CONVERSION OF AZIDES INTO DIAZO COMPOUNDS IN WATER

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JACS 2013, 135, 14936-14939

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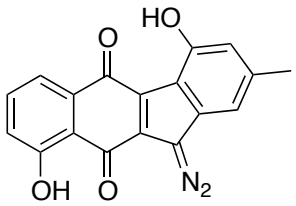
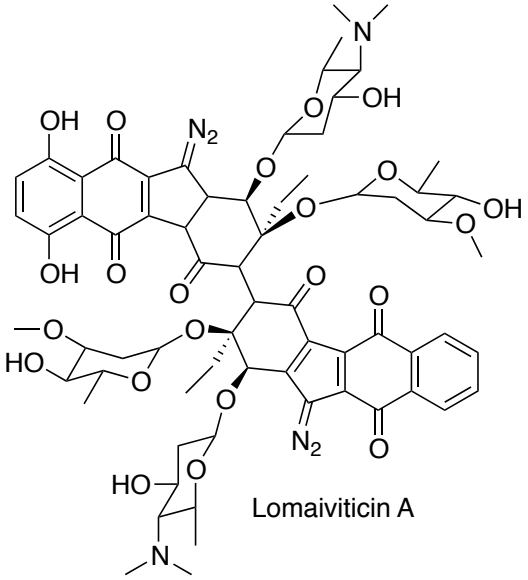
Current Lit 10/12/13
Wipf Group

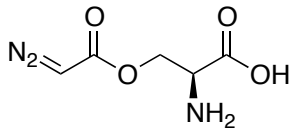
Naturally Occurring Diazo Compounds



Prekinamycin

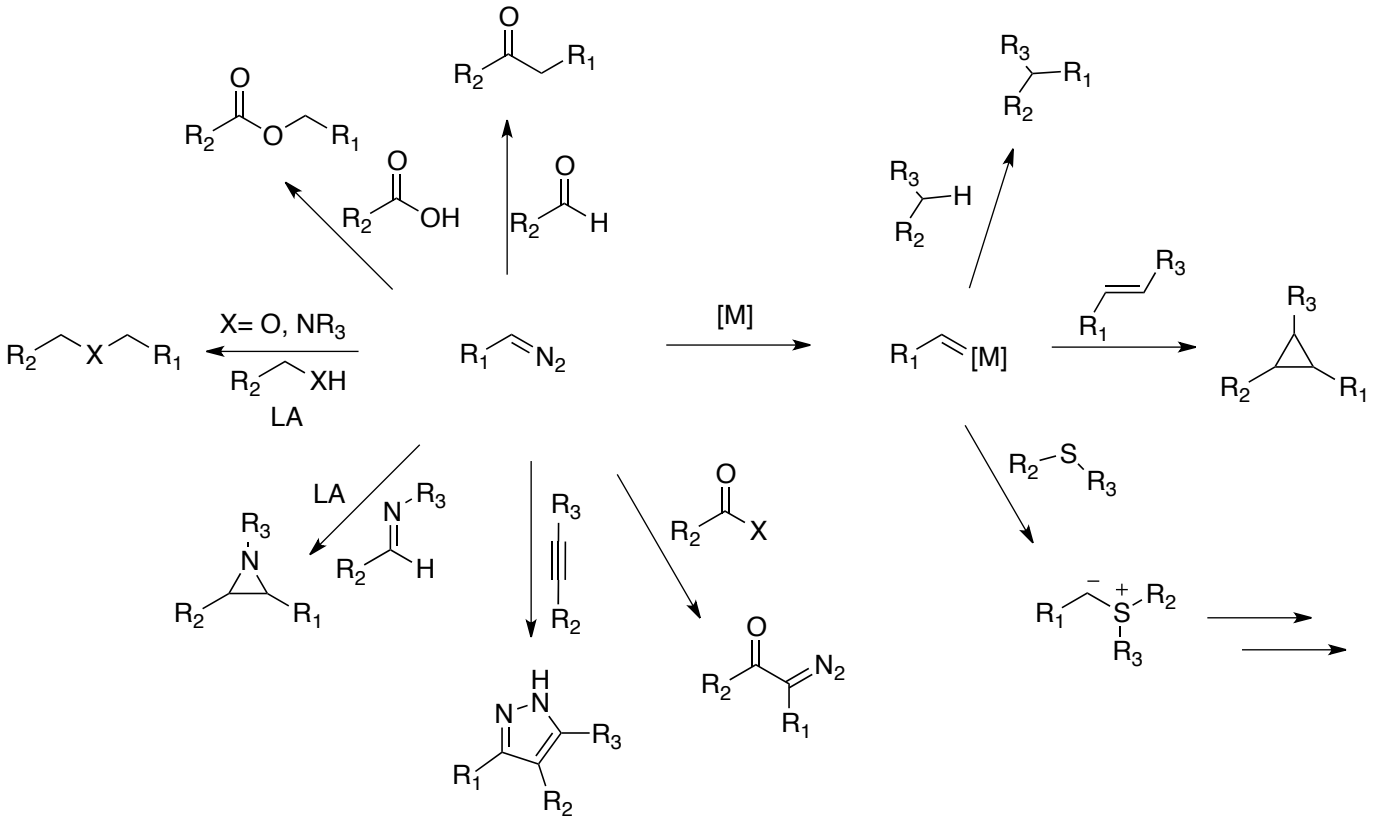


Lomaiviticin A



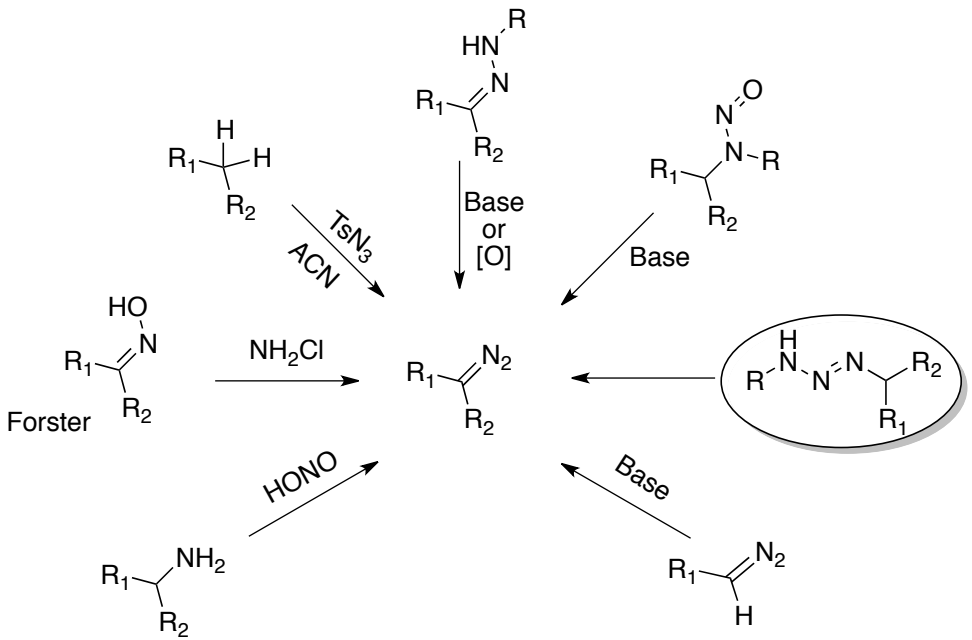
Azaserine

Diazo compounds in Organic synthesis



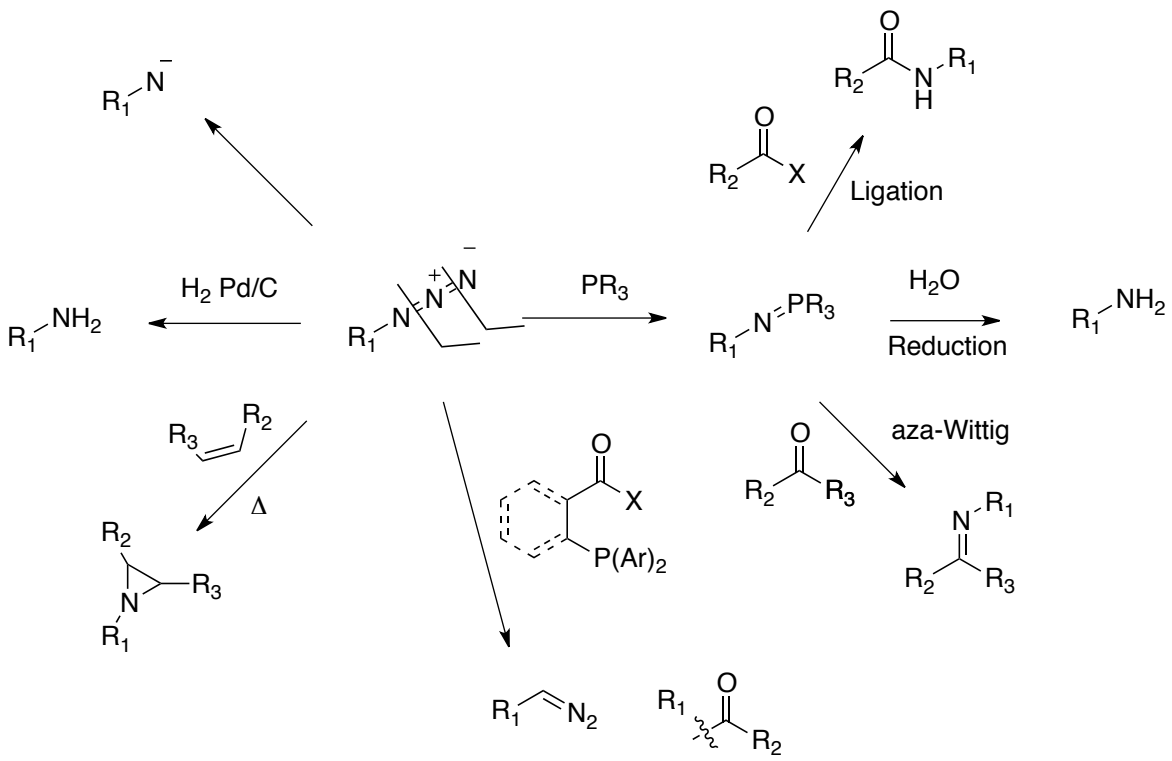
EJOC. 2005, 1479

Formation of Diazo Compounds



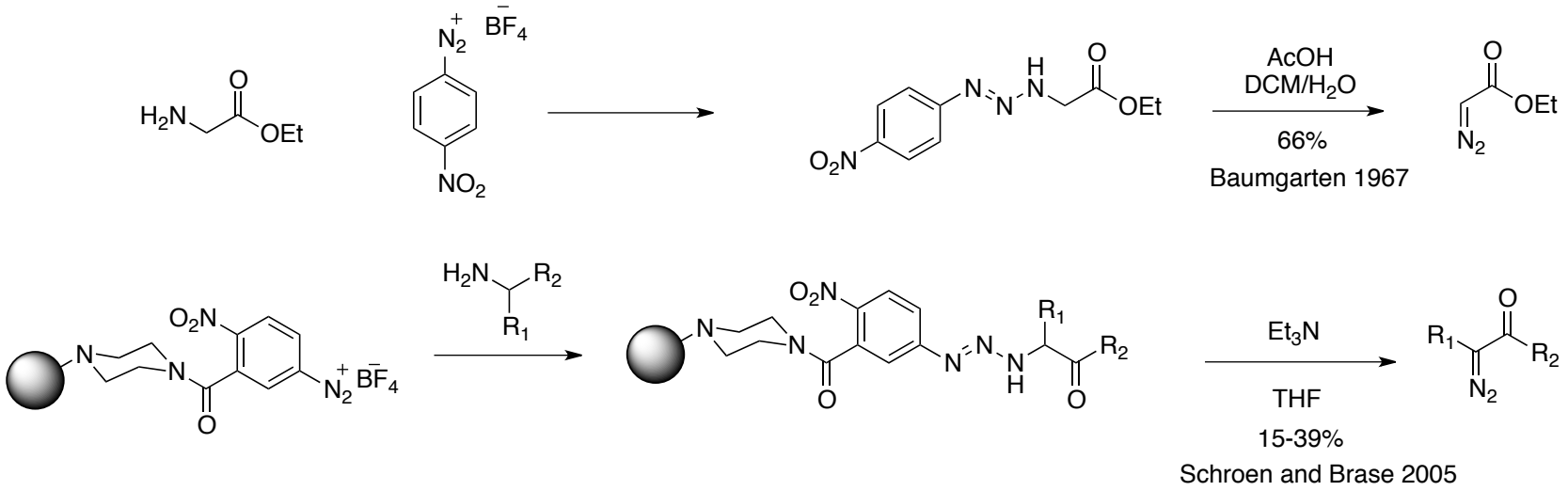
ACIE 2009, 48, 2359

Azide Fragmentations



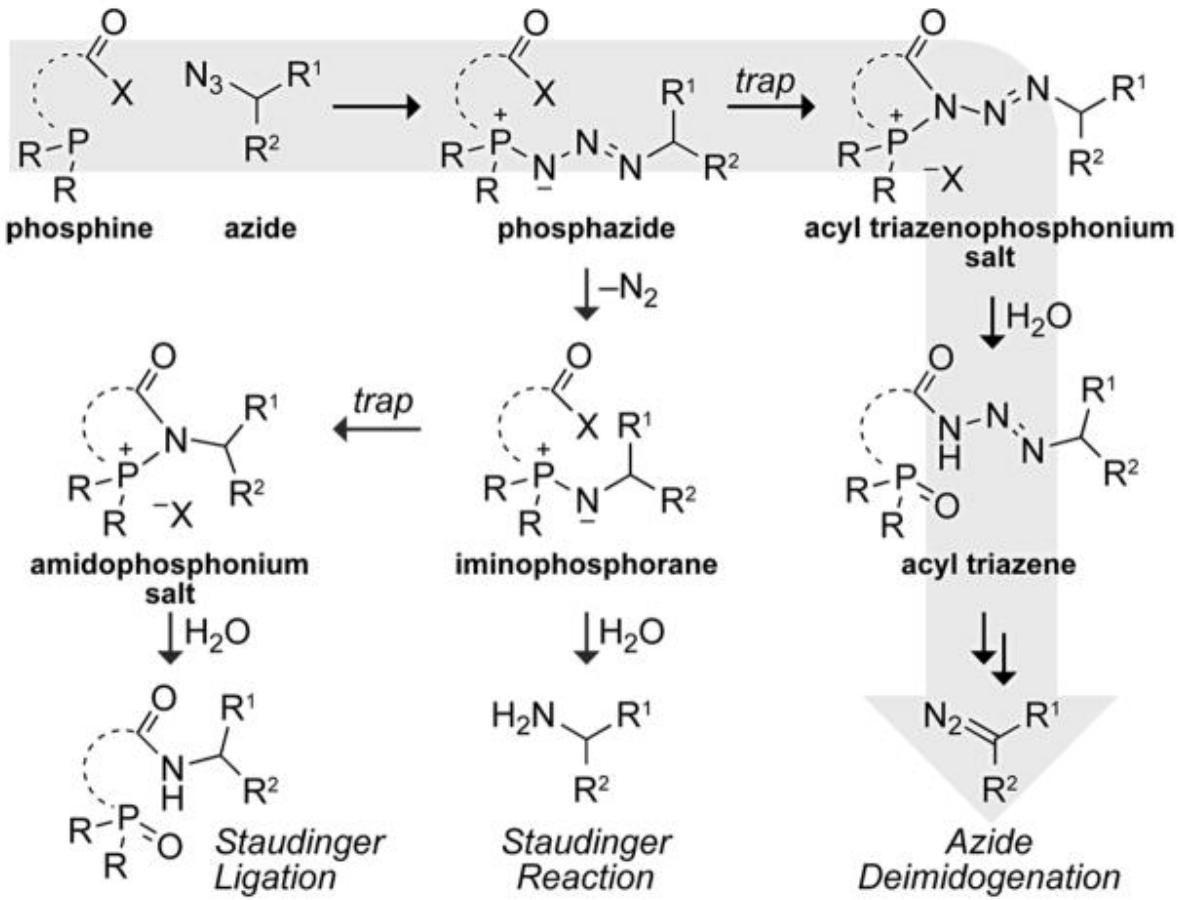
ACIE. 2005, 44, 5188

Previous methodology using triazene cleavage.



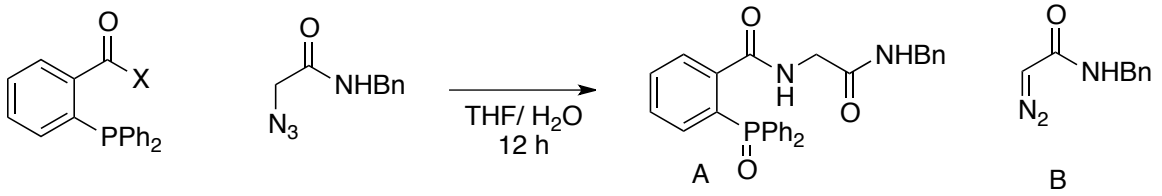
JOC, 1967, 32, 484
Tetrahedron 2005, **61**, 12186

Initial plan for reaction development



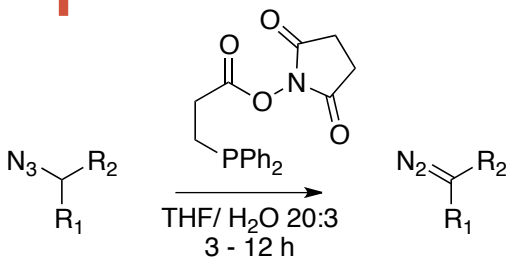
ACIE 2009, 48, 2359

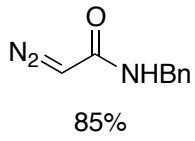
Phosphine mediated conversion of azides to diazo compounds.

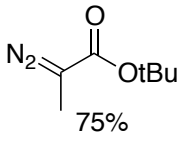


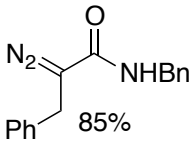
X	% yield A	% yield B
OMe	90	0
SEt	60	30
NHS	0	91

Reaction Scope




85%


75%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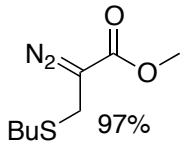
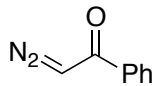

97%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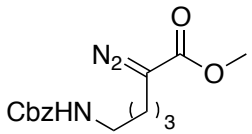
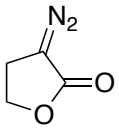

76%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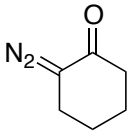
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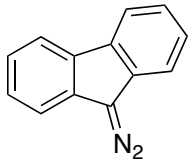
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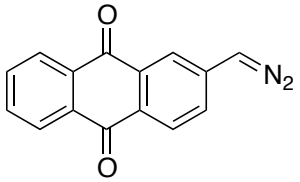
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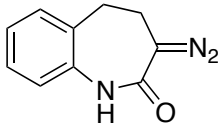
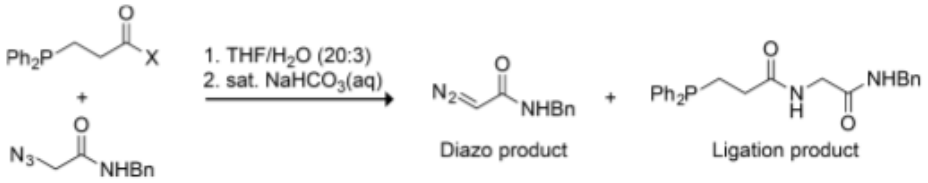

