TPGS–750–M: Second Generation Amphiphile for Organometallic Chemistry in Water @ RT

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2015.3

Applications

Sonogashira couplings

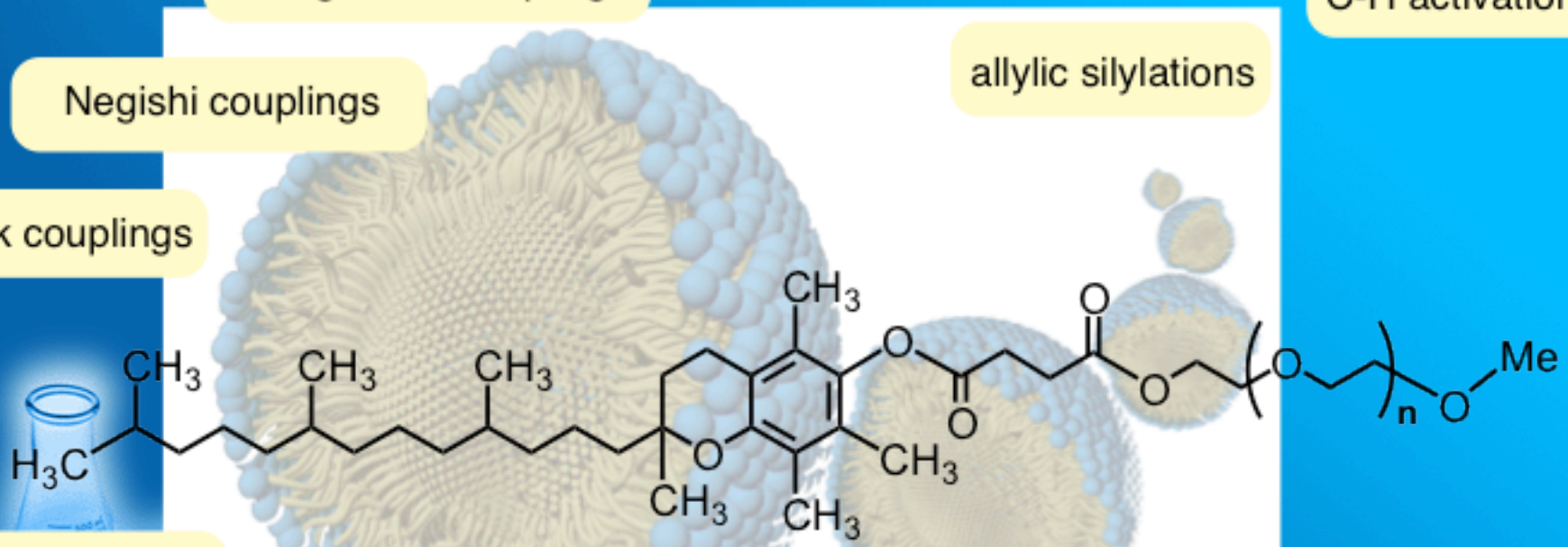
olefin metathesis

C-H activation

Negishi couplings

allylic silylations

Heck couplings



aryl aminations

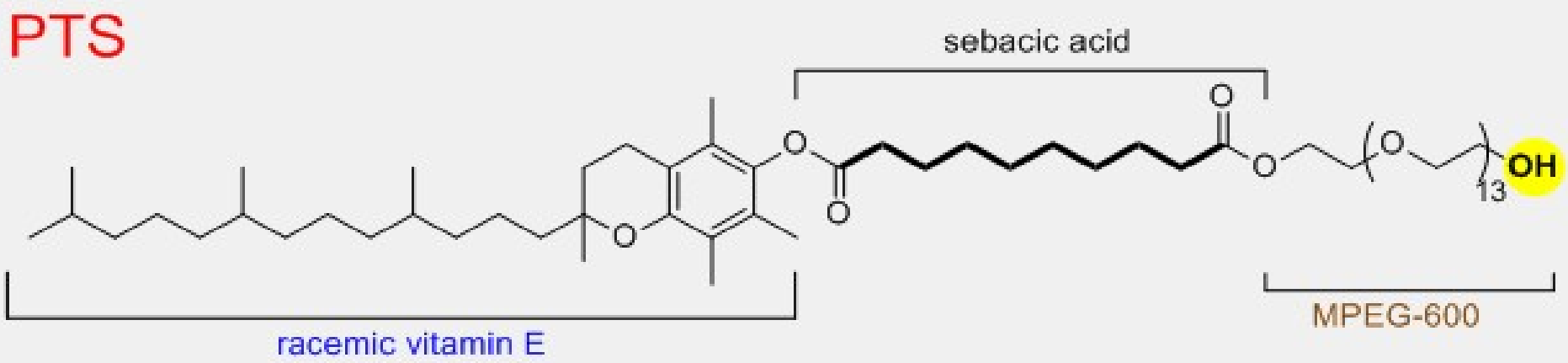
allylic aminations

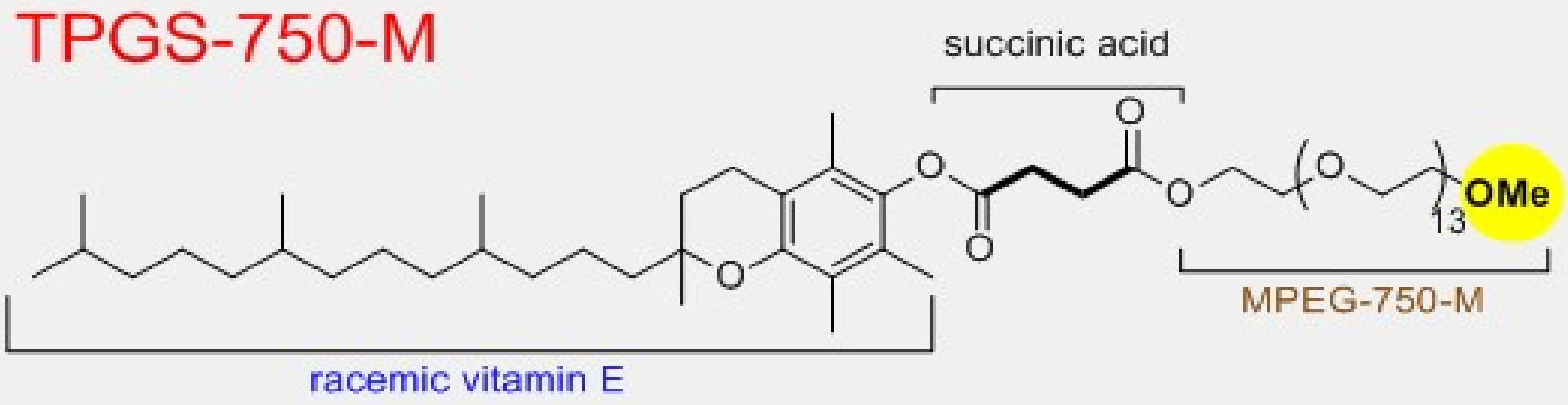
Suzuki-Miyaura couplings

asymmetric CuH reactions

aromatic borylations

STRUCTURE


PTS
sebacic acid
OH
13
MPEG-600
racemic vitamin E

