1 : 0.09**	**92%**
PhCOOH	no	1 : 0.98	51% / 15% / 8% / 21%
camphorsulphonic	yes	1 : 0.66	60% / 8% / 7% / 24%
$HClO_4 \cdot SiO_2$	yes	1 : 0.62	62% / 23% / 9%

Optimization of grinding auxiliaries

grinding auxiliaries

entry	grinding auxiliary	amide conversion[b] [%]
1	molecular sieves 4A	0
2	silica gel	0
3	neutral Al_2O_3	0
4	NaCl	32
5	Na_2SO_4	90
6	**soda-lime glass beads**	**96**

mass transfer


without grinding auxiliary


with grinding auxiliary

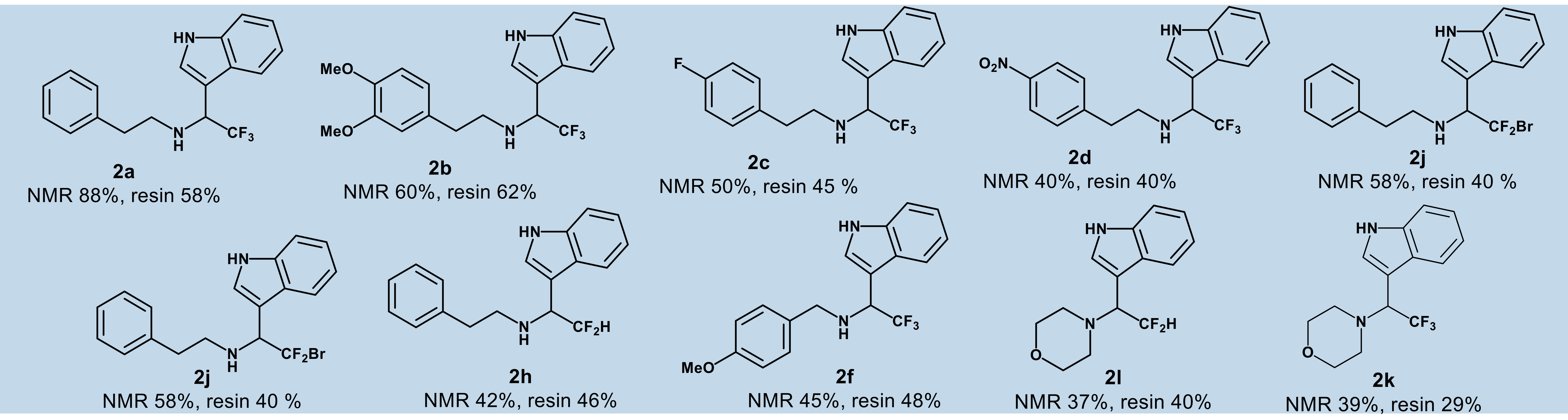

with grinding auxiliary and intervals with direction reversal

Reaction time and liquid additives impact

time, liquid assistance and control experiments

reducing system	time [h] (2nd step)	LAG (2nd step)	atmosphere	yield [%]
Cp_2ZrCl_2/LTBA	2	-	inert	68
Cp_2ZrCl_2/LTBA	4	-	inert	63
Cp_2ZrCl_2/LTBA	2	MeCN	inert	40
Cp_2ZrCl_2/LTBA	2	hexane	inert	62
Cp_2ZrCl_2/LTBA	**2**	**toluene**	**inert**	**78**
Cp_2ZrCl_2/LTBA	2	toluene	air	50
$Cp_2Zr(H)Cl$	2	toluene	inert	20
LTBA	2	toluene	inert	0

Scope of amides



- **2a** NMR 88%, resin 58%
- **2b** NMR 60%, resin 62%
- **2c** NMR 50%, resin 45 %
- **2d** NMR 40%, resin 40%
- **2j** NMR 58%, resin 40 %
- **2j** NMR 58%, resin 40 %
- **2h** NMR 42%, resin 46%
- **2f** NMR 45%, resin 48%
- **2l** NMR 37%, resin 40%
- **2k** NMR 39%, resin 29%

Sustainability of the process

green metrics

type of the process	sEF (the less the better)	cEF (the less the better)	EcoScale (the more the better)
in solution	2666	8894	42
mechanochemically	**106**	**5861**	**51**

Acknowledgements

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