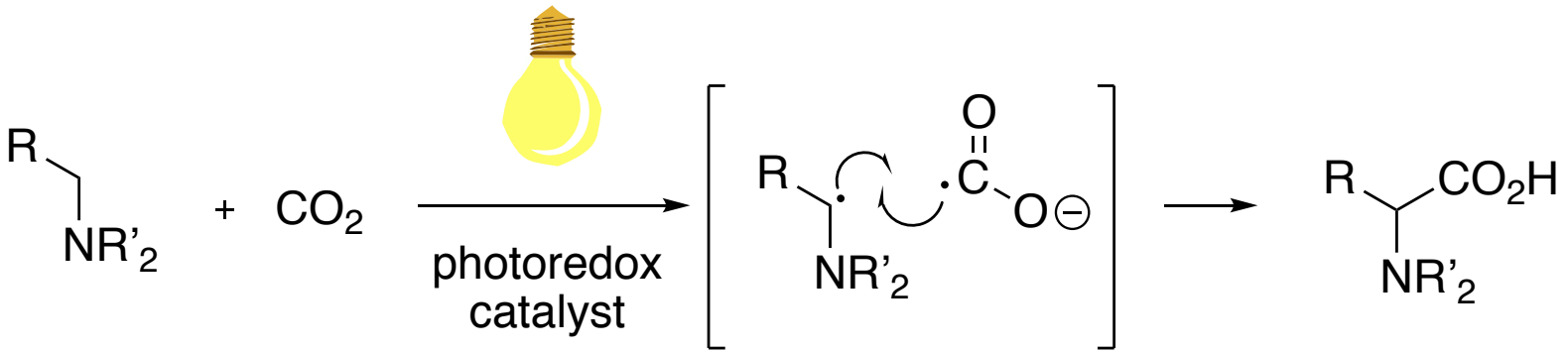
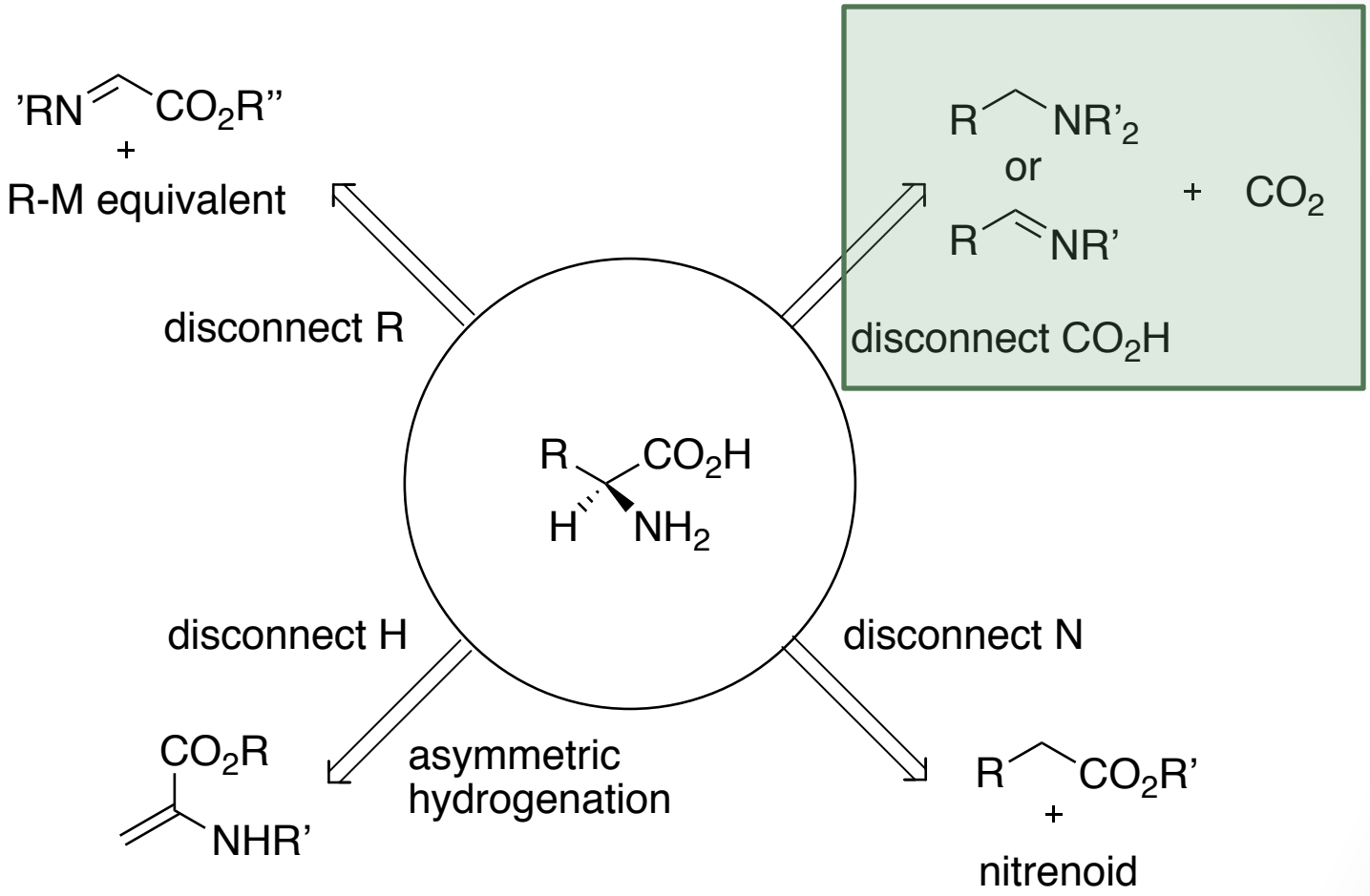
Photoredox activation of CO_2 for amino acid synthesis in continuous flow



