Reductive Carbodiazenylation of Nonactivated Olefins via Aryl Diazonium Salts

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Org. *Lett*. ASAP, ol0611393
web release date: 6-23-06

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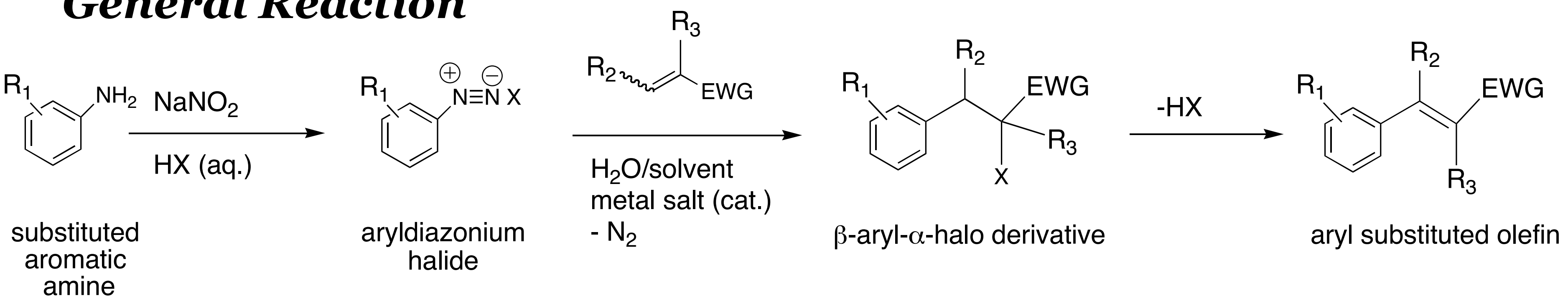
July, 1, 2006

Outline

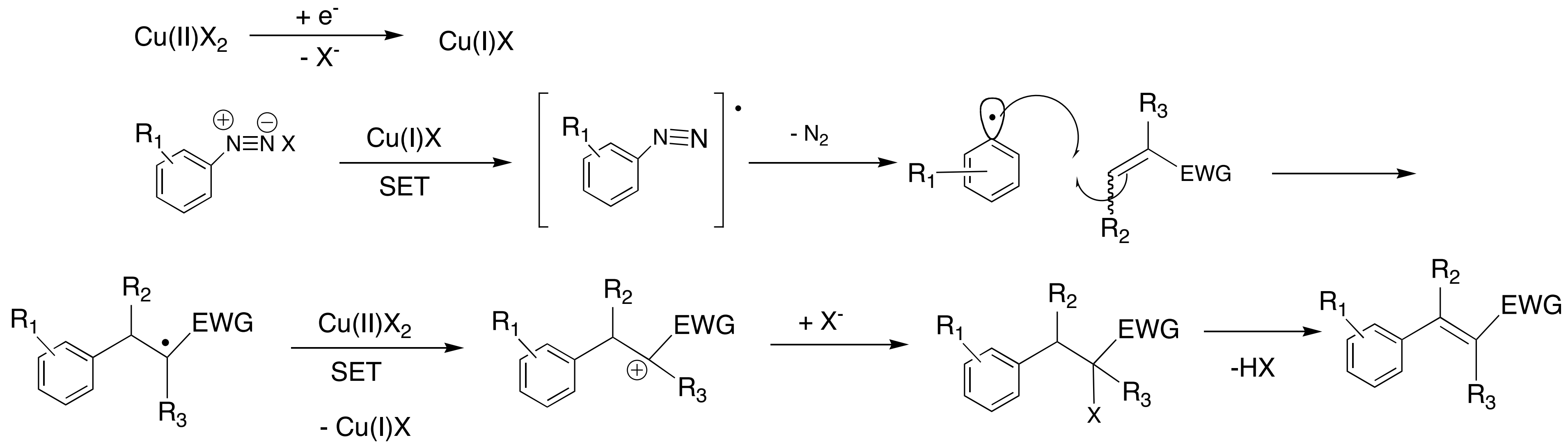
- Background:
    - The Meerwein Arylation
    - Examples of Carboamination and Carbodiazenylation
- Key Reaction and Mechanism: Carbodiazenylation
- Exploring the Scope
- Accessing Potential Synthetic Targets
- Summary and Future Work

