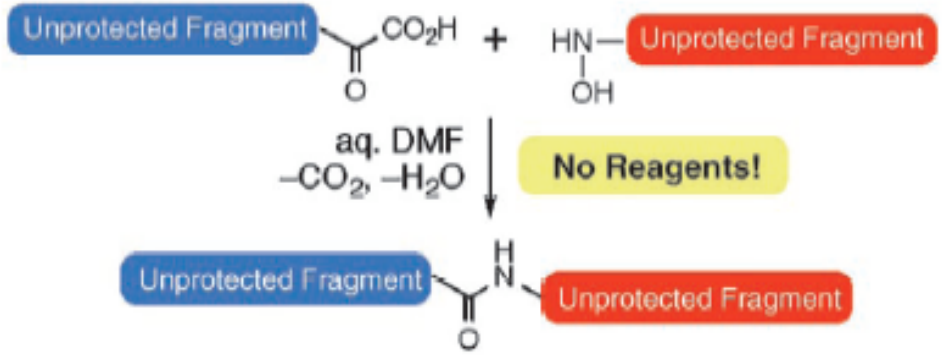
Chemoselective Amide Ligations by Decarboxylative Condensations of *N*-Alkylhydroxylamines and α-Ketoacids

Bode, J. M.; Fox, R. M.; Baucom, K. D. *Angew. Chem. Int. Ed.* **2006**, *45*, 1248-1252.



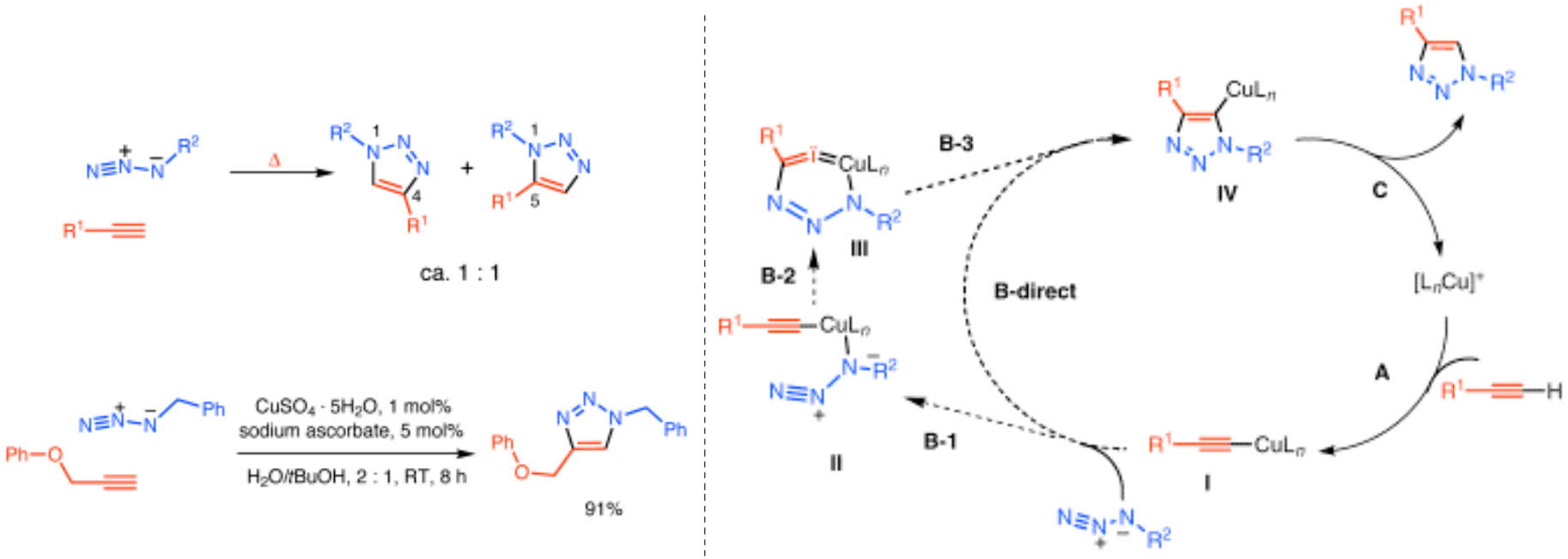
Zhiyong Wang
Wipf Group
Current Literature Presentation
March 4th, 2006

Introduction: Ligation Reactions

An ideal ligation process:

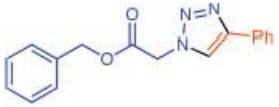
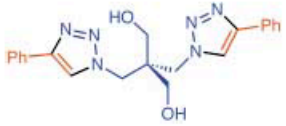
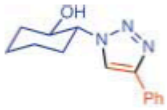
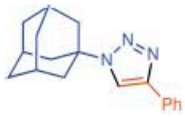
- Chemoselective covalent bond formation between two fragments containing unprotected functional groups
- Mild (often aqueous) conditions
- Low molar concentrations of reactants
- No need for reagents or catalysts
- No production of chemical by-products

Ligation of Azides and Terminal Alkynes



Sharpless, K. B. et al. *Angew. Chem. Int. Ed.* **2002**, *41*, 2596-2599.