Seo, H.; Katcher, M. H.; Jamison, T. F. *Nat. Chem.* DOI: 10.1038/NCHEM.2690

John Milligan
Wipf Group Meeting

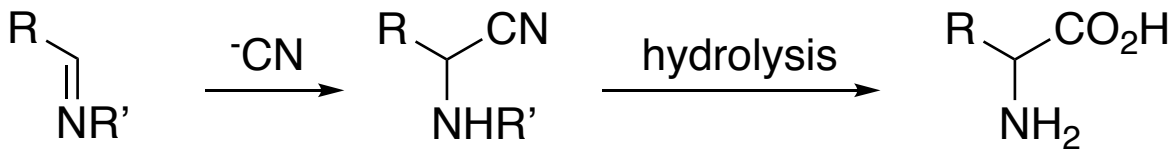
Current Literature
January 21, 2017



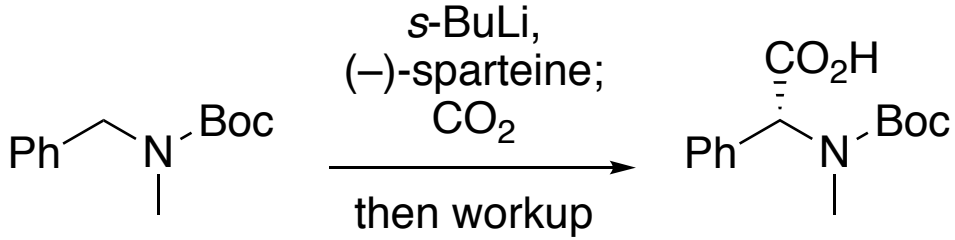
Najera, C.; Sansano, J. M. *Chem. Rev.* **2007**, *107*, 4584-4671.

Amino acids via CO_2 introduction

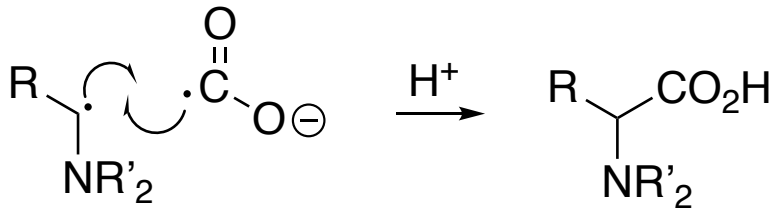
CO_2 surrogate as a nucelophile: The Strecker reaction



CO_2 as an electrophile:

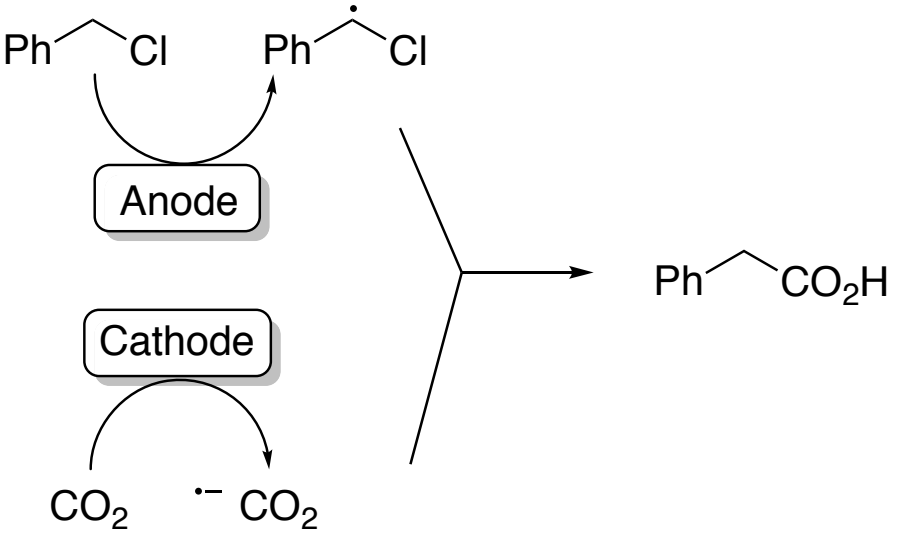


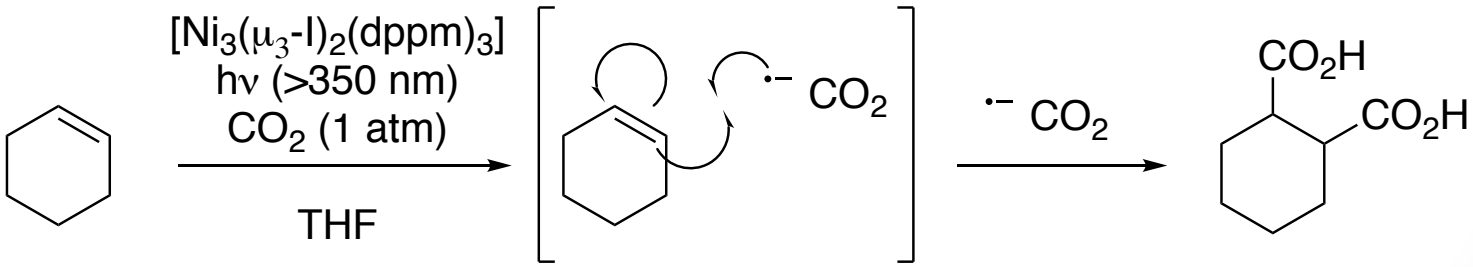
1 e$^-$ coupling pathway: this work



Barberis, C.; Voyer, N.; Roby, J.; Chenard, S.; Temblay, M.; Labrie, P. *Tetrahedron* **2001**, *57*, 2965-2972.

CO_2 radical anion: previous studies





Otero, M. D.; Batanero, B.; Barba, F. *Tetrahedron Lett.* **2006**, *47*, 2171-2173

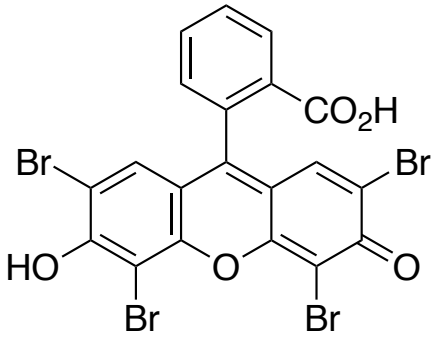
Morgenstern, D. A.; Wittrig, R. E.; Fanwick, P. E.; Kubiak, C. P. *J. Am. Chem. Soc.* **1993**, *115*, 6470-6471.

Photochemical CO_2 reduction: is it possible?

CO_2
$E^0 = -2.21$ V vs SCE
(w/ 0.1–0.6 V overpotential)

$Ru(bpy)_3^{+2}$

$E_{1/2}^{III/II} = -0.81$ V

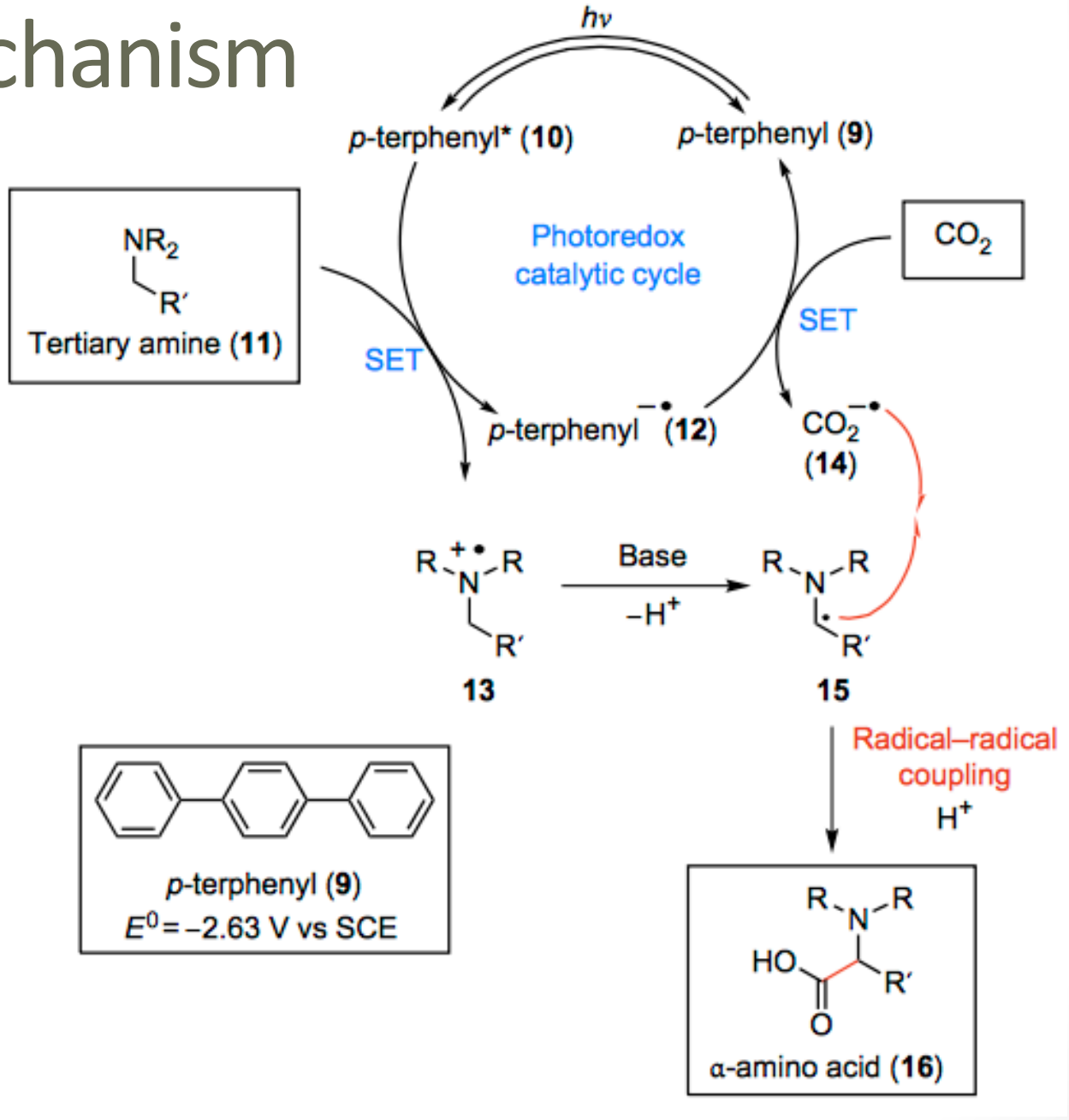


Eosin Y
$E^0 = -1.11$ V vs SCE

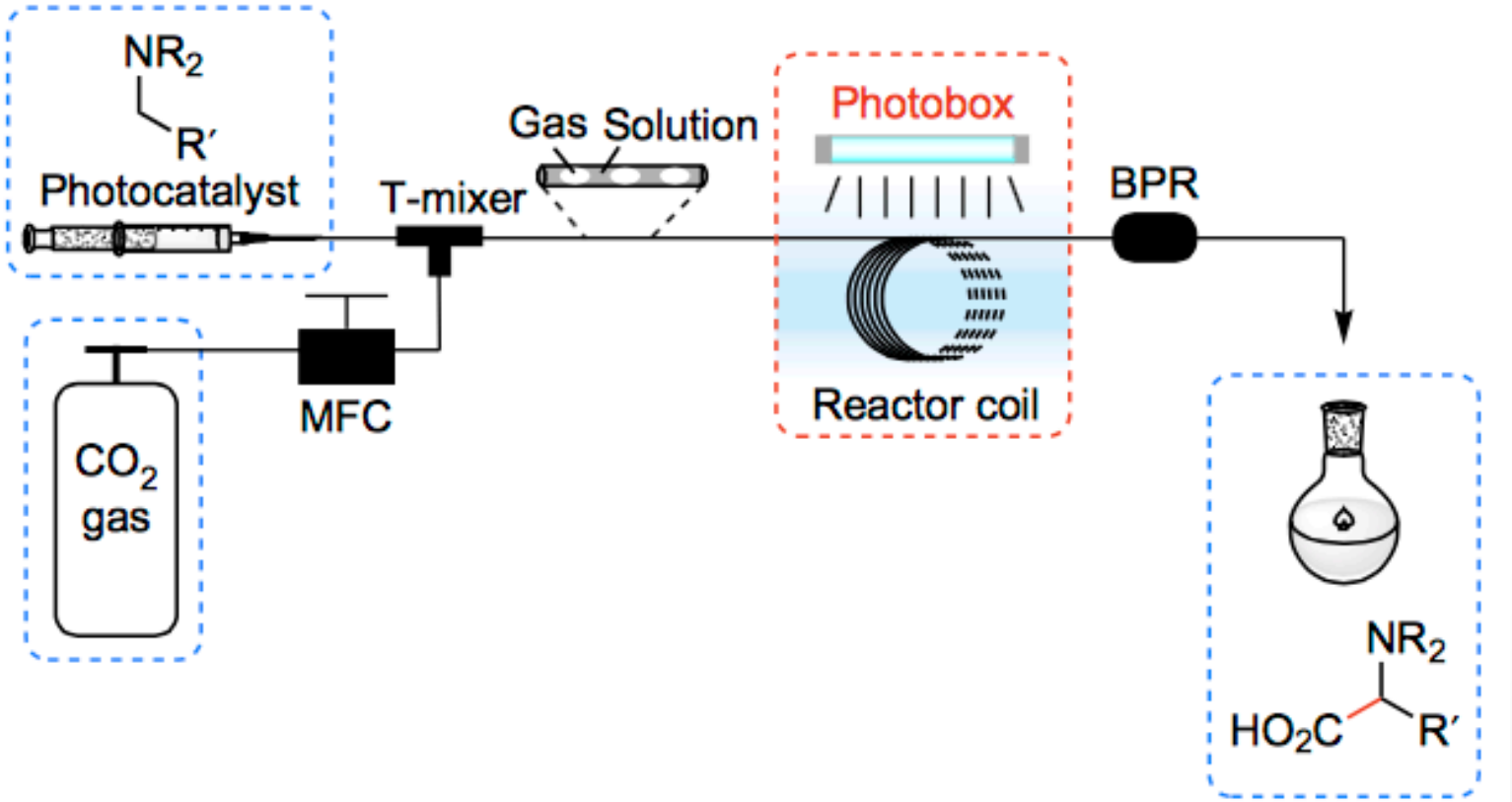
p-terphenyl
$E^0 = -2.63$ V vs SCE

Prier, C. K.; Rankic, D. A.; MacMillian, D. W. C. *Chem. Rev.* **2013**, *113*, 5322-5363.
Hari, D. P.; Konig, B. *Chem. Commun.* **2014**, *50*, 6688-6699.
Matsuoka, S.; Kohzuki, T.; Pac, C.; Ishida, A.; Takamuku, S.; Kusaba, M.; Nakashima, N. Yanagida, S. *J. Phys. Chem.* **1992**, *96*, 4437-4442.

Mechanism

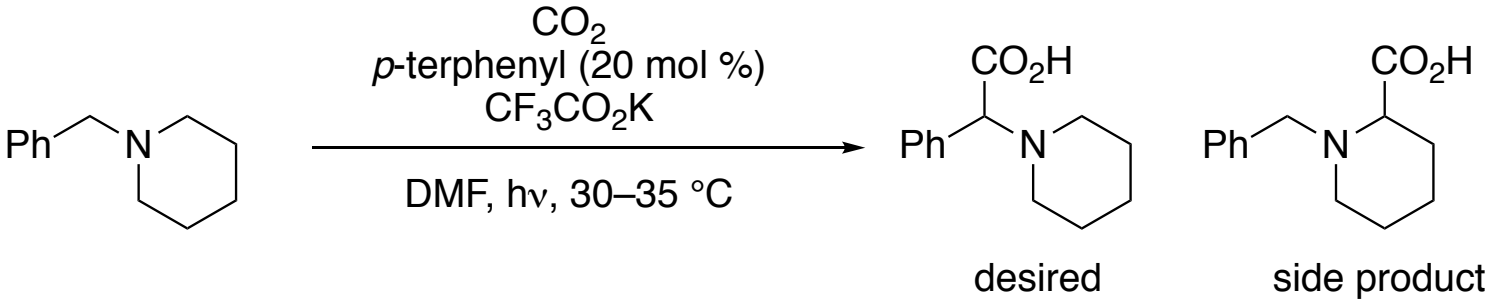

hν
p-terphenyl* (10)
p-terphenyl (9)
Photoredox
catalytic cycle
NR2
R′
Tertiary amine (11)
SET
SET
CO2
p-terphenyl −• (12)
CO2 −•
(14)
Base
−H+
13
15
Radical–radical
coupling
H+
p-terphenyl (9)
E0 = −2.63 V vs SCE
HO
O
α-amino acid (16)

Apparatus


NR2
R′
Photocatalyst
Gas Solution
T-mixer
Photobox
BPR
MFC
CO2
gas
Reactor coil
NR2
HO2C
R′

Optimization

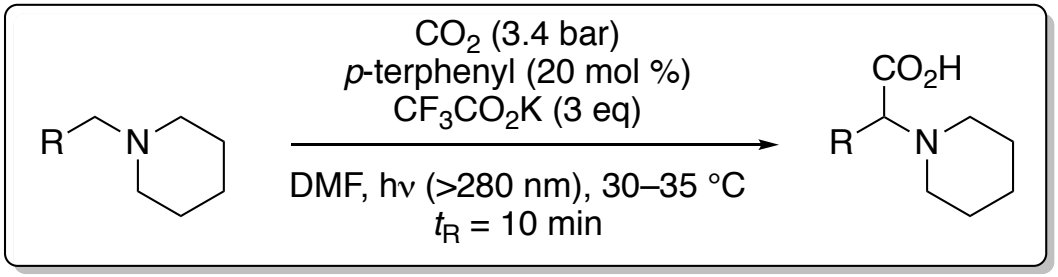
- Optimized base, UV source, and CO_2 pressure

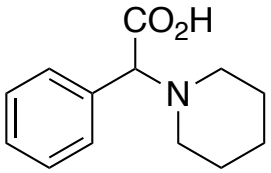


desired side product

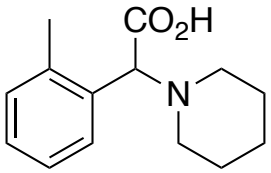
base (eq)	CO_2 (bar)	t_R (min)	UV filter	combined yield	selectivity
0	6.9	5	none	21%	6.6:1
1	6.9	5	none	45%	33:1
3	3.4	4	none	78%	30:1
3	3.4	10	>280 nm	92%	52:1

Scope

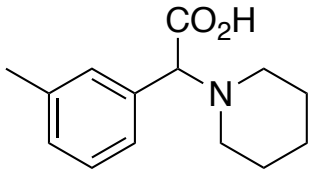




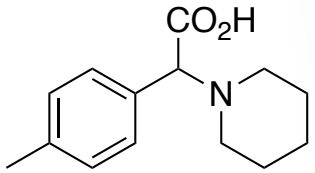
92%



99%



93%



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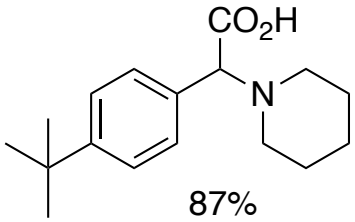

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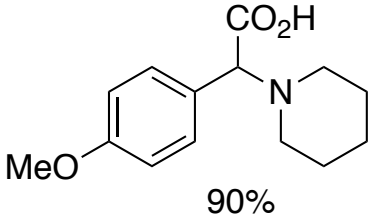

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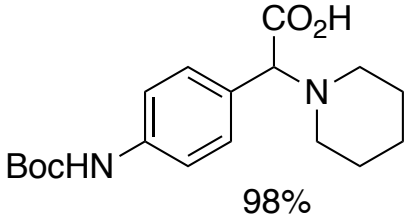

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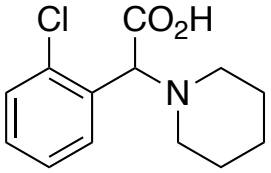
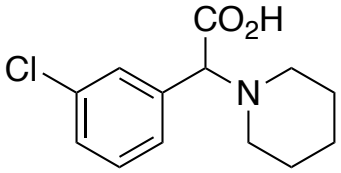


58%



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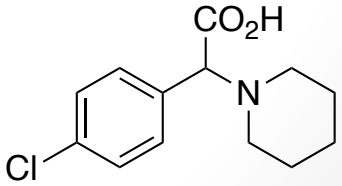
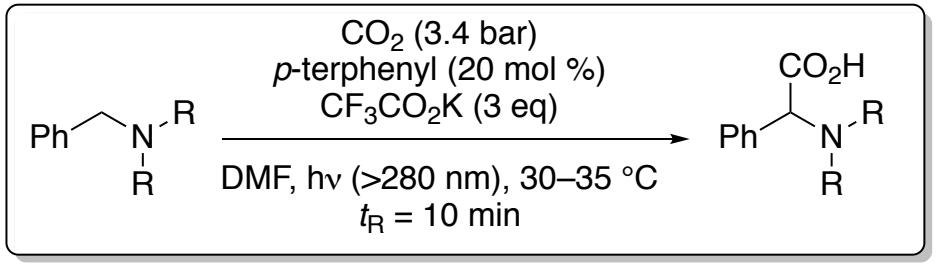
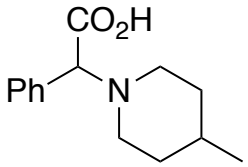


95%

Scope





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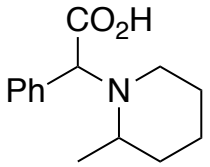
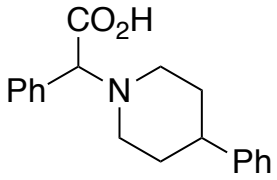


55%, 13:1 dr



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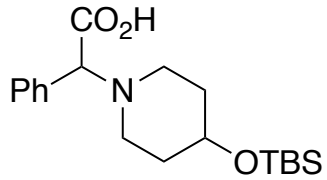

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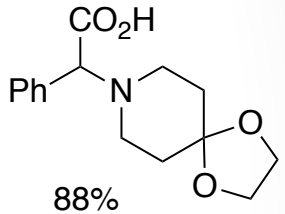

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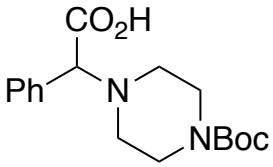

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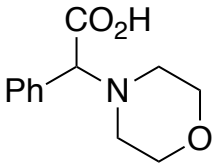

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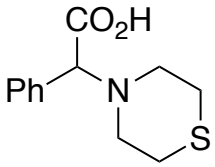

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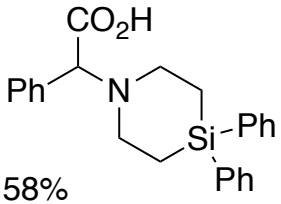
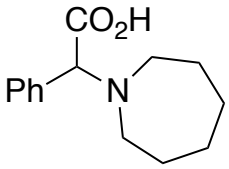


58%
(reduced CO_2 pressure)



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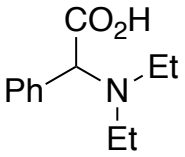

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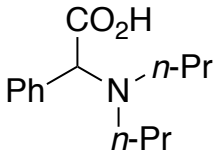

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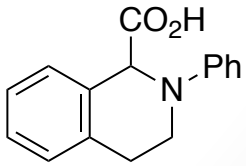
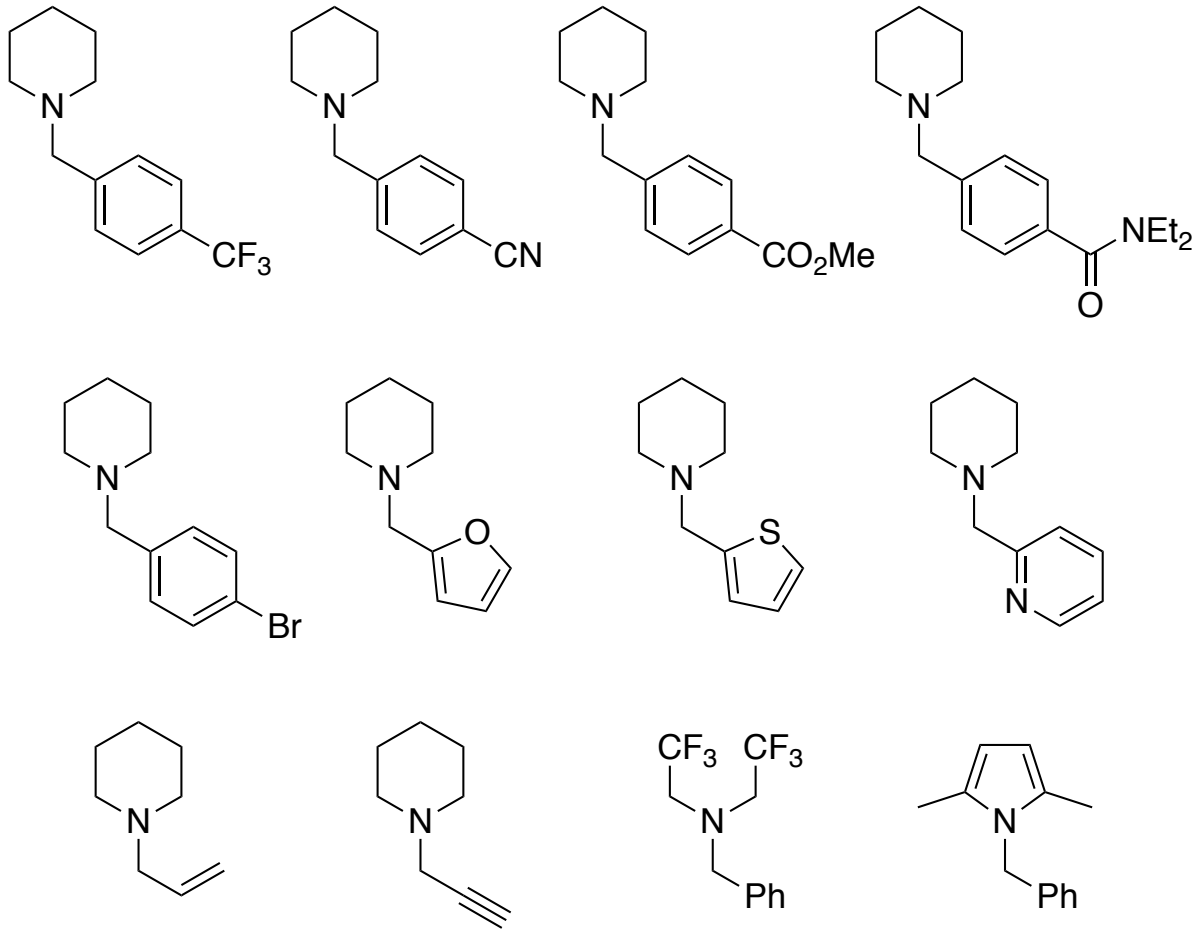
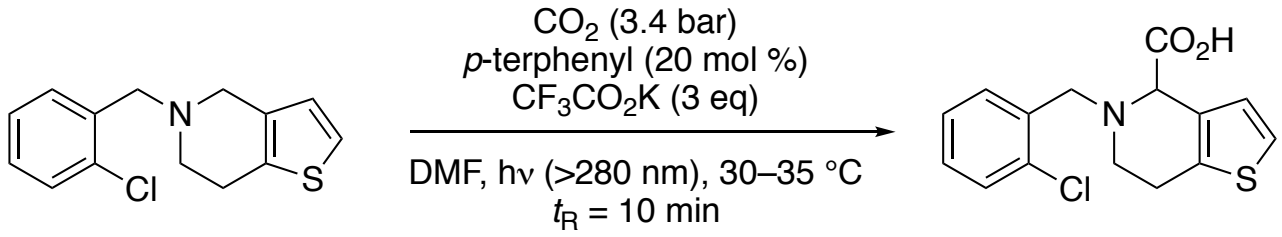


46%

Unsuccessful Substrates



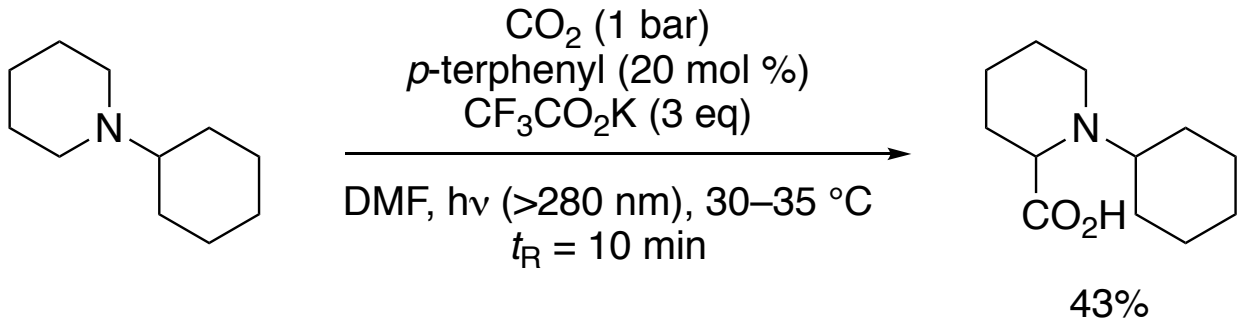
Heterocycle example



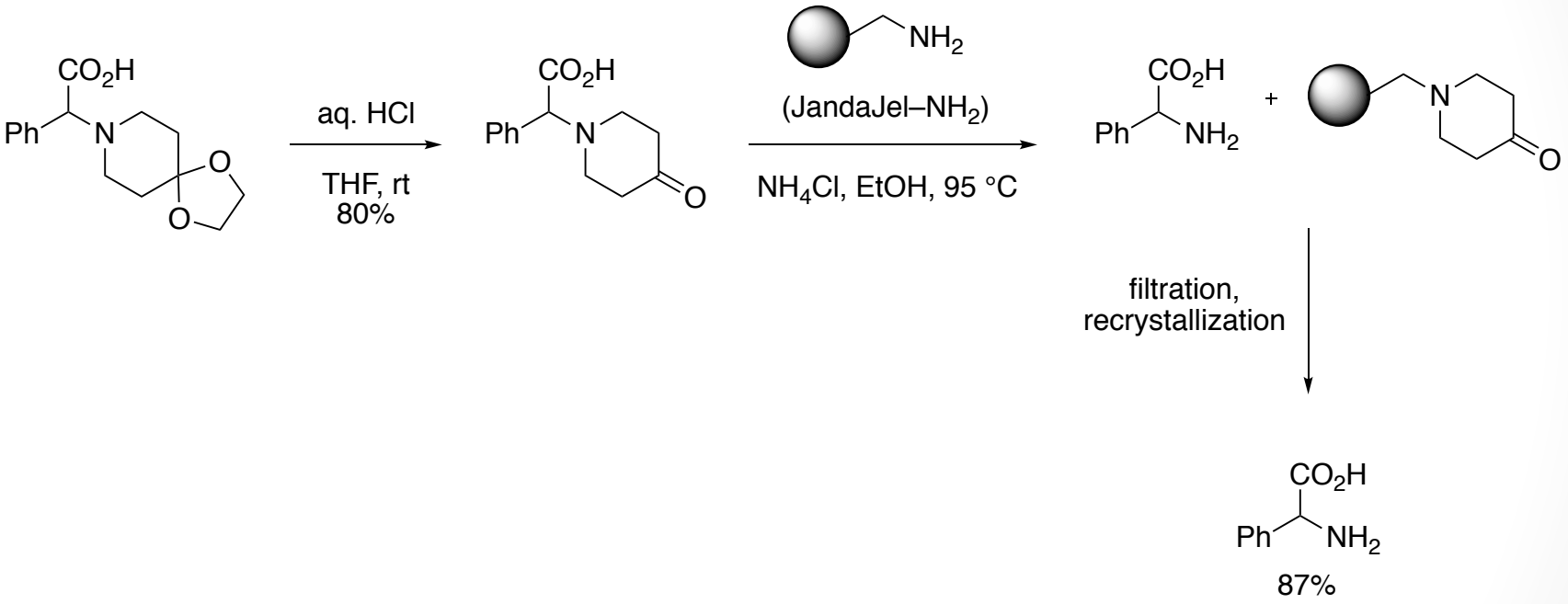
Ticlopidine
(legacy antiplatlet drug)

38%

All-alkyl example



Deprotection



Piperidnone deprotection with a solid-supported amine: Aschwanden, P.; Stephenson, C. R. J.; Carreira, E. M. *Org. Lett.* **2008**, *8* (11), 2437-2440.

Conclusion

- This work constitutes:
  - A novel synthesis of amino acids from simple amines and CO_2
  - One of the first synthetic applications of the CO_2 radical anion
  - The use of terphenyl as a photoredox catalyst

- Present limitations include:
  - The reaction is inherently racemic
  - It requires specialized equipment (flow setup, Hg lamp)
  - UV photoredox may not be as broadly tolerant of functional groups (as compared to Ru/Ir complexes with visible light)