Meerwein Arylation

General Reaction



Proposed mechanism



Kurti L., Czako B. Strategic Applications of Named Reactions in Organic Synthesis. Elsevier Academic Press. Burlington, MA 2005

Meerwein Arylation

Key Features

- Formation of the diazonium salt in situ, no isolation necessary
- Substitution of aromatic ring:
  - EWGs leads to higher yields, EDGs are low yielding
- Substitution of olefin:
  - Usually contain EWG group
  - If disubstituted, aryl radical adds to least substituted carbon
  - Potential formation of regioisomers

Draw Backs

- Overall moderate yields obtained due to side reactions (Sandmeyer Reaction, Azo Coupling etc.)

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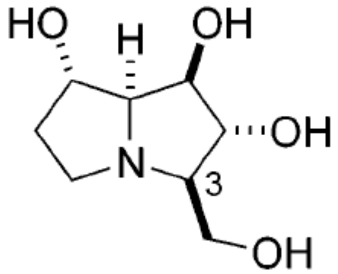
Carboazidation in Total Synthesis

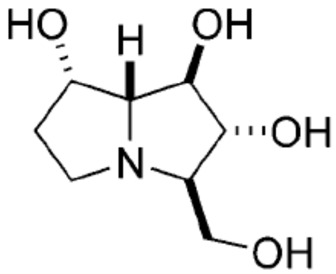
Polyhydroxylated Pyrrolizidine Alkaloids

- Hyacinthacines isolated from *Muscari Armeniacum*
- New potent inhibitors of glycosidase

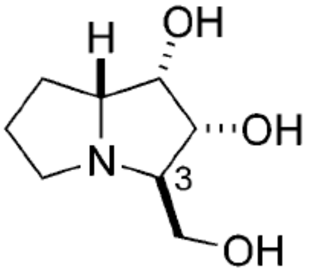
- Synthetic strategy based on free-radical carboazidation of a chiral allylsilane as a key step