Reaction Scope

Product	Yield [%]
	92
	93
	82
	84

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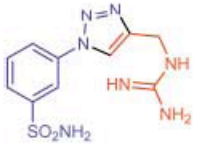
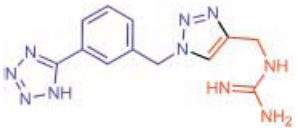
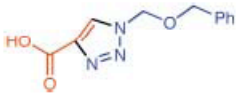
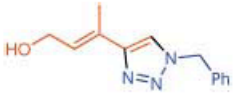
	91
	88
	88
	84

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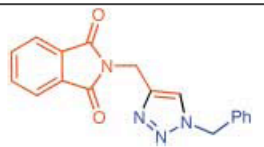
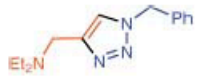
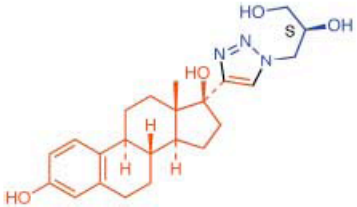
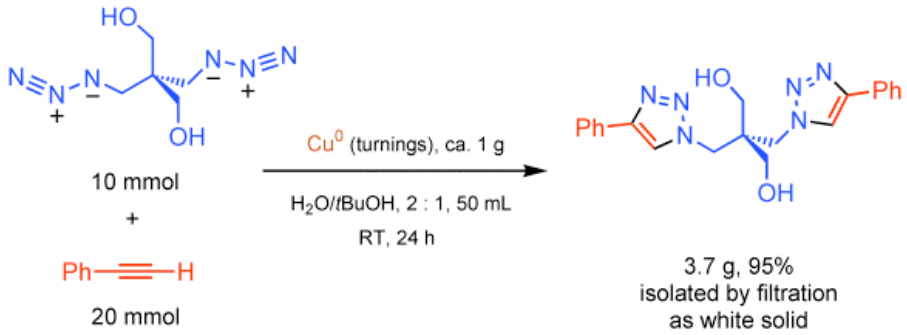
	88
	90
	94

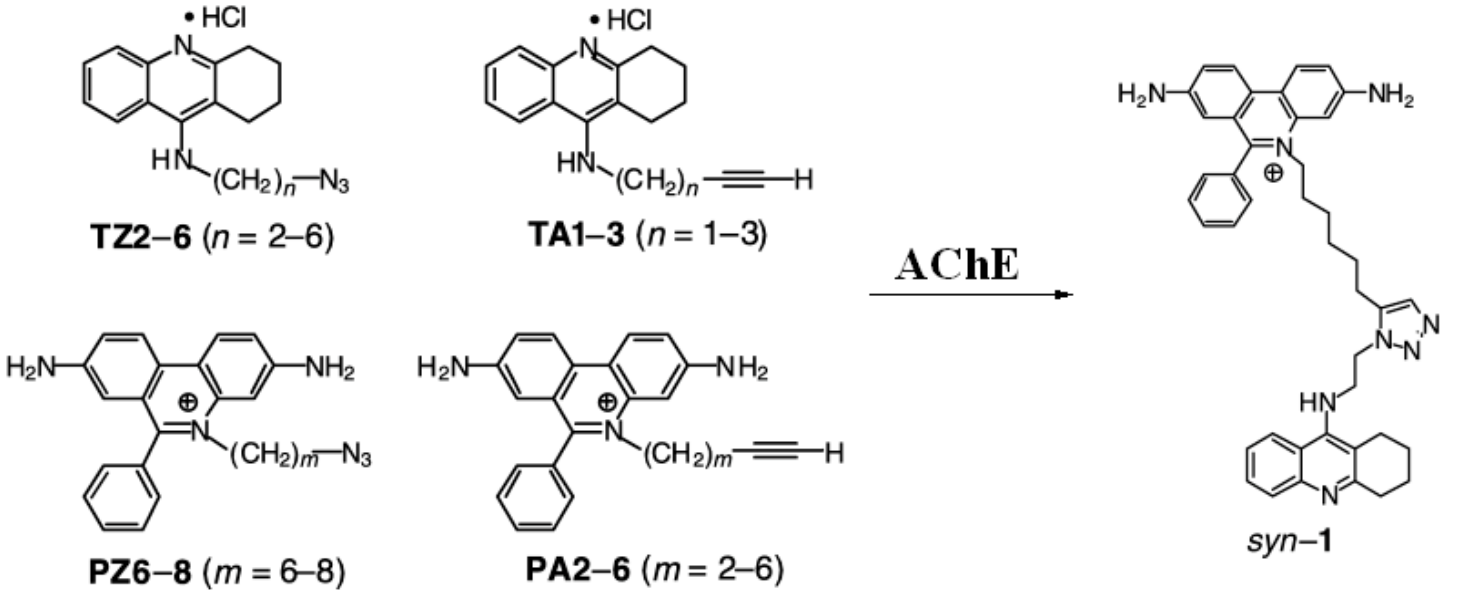
* All reactions were carried out in water with tert-butyl alcohol as cosolvent, 0.25 ± 0.5 in reactants, with 1 mol% of $CuSO_4$ and 10 mol% of sodium ascorbate, and were complete in 12 ± 24 h.