95%

ACIE 2009, 48, 2359

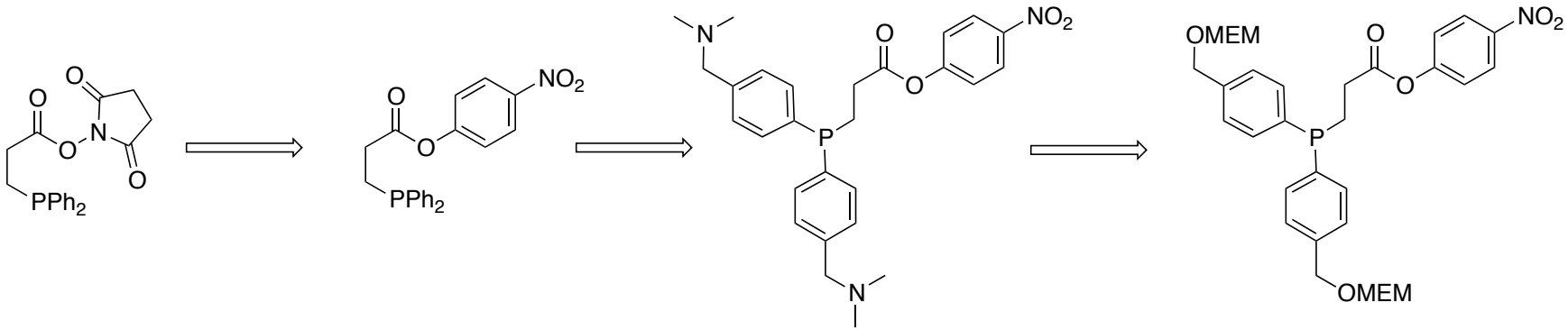
Stability and Reactivity of Phosphinoester



XH	pK_a	product ratio[a]		% decomposition at pH			
		diazo compound	amide	4.0	7.0	9.0	12.0
methanol	15.5	0	100				
ethanethiol	10.6	0	100				
4-fluorophenol	10.0	0	100				
benzylmercaptan	9.4	0	100				
3-(dimethylamino)phenol	9.2	0	100				
3-chlorophenol	9.0	33	67				
3,5-difluorophenol	8.7	63	27	<5	<5	5	21
3-hydroxypyridine	8.5	67	33	<5	<5	12	62
2,2,2-trifluoroethanethiol	7.6	83	17	<5	<5	13	35
4-nitrophenol	7.1	97	3	<5	<5	10	46
2,4,6-trifluorophenol	6.9	97	3	<5	<5	<5	13
N-hydroxysuccinimide	6.0	98	2	12	40	54	98
pentafluorophenol	5.5	97	3	<5	<5	<5	16

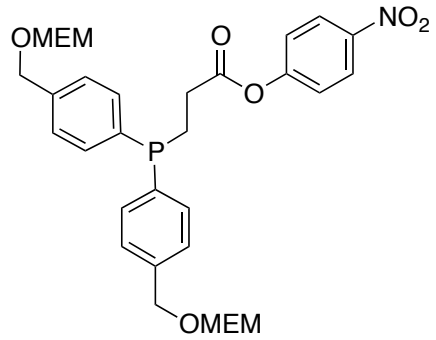
JACS., **2013**, *135*, 14936

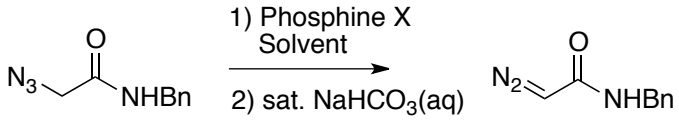
Water soluble esters



JOC. 1994, 59, 4262
JACS. 2007, 129, 11421
BMC. 2009, 17, 1055

Solvent Screening

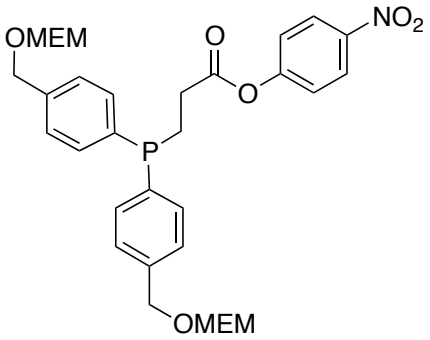


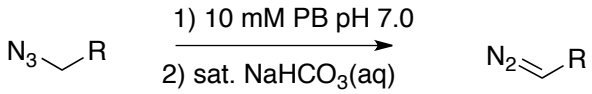


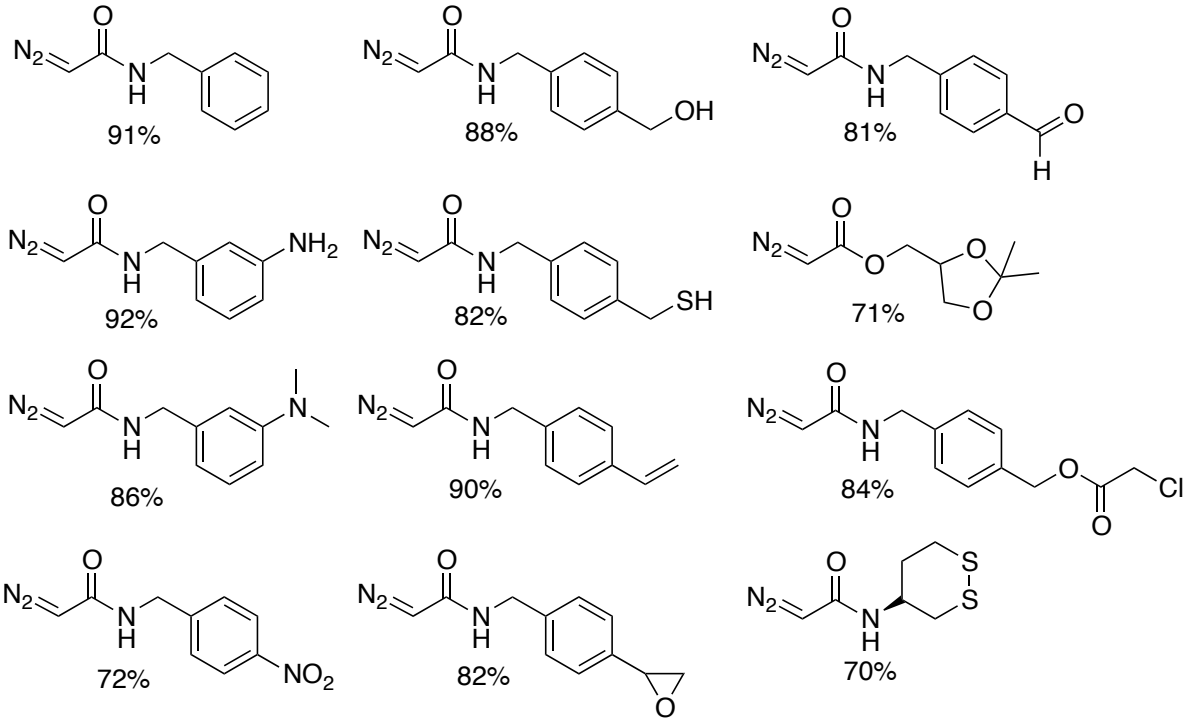
Solvent	Yield (%)
pH 5.0	69
pH 6.0	88
pH 7.0	91
pH 8.0	71
50% v/v MeOH	80
50% v/v CH_3CN	74
50% v/v DMF	75
1% v/v DMSO	84
20% v/v E.G.	78

E.G ethylene glycol, 10mM Phosphate buffer soln.

Reaction Scope







Conclusion

- Developed a methodology that can convert azides to diazo species under physiological conditions
- Tolerant of a number of functional groups
- Has been screened using RNase A and shown to not covalently modify the protein
- Uses an easily prepared phosphine

Synthesis of Phosphine