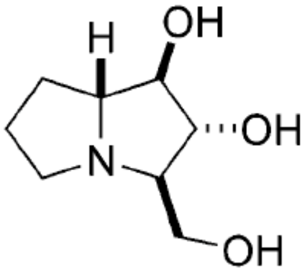
Alexine **1**



Australine **2**



Hyacinthacine A_1 **3**

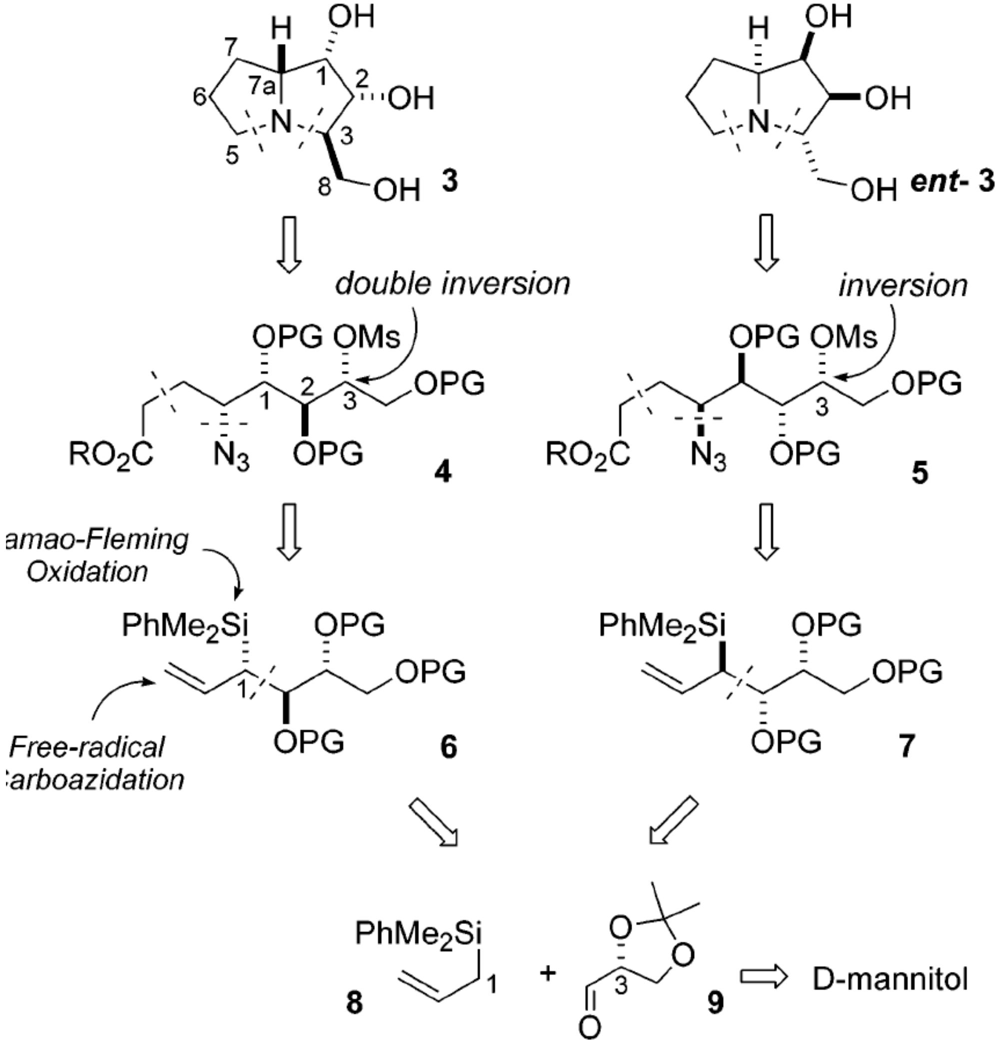


Hyacinthacine A_2 **4**

OL. **2005**, *7*, 2587

Carboazidation in Total Synthesis

Scheme 2. Retrosynthetic Analysis

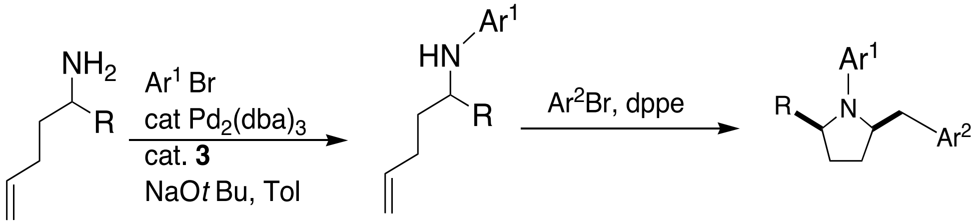


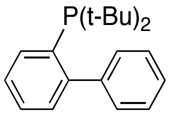
OL. **2005,** *7*, 2587

Methods of Carboamination

Organometallic Methods

Pd-catalyzed tandem N-arylation/ carboamination of pirmary aliphatic amines





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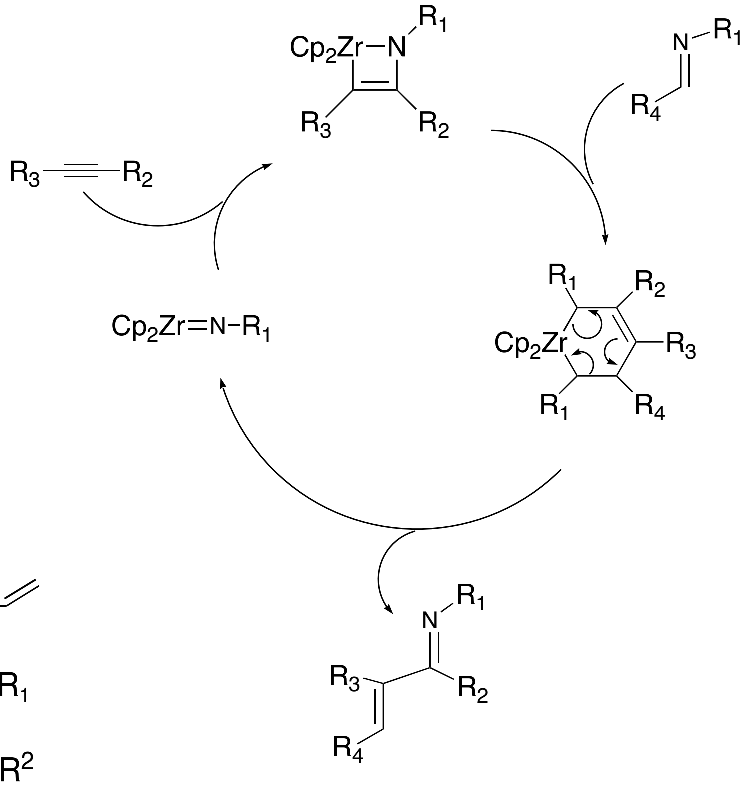
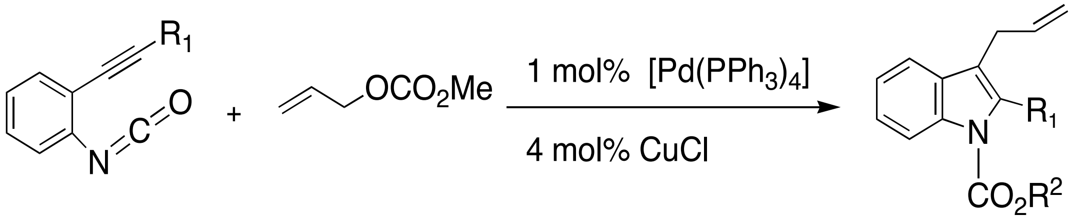
OL. **2005,** *7,* 2575

Additions of Imine C=N bonds across Alkynes via imidozirconium complexes



ACIE. **2004,** *43,* 5372

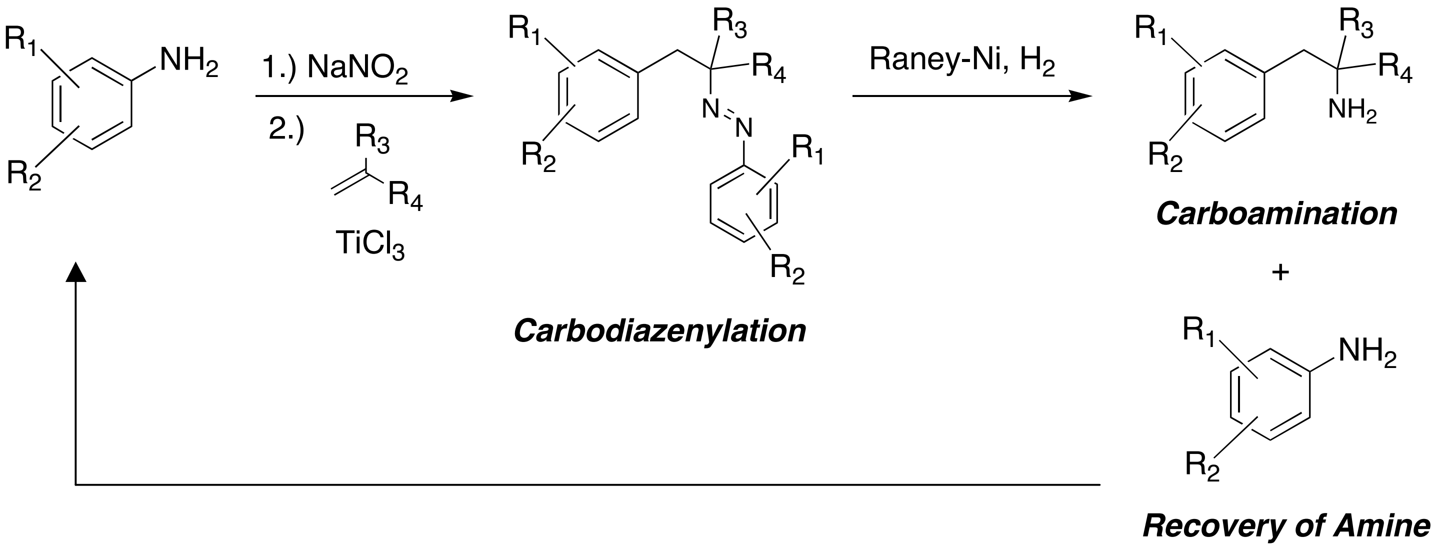
Pd-Cu bimetallic catalyzed Indole Formation



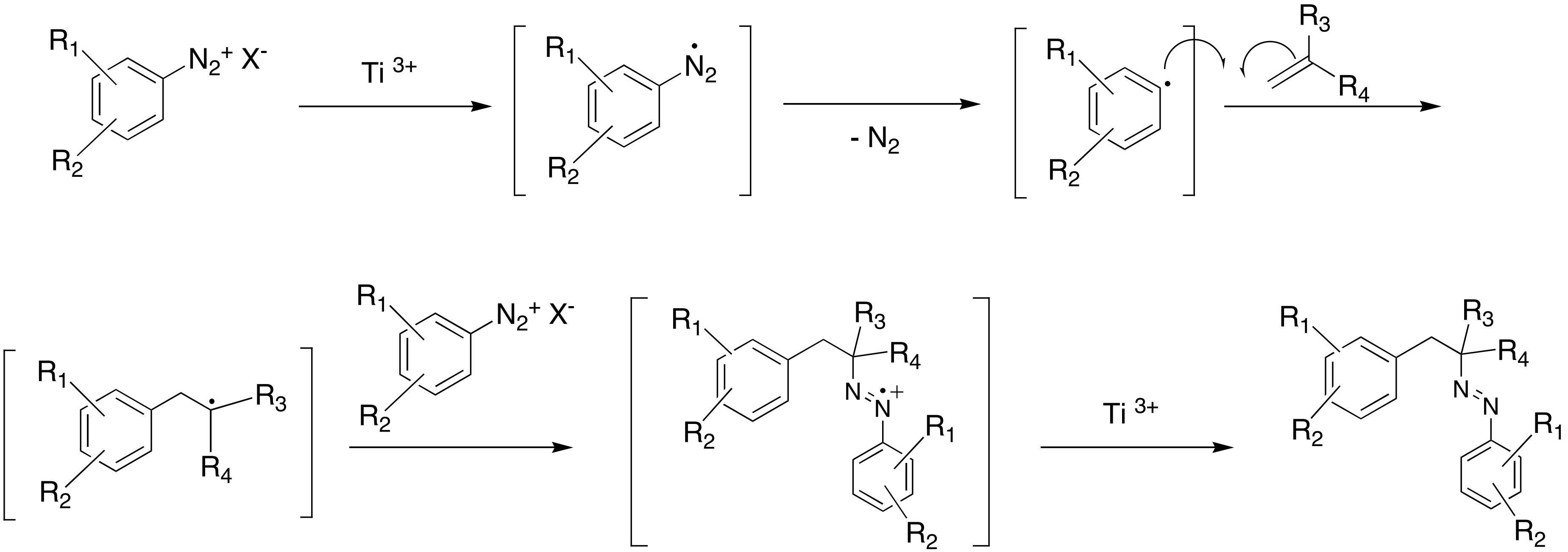
ACIE. **2002,** *41,* 3230

Key Reaction

Key Point: *the reduction of aryl diazonium salts in the presence of nonactivated olefins provides rapid entry to carbodiazenylation products, which can undergo transformation to synthetically useful precursors.*