Sharpless, K. B. et al. *Angew. Chem. Int. Ed.* **2002**, *41*, 2596-2599.

Application in Medicinal Chemistry

Acetylcholinesterase (AChE): key enzyme in neurotransmitter hydrolysis and target for Alzheimer's dementia

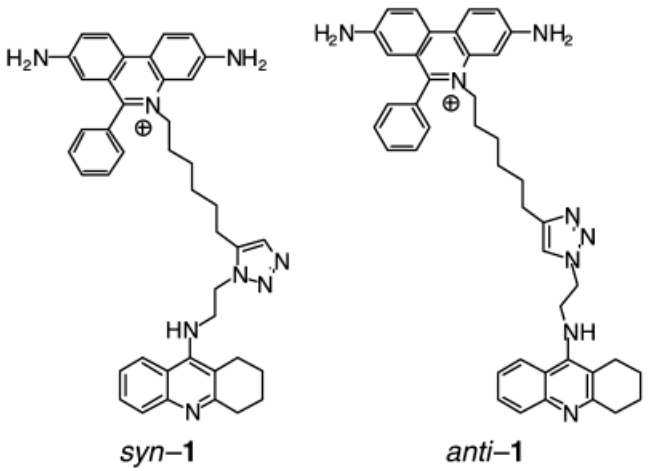


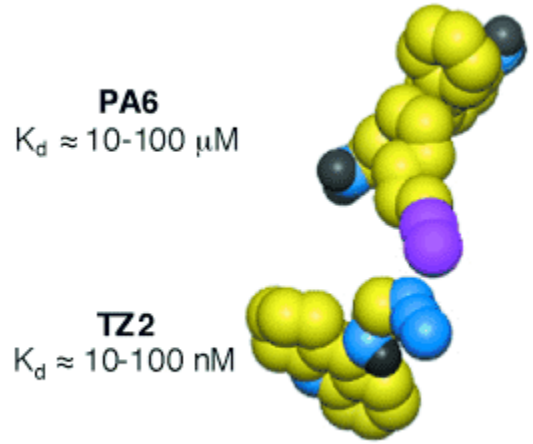
femtomolar inhibitor!

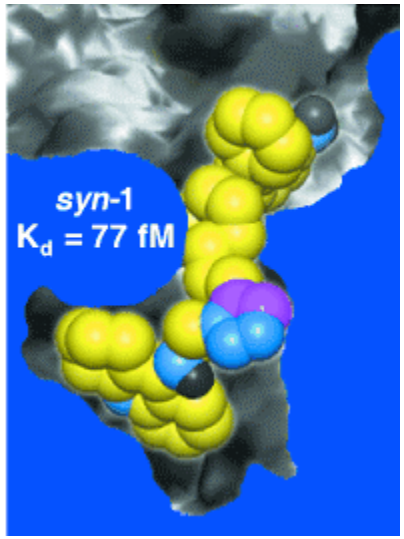
Sharpless, K. B. et al. *Angew. Chem. Int. Ed.* **2002**, *41*, 1053-1057.

A Comparison of the Inhibitory Activities

Inhibitor	k_{on} [10^{10} M^{-1}min^{-1}]	k_{off} [min^{-1}]	K_d	AChE source
syn-**1**	1.5	0.0015	99 fM	*E. electricus*
	1.3	0.0011	77 fM	*T. californica*
	1.3	0.0079	410 fM	mouse
anti-**1**	1.8	0.25	14000 fM	*E. electricus*
	3.2	0.026	720 fM	*T. californica*
	2.4	0.30	8900 fM	mouse
tacrine[38]	0.78	138	18 nM	mouse
propidium[38]	1.4	15000	1100 nM	mouse
huprine X[55]	0.044	0.009	26 pM	human
ambenonium[35]	0.31	0.78	250 pM	human



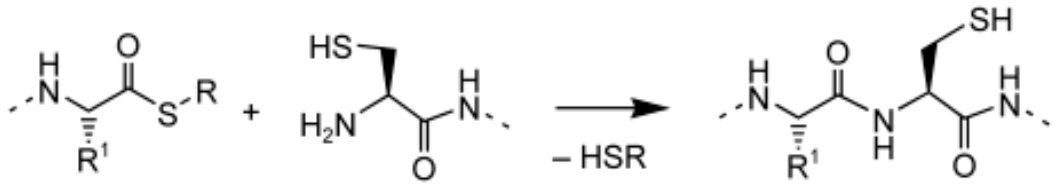




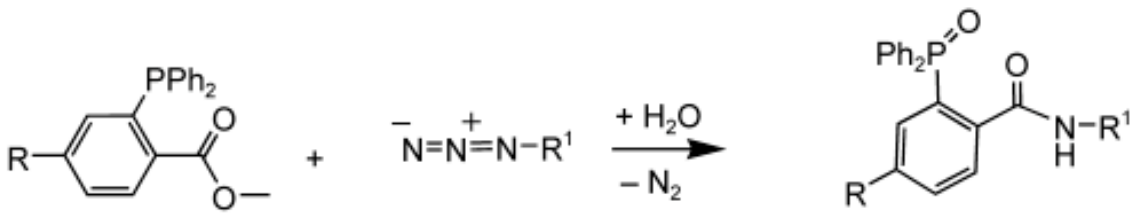
Sharpless, K. B. et al. *Angew. Chem. Int. Ed.* **2002**, *41*, 1053-1057.

Other Common Ligation Techniques

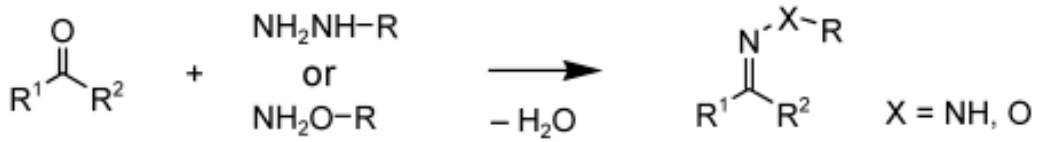
Thioester ligation



Staudinger ligation



Oxime or hydrazone ligation

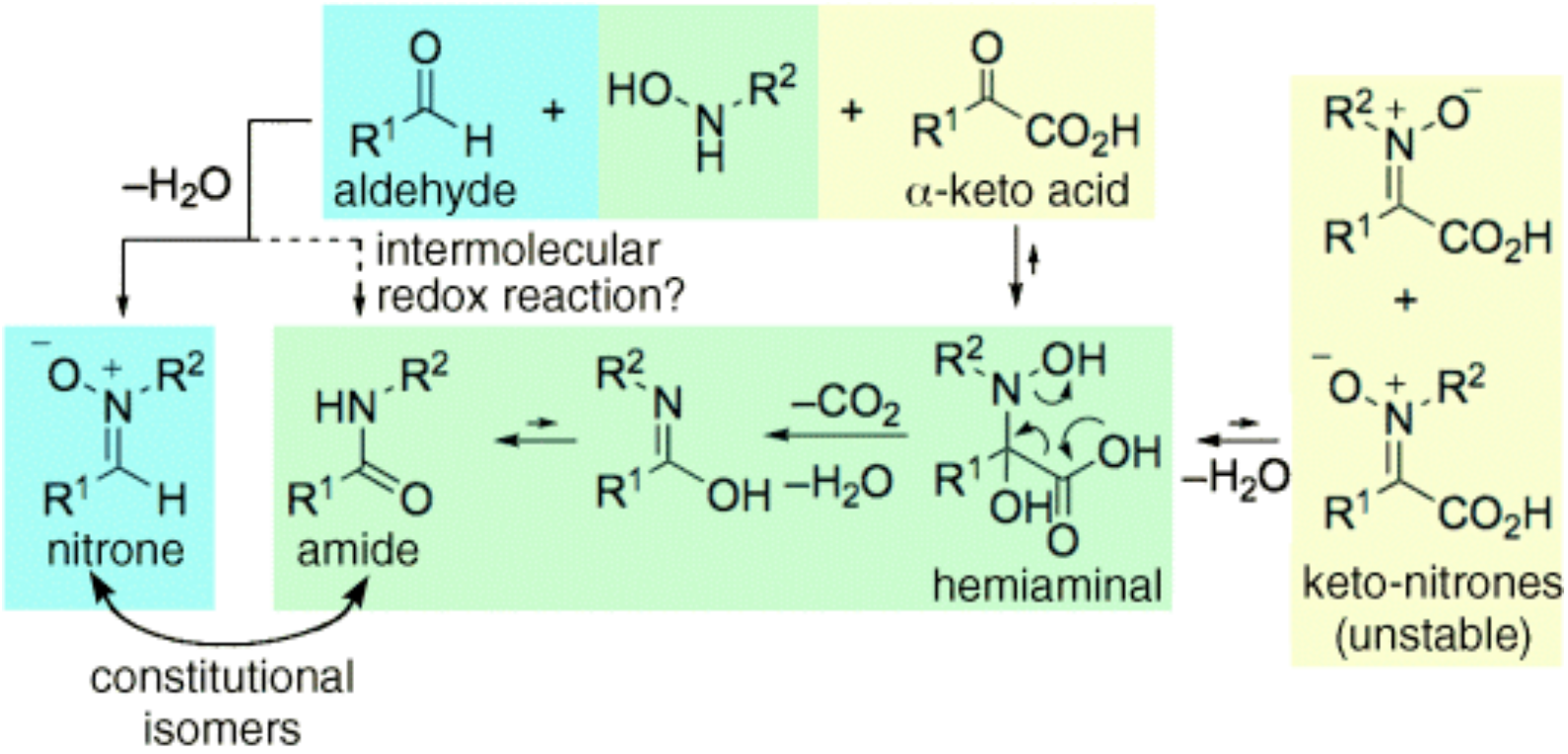


Disulfide ligation

Rademann, J. *Angew. Chem. Int. Ed.* **2004**, *43*, 4554-4556.

Current Paper: Chemoselective Amide Ligation

Reaction Discovery



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Reaction Optimization

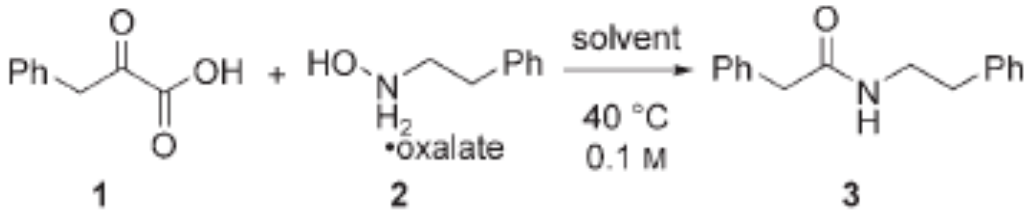

Table 1: Reaction conditions for amide formation from hydroxylamine **1** and α-ketoacid **2**.

Entry	Conditions[a]	*t* [h]	Yield[b] [%]
1	DMF, hydroxylamine free base	15	70
2	DMF	15	79 (88)[c]
3	DMF, ketoacid sodium salt	15	75
4	MeOH	24	72
5	DMSO	15	80
6	DMF/H_2O (5:1)	15	72 (77)[c]
7	acetate buffer (pH 4)	24	(70)[c]
8	6 N NH_4Cl, 60 °C	15	68 (70)[c]

[a] All reaction performed on a 0.2 mmol scale; [b] Yields following chromatography; [c] HPLC yields of unpurified reaction mixtures given in parentheses.

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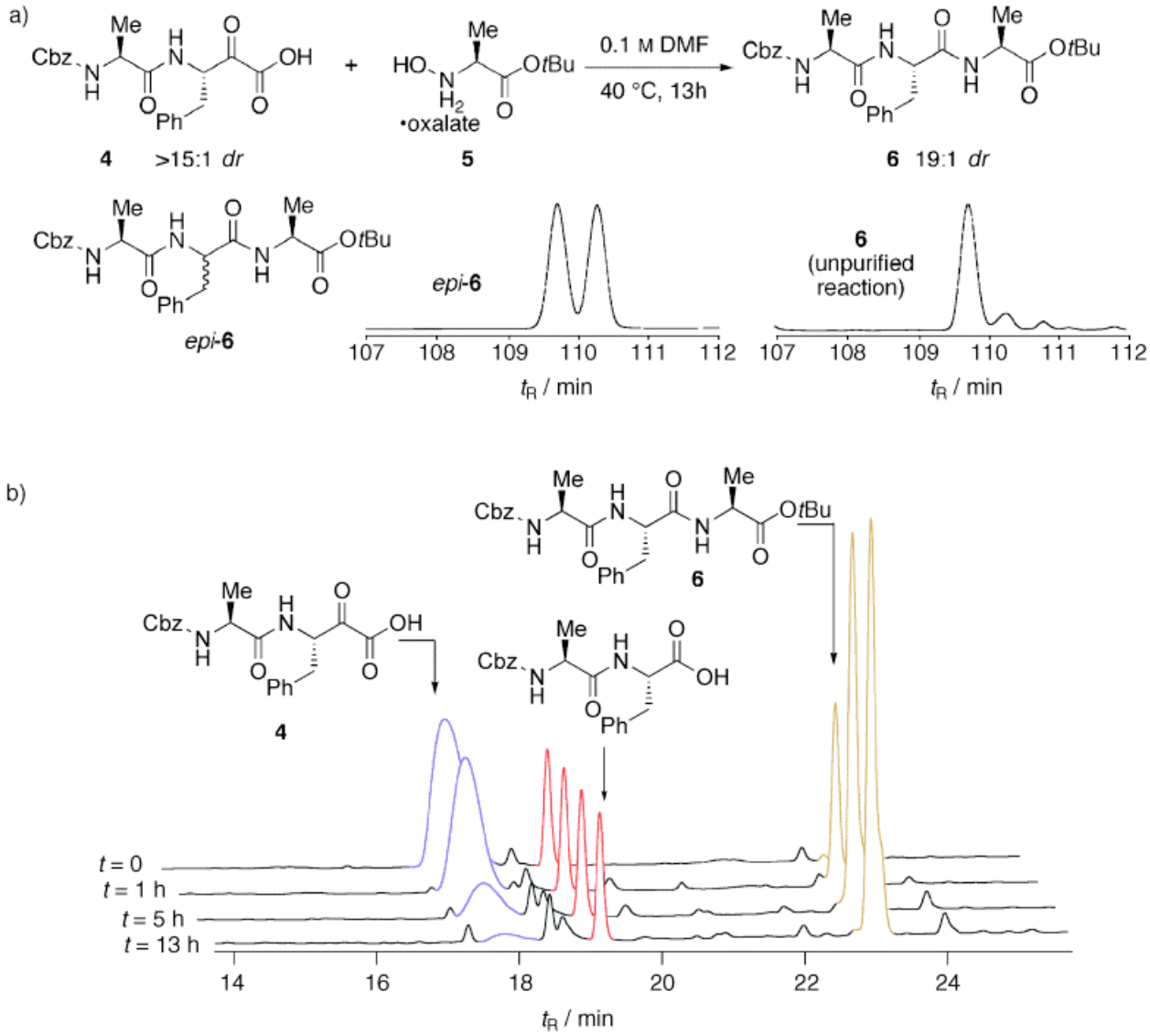
A Racemization/Epimerization-Free Process



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Reaction Scope

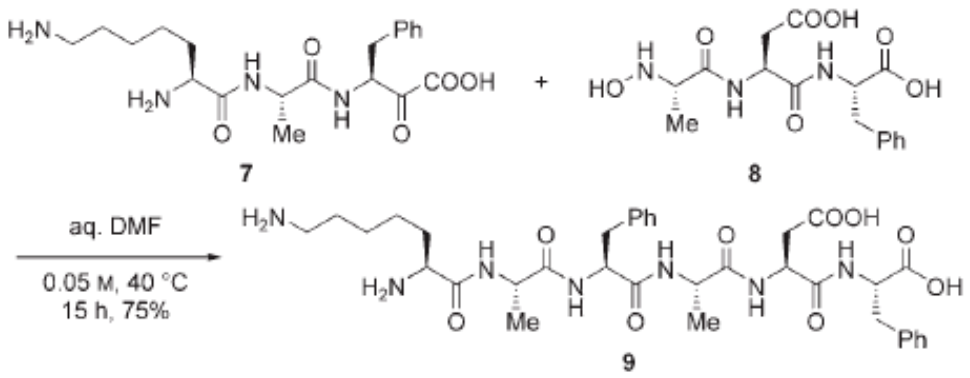

Table 2: Ketoacid–hydroxylamine peptide ligations of selected protected- and unprotected-peptide substrates.

Entry	Ketoacid	Hydroxylamine	Product[a]	Yield[b] [%]
1	FmocAlaPro	AlaO*t*Bu	Fmoc-AlaProAla-O*t*Bu	72
2	FmocAlaVal	GlyOEt	Fmoc-AlaValGly-OEt	58
3	FmocLys(Boc)-Glu(*t*Bu)PheAla	AlaO*t*Bu	Fmoc-Lys(Boc)Glu(*t*Bu)Phe-AlaAla-O*t*Bu[c]	80
4	H_2N-LysAlaPhe	AlaAsp(*t*Bu)PheO*t*Bu	H_2N-LysAlaPhe-AlaAsp(*t*Bu)Phe-O*t*Bu	74
5	FmocAspAlaPhe	AlaAsp(*t*Bu)PheO*t*Bu	Fmoc-AspAlaPhe-AlaAsp(*t*Bu)PheO*t*Bu	74

[a] All reaction performed at 0.02–0.1 M in DMF or DMSO containing ca. 5% H_2O at 40°C for 10–24 h using 1 equiv ketoacid and 1.2–2 equiv hydroxylamine oxalates; [b] Yields of pure products following preparative TLC or RP-HPLC. The reported yields include the preparation of the ketoacids by oxidation of the appropriate cyanoylide followed by coupling with the hydroxylamine; [c] 0.01 M, 48 h.

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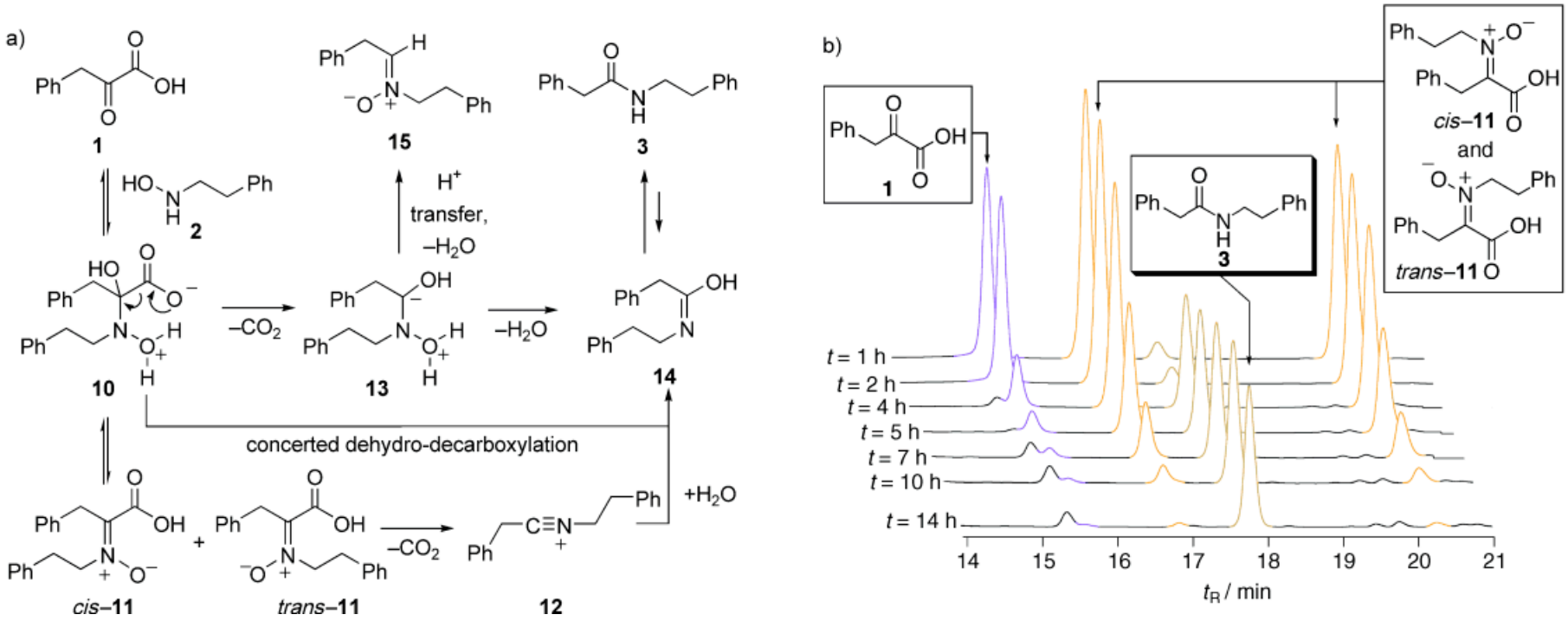
Reaction Mechanism



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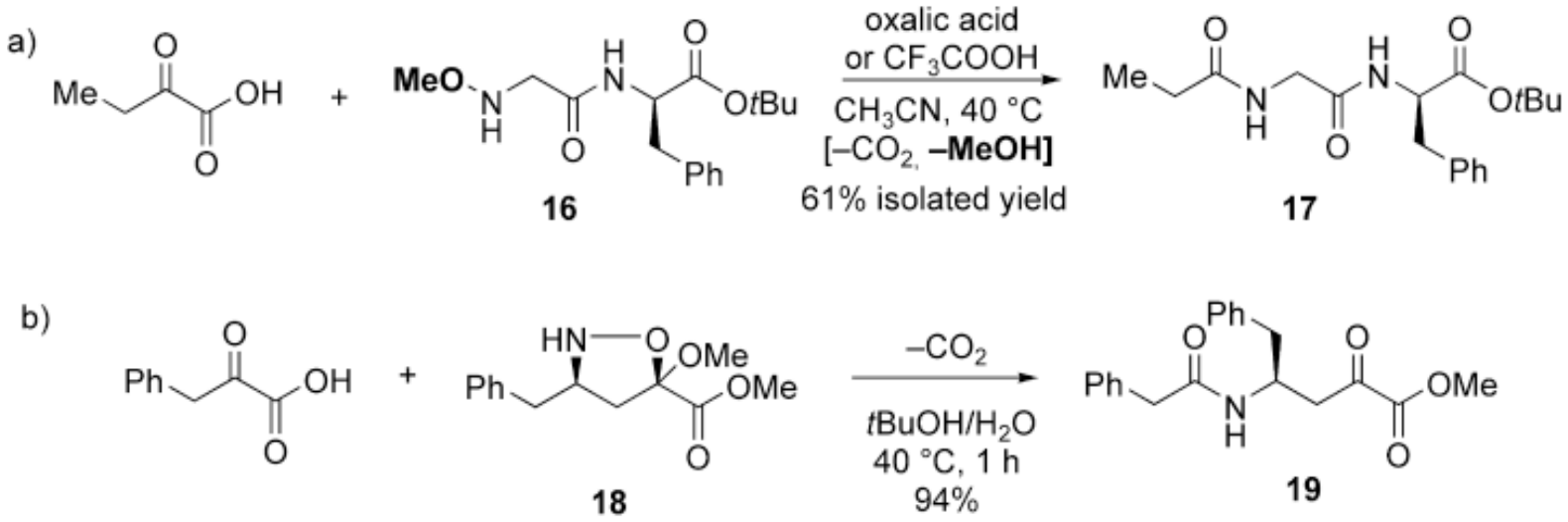
Reaction with Substituted Hydroxylamine



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Synthesis of the α-Ketoacids

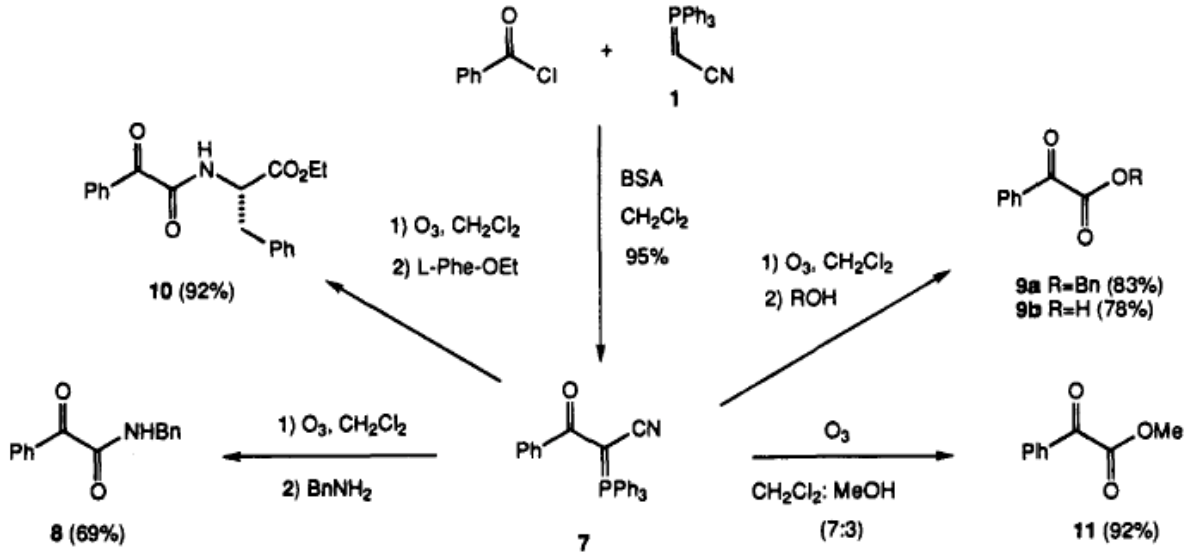
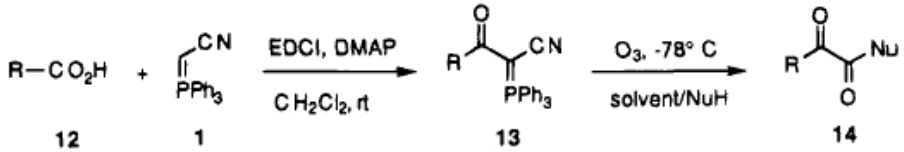


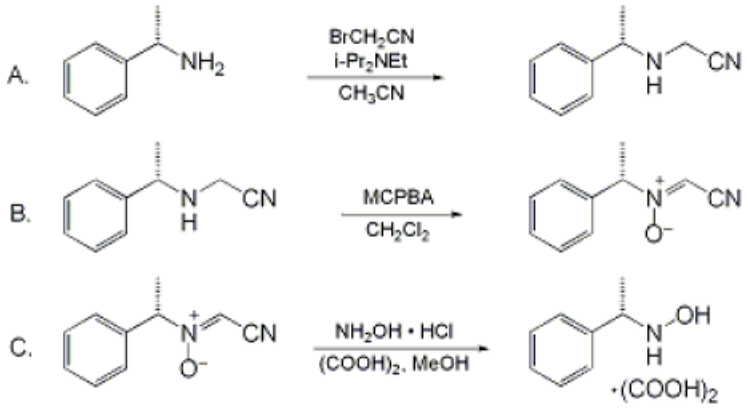
Table 1. Synthesis of α-Keto Acids, Esters, and Amides from Carboxylic Acids

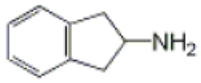
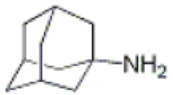
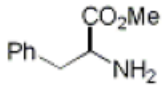


		ketocyano ylide			α-keto acid, esters, and amides[a]	
entry	RCO_2H **12**	**13**	yield (%)	solvent/NuH	**14**	yield (%)
1	Cbz-HN-$(CH_2)_{11}$-CO_2H (**12a**)	**13a**	78	(7:3) CH_2Cl_2–MeOH	**14a** (Nu = OMe)	83
2	HO-$(CH_2)_{11}$-CO_2H (**12b**)	**13b**	*b*	(7:3) CH_2Cl_2–MeOH	**14b** (Nu = OMe)	85
3	Boc-Phe-OH (**12c**)	**13c**	80	CH_2Cl_2/(4/1) THF–H_2O[c]	**14c** (Nu = OH)[d]	74
4	Boc-Phe-OH (**12c**)	**13c**	80	(7:3) CH_2Cl_2–MeOH	**14d** (Nu = OMe)	89
5	Cbz-Gly-Gly-OH (**12e**)	**13e**	59	(7:3) CH_2Cl_2–MeOH	**14e** (Nu = OMe)	74
6	Cbz-Ala-Gly-Gly-OH (**12f**)	**13f**	64	(7:3) CH_2Cl_2–MeOH	**14f** (Nu = OMe)	88
7	Boc-Phe-OH (**12c**)	**13c**	80	CH_2Cl_2/Phe-OEt[e,f]	**14g** (Nu = Phe-OEt)	63
8	Boc-Phe-OH (**12c**)	**13c**	80	CH_2Cl_2/Leu-OMe[e,f]/^{i}Pr_2NEt	**14h** (Nu = Leu-OMