Green Chemistry

SUPPLEMENTARY INFORMATION

Key Green Chemistry Research Areas from a Pharmaceutical Manufacturers' Perspective Revisited.

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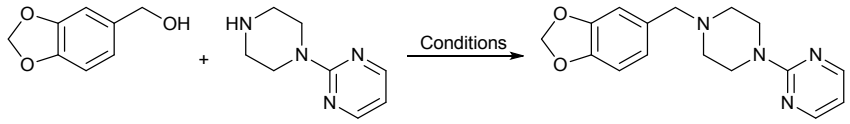
Roundtable Member Companies participating in the vote:
Amgen,
AstraZeneca
Boehringer Ingelheim
Bristol-Myers Squibb
Codexis
Dr. Reddy's
Eli Lilly and Company
F-Hoffmann-La Roche Ltd./Genentech
GlaxoSmithKline
Johnson & Johnson
Merck & Co., Inc.
Novartis
Pfizer, Inc.
Sanofi

Table 1: Long Lists and Votes

Research Area	Votes
Development of effective and versatile methodology utilizing cheap/ sustainable metals (i.e. palladium replacement/ development of environmentally benign catalysts)	11
General methods for catalytic/sustainable (direct) amide or peptide formation	10
Aliphatic and aromatic C-H activation using green oxidants and giving predictable site selectivities	10
Amide reductions avoiding LAH and diborane	9
Direct substitution of alcohols	8
Catalyst immobilization without significant loss in kinetics	8
Asymmetric hydrogenation of unfunctionalized olefins/enamines/imines	7
Improved methods for Fluorination/Trifluoromethoxylation	6
Wittig chemistry without Ph_3PO	5
Greener alternatives for oxidations and C-O or C-N redox processes	5
Preparation of non-small molecule APIs *e.g.* Oligonucleotides, antibody/drug conjugates, proteins.	4
Friedel–Crafts reactions on unactivated substrates	4
N-Centred chemistry avoiding azides, hydrazine etc.	4
Asymmetric hydroamination of olefins	4
sp^3-sp^2 and sp^3-sp^3 carbon-carbon bond formations	4
Tandem catalytic systems	4
Asymmetric hydrocyanation	3
Organocatalysis	3
Demethylation reactions	2
Aldehyde or ketone + NH_3 + ''X'' to give a chiral amine	2
Oxygen nucleophiles with high reactivity	2
Hydroxylation	2
Methods of coupling challenging heterocycles prone to protodeboronation	2
Synthesis of aliphatic /aromatic ethers	1
Green / scalable olefin metathesis (macrocyclization) at high concentration	1
Nitration reactions	1
Radical chemistry without Bu_3SnH	1
Asymmetric hydroformylation	1
Direct arylation	1
Coupling of hindered amines with aryl halides	1
Better racemization catalysts for Dynamic Kinetic Resolutions	1
Catalytic selective alkylation	1
Sulfonation reactions	0
Ester hydrolysis	0
Asymmetric hydrolysis of nitriles	0
C-H halogenation	0
Photocatalysis for redox reactions	0
Oxidation/Epoxidation methods without the use of chlorinated solvents	0

Solvent Themes	Votes
Viable replacements for polar aprotic solvents	9
Viable replacements for halogenated solvents	8
Use of sustainable reaction media/solvents applicable to process scale chemistry	6
Improved chemistry methodology in aqueous systems	4
Viable replacements for ethereal solvents	0

Table 2: Hydrogen borrowing approaches to Piribedil



	Catalyst	Solvent/base	Temp/Pressure/Time	Scale, Yield
1	$[Ru(p\text{-cymene})Cl_2]_2$ (1.25 mol %), dppf (2.5 mol %)	toluene	Reflux, 24 h	87%
2	$[Ru(p\text{-cymene})Cl_2]_2$ (2.5 mol %), DPEphos (5 mol %)	neat	Microwave, 115 °C, 1.5 h	Alcohol (2 mmol), 89% (chromatography)
3	Ir cat (0.005 mmol)	TFE (2.6 mL), K_2CO_3 (0.025 mmol),	100 °C, 24 h	Alcohol (0.5 mmol), amine (0.6 mmol), 99%
4	Fe Knolker complex (5 mol %) Homogeneous	CPME Ne_3NO (10 mol %)	130 °C, 42 h	Alcohol (4 equiv., 0.5 mmol), 54%
5	Polystyrene supported Ru (0.29 mmol Ru/g) (5 mol %) Heterogeneous	toluene	140 °C, sealed tube, 48 h	Alcohol (1.2 equiv.), amine (1 mmol), 98%
6	$NiCuFeO_x$ (50 mg), Ni 43.4, Cu 13.4, and Fe 12.1 wt %. Heterogeneous	xylene	Reflux, sealed tube, 24 h	Alcohol (1.0 mmol), Amine (1.0 mmol), 93%
7	Au/TiO_2 1 wt% (1.8 mol% Au) Heterogeneous	toluene	200 °C, 50 bar	Alcohol (1 g), piperazine (2 g), both (0.5M), 79% conversion, 77% yield after recryst, no column.
8	Palladacycle (0.5 mol %), $P(2\text{-furyl})_3$ (1 mol %) Homogeneous	Neat, LiOH, 4A sieves,	120 °C, 24 h	Alcohol (1.2 equiv.), piperazine (assumed 3 mmol), 76% No experimental
9	Raney Nickel (0.5 g) Heterogeneous	xylene (10 – 12 mL)	Reflux, 24 h	Alcohol (4 equiv.), piperazine (4 mmol), 85% (chromatography)