Carbodiazenylation: Mechanism



Exploring the Scope

Carbodiazenylation of Olefins

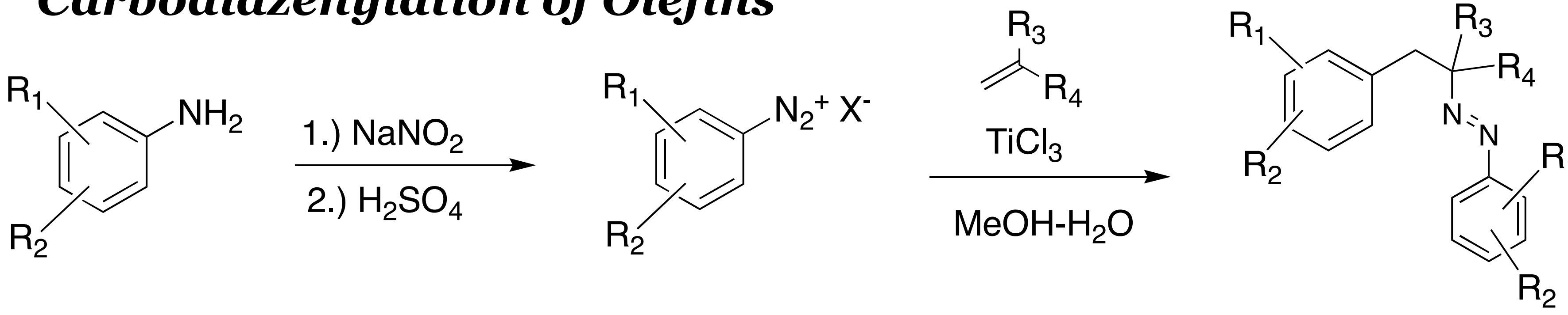
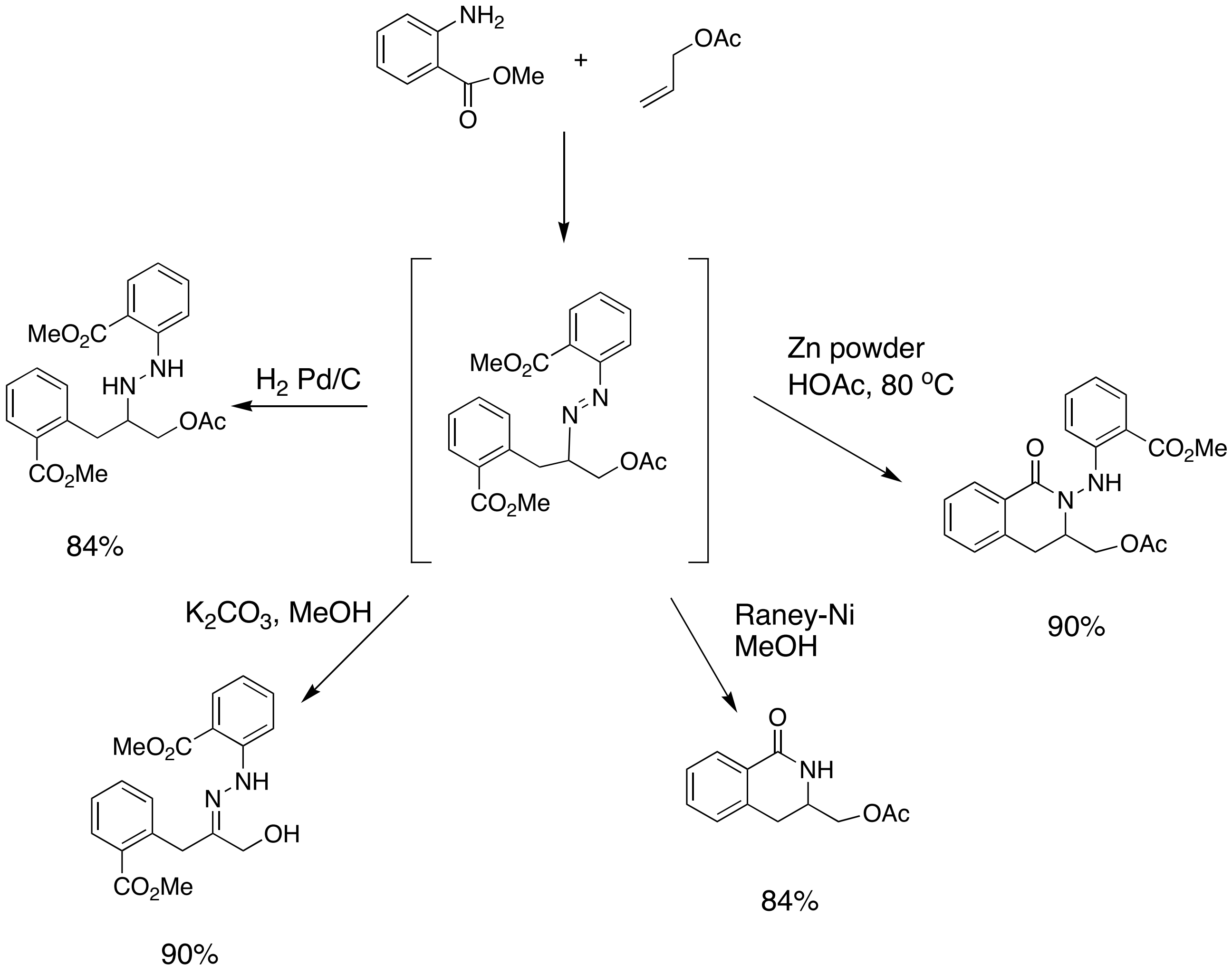


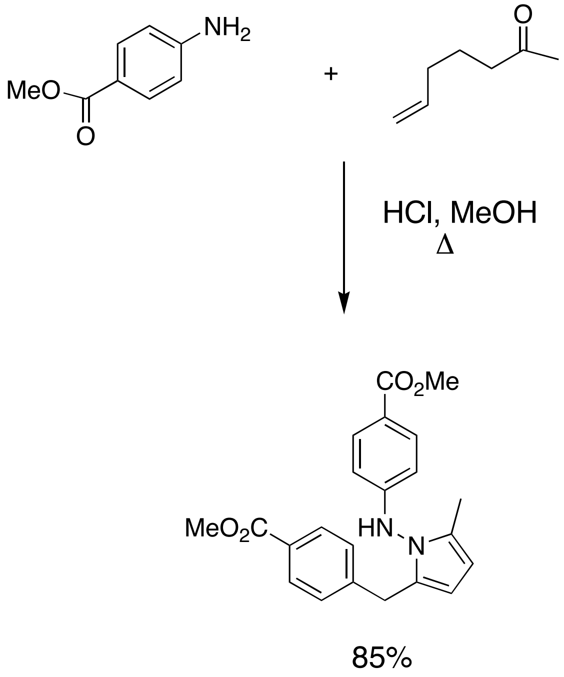
Table 1. Carbodiazenylation of Olefins

	aniline	R^1	R^2	olefin	R^3	R^4	product	yield[a] (%)
1	**1a**	H	H	**3a**	CH_2OAc	H	**4a**	47[b]
2	**1b**	*o*-Cl	H	**3a**	CH_2OAc	H	**4b**	67 (61)[b]
3	**1c**	*m*-Cl	*p*-CO_2H	**3a**	CH_2OAc	H	**4c**	55[b]
4	**1d**	*p*-CO_2Me	H	**3a**	CH_2OAc	H	**4d**	80
5	**1e**	*o*-CO_2Me	H	**3a**	CH_2OAc	H	**4e**	59 (64)[c]
6	**1f**	*p*-CF_3	H	**3a**	CH_2OAc	H	**4f**	68
7	**1d**	*p*-CO_2Me	H	**3b**	CH_2CN	H	**4g**	70
8	**1d**	*p*-CO_2Me	H	**3c**	$(CH_2)_2COMe$	H	**4h**	60
9	**1d**	*p*-CO_2Me	H	**3d**	CH_2OAc	Me	**4i**	58[d]
10	**1d**	*p*-CO_2Me	H	**3e**	CH_2OH	Me	**4j**	73[d]

[a] Yield according to method A (2.1 equiv of $TiCl_3$) and column chromatography. [b] Yield according to method B (1.1 equiv of $TiCl_3$ and 4.0 equiv of $FeSO_4$). [c] Reaction on a larger scale (5×). [d] Byproduct: 10−20% hydrazine.

Accessing Potential Synthetic Targets





Summary and Future Work

Summary

- Simple, practical method for diazenylation of non-activated olefins
- Can be carried out under non-hazardous conditions
- Formation of valuable precursors for polyfunctionalized target molecules in high yields
- Raney-Ni reductive conditions yielded product and recovered aniline starting material

Future Work

- To continue to apply this methodology toward new synthetic targets and pathways