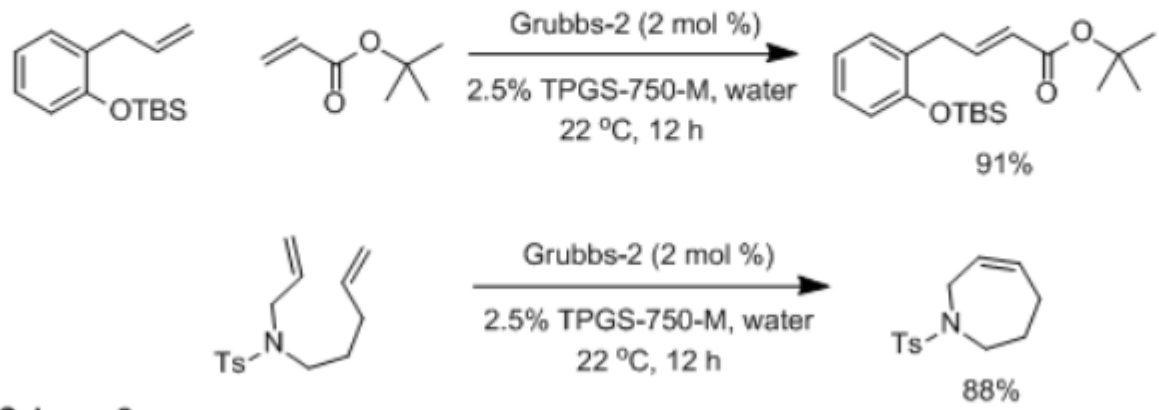

TPGS-750-M
succinic acid
OMe
13
MPEG-750-M
racemic vitamin E

BACKGROUND

Beginning in 2008, Lipshutz et al. have published a series of papers demonstrating the viability of surfactant promoted, transition metal-catalyzed chemistry in water at room temperature. Using a variety of commercially available surfactants, a number of palladium- and ruthenium-catalyzed processes were found to be amenable to mild, room temperature reactions in water. Products can be recovered from the aqueous phase using standard extraction procedures and in high isolated yields

Olefin Metathesis

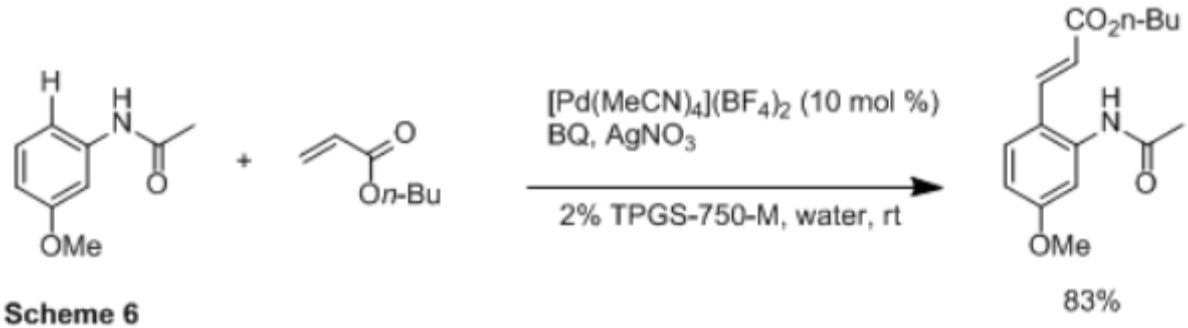
Employing the second generation Grubbs catalyst (2 mol %) a variety of lypophillic substrates successfully undergo ring-closing or cross-metathesis in water at room temperature to produce high isolated yields of the desired products (**Scheme 2**). Reactions were conducted in 2.5% TPGS-750-M/water, with yields equal to or slightly better than those performed using various other surfactant-water combinations.



Scheme 2

C-H Activation Reactions

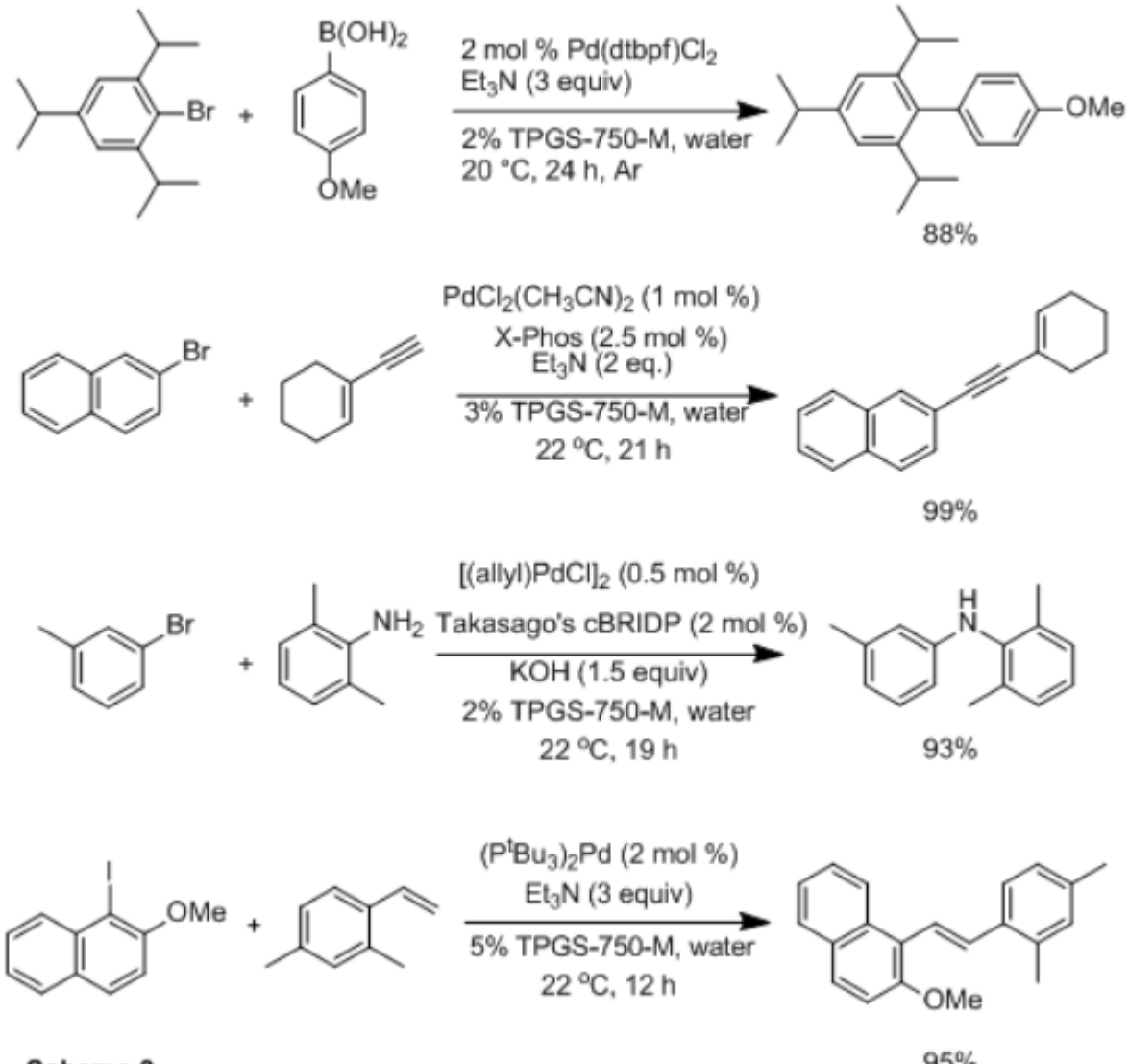
Cationic palladium in combination with stoichiometric oxidant benzoquinone and silver nitrate successfully catalyzes ortho functionalization of a variety of aryl acetamides in water at room temperature using this amphiphile (**Scheme 6**).



Scheme 6

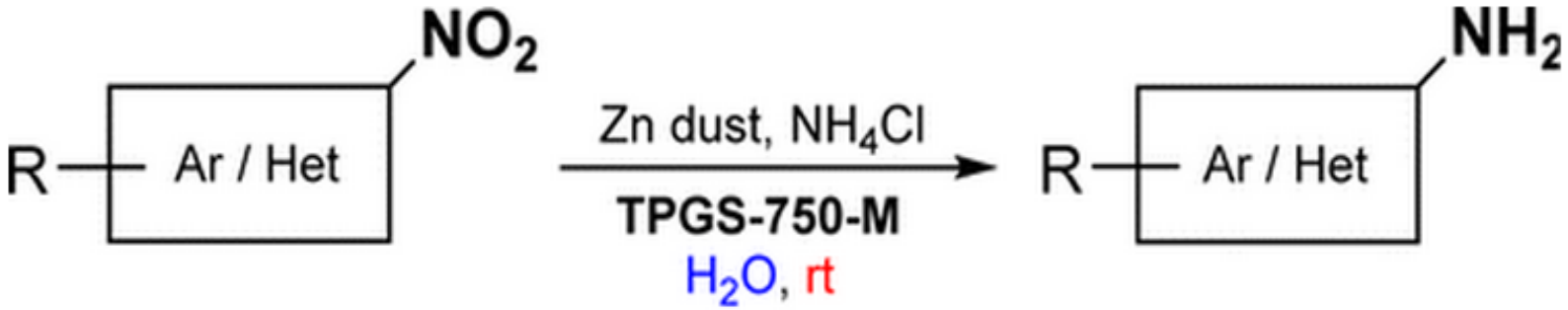
Pd-Catalyzed Cross Coupling Reactions

A variety of widely used palladium-catalyzed cross-coupling reactions can now be run under mild room temperature conditions in water with TPGS-750-M, using a variety of commercially available palladium complexes and ligands. These transformations, including Heck, Suzuki-Miyaura Sonogashira, and Buchwald-Hartwig aminations, are amongst the most heavily used bond forming reactions, both industrially and academically (**Scheme 3**).



Scheme 3

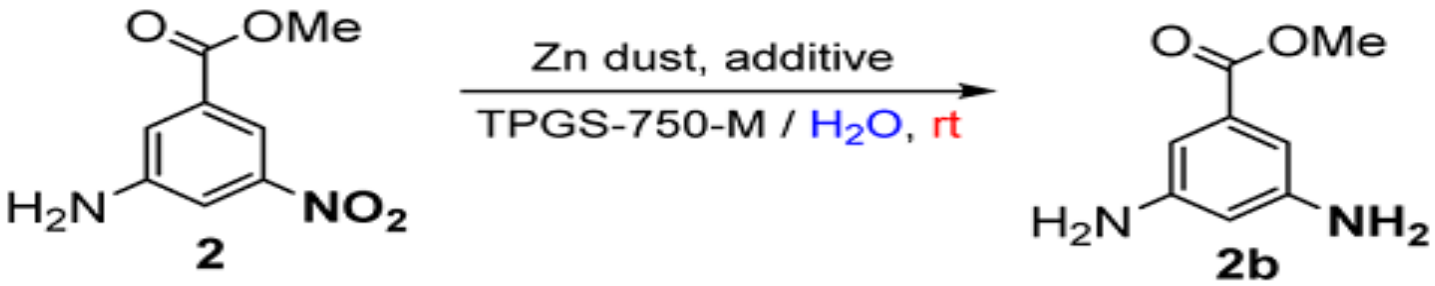
Chemoselective Reductions of Nitroaromatics in Water at RoomTemperature



R = alkane, alkene, alkyne, halide, amide, ester, ketone, aldehyde, amine, ether,

A robust and green protocol for the reduction of functionalized nitroarenes to the corresponding primary amines has been developed. It relies on inexpensive zinc dust in water containing nanomicelles derived from the commercially available designer surfactant TPGS-750-M. This mild process takes place at room temperature and tolerates a wide range of functionalities. Highly selective reductions can also be achieved in the presence of common protecting groups.

Table 1. Optimization of Zinc-Mediated Reductions



zinc (equiv)	additive (2 equiv)	conc (M)	time (h)	conversion (%)
3	NH_4Cl	0.5	2	60
5	NH_4Cl	0.5	2	84
10	NH_4Cl	0.5	2	87
5	**NH_4Cl**	**0.5**	**4**	**100**
5	NH_4Cl only[a]	0.5	4	62
5[b]	acetic acid	0.5	2	100
5[b]	formic acid	0.5	2	100
5	TMEDA	0.5	24	0
5	pH 6 phosphate	0.5	4	93
5	pH 8 phosphate	0.5	24	0
5	**NH_4Cl[c]**	**1.0**	**4**	**100**
5	NH_4Cl[c]	1.5	4	72

[a]"On water", no surfactact. [b]Two batchwise zinc additions. [c]1.2 equiv.

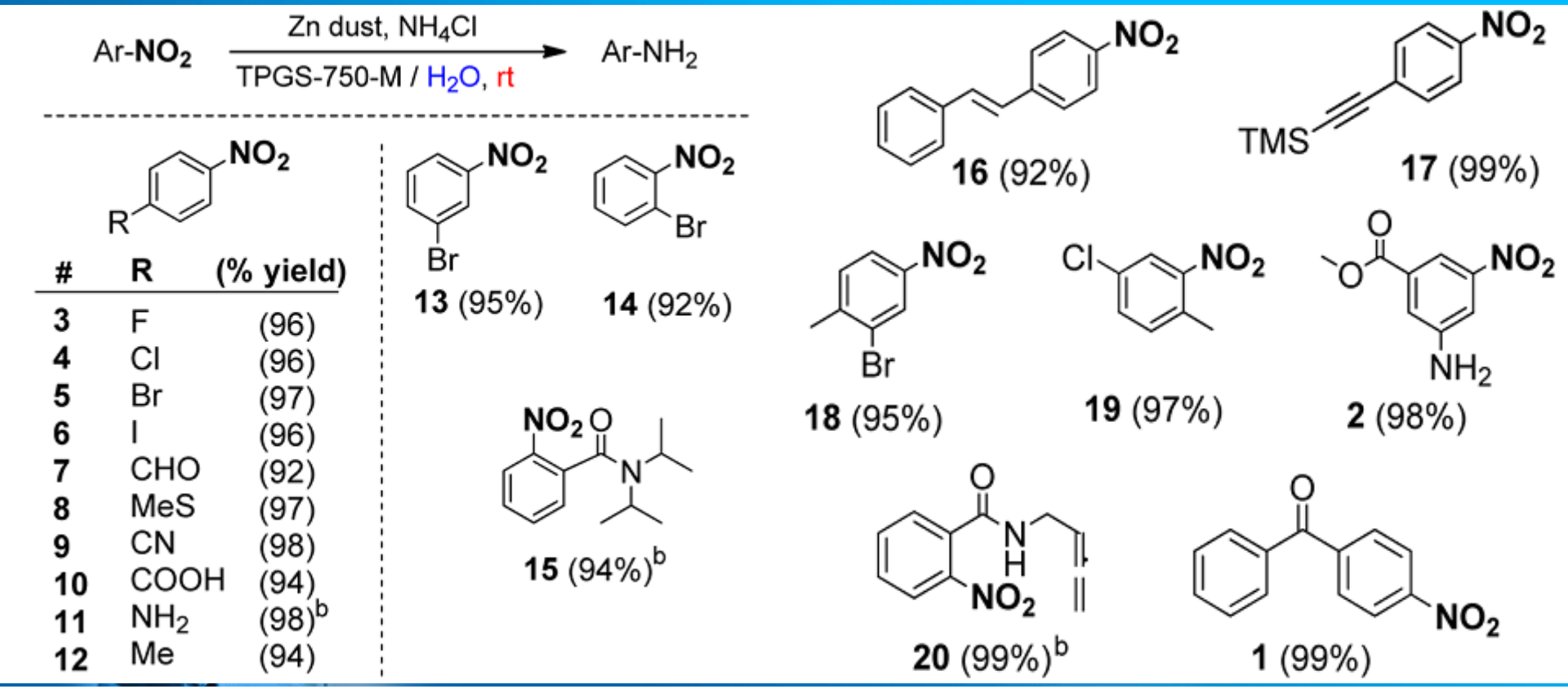
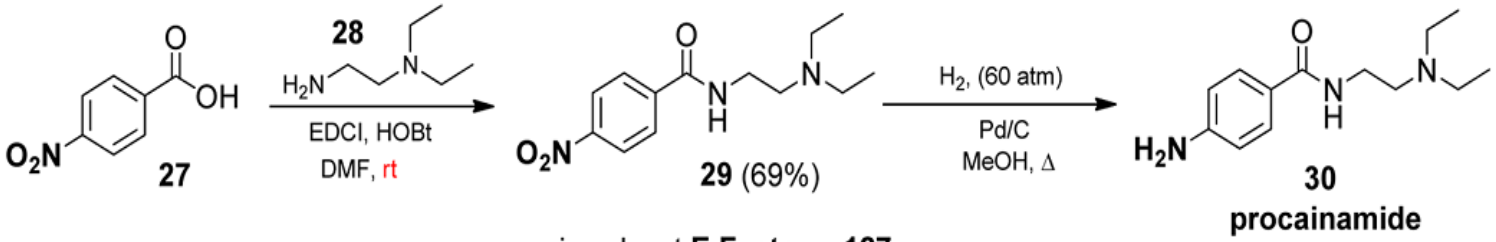


Figure 1. Substrate scope: Zn-mediated reductions of aromatic nitro groups in TPGS-750-M/water at room temperature: (a) yield after workup; (b) 2 equiv of NH_4Cl used.

EXAMPLE

Scheme 2. Procainamide Synthesis: Comparison of Route in Organic Solvents vs in Water at Room Temperature

patented route to procainamide:



organic solvent **E Factor = 127**
with water **E Factor = 150**

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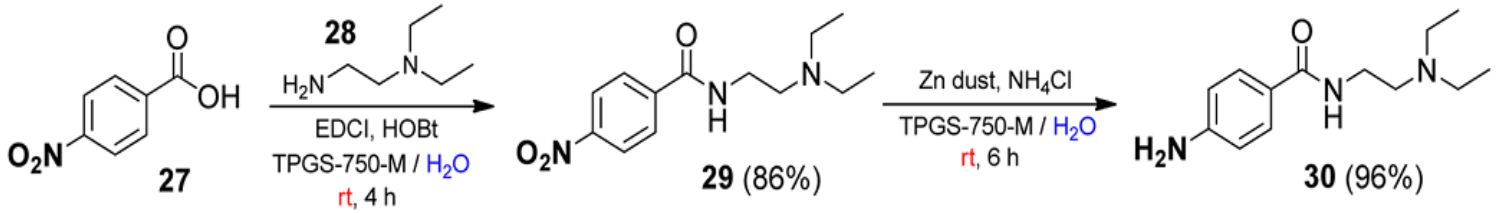
nanotechnology route: both steps in water at RT



organic solvent **E Factor = 6**
with water **E Factor = 13**

organic solvent **E Factor = 5**
with water **E Factor = 9**

- **Thank you**