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3. Q. Zou, C. Wang, J. Smith, D. Xue and J. Xiao, *Chem. Eur.—J.*, 2015, **21**, 9656.
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5. S. P. Shan, T. T. Dang, A. M. Seayad and B. Ramalingam, *ChemCatChem*., 2014, **6**, 808.
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7. N. Zotova, F. J. Roberts, G. H. Kelsall, A. S. Jessiman, K. Hellgardt and K. K. Hii, *Green Chem*., 2012, **14**, 226.
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Table 3: Nucleophilic deoxyfluorination reagents

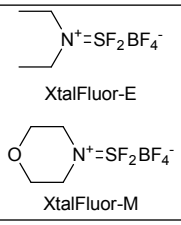
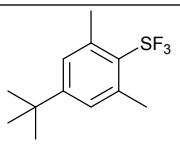
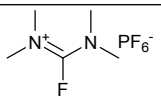
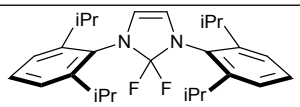
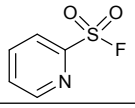
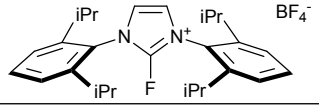
Name	Structure	Comments
X-Talfluor-E and -M[1]	 XtalFluor-E XtalFluor-M	SF_2 reagents with improved thermal stability over DAST. Deoxyfluorination, using triethylamine tris-HF (TREAT-HF) or DBU as additives in DCM or DCE.
Fluolead[2]		SF_3 fluorinating agent with a higher temperature of thermal decomposition than DAST; doesn't react with water. Deoxyfluorination of secondary alcohols with inversion, ketones are converted to gem-difluorides with pyridine-HF additive and carboxylic acid to $-CF_3$ by heating neat at 100 °C. Alcohols and ketones reacted in DCM or DCE solvent.
Tetramethylfluoroformamidinium hexafluorophosphate (TFFH)[3]		C–F reagent for fluorination of allylic, benzylic and tertiary alcohols in ethyl acetate using TREAT-HF and triethylamine additives; elimination occurs predominantly with secondary alcohols.
PhenoFluor[4]		Imidazolium C–F reagent capable of direct substitution of phenols to aryl fluorides extended to deoxyfluorination of alcohols; moisture sensitive.
PyFluor[5]		Deoxyfluorination with low elimination by-products in toluene using only DBU as additive.
AlkylFluor[6]		Moisture stable reagent for deoxyfluorination of primary and secondary alcohols, superior performance for sterically challenging alcohols. KF additive in dioxane, or convert to PhenoFluor *in situ* with CsF in toluene.

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Table 4: Dipolar Aprotic Solvents Toxicity Data

	DMF[1]	DMAc[2]	NBP[3]	N-Formylmorpholine[4]
CAS No.	[68-12-2]	[127-19-5]	[3470-98-2]	[4394-85-8]
Rat Oral LD50	2200-7550 mg/kg	3000-6000 mg/kg	300-2000 mg/kg	>7300 mg/kg
Rat Dermal LC50	>3160 mg/kg	7500 mg/kg	>2000 mg/kg	>18400 mg/kg
Skin Irritation (Rabbits)	negative	negative	irritant	negative
Eye Irritation (Rabbits)	severe	mild to moderate	irritant	negative
Reproductive toxicity	positive	positive	negative	not tested

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3. J. Sherwood, H. L. Parker, K. Moonen, T. J. Farmer and A. J. Hunt, *Green Chem*., 2016, **18**, 3990.
4. http://worldaccount.basf.com/wa/NAFTA~en_GB/Catalog/ChemicalsNAFTA/doc4/BASF/PRD/30036893/.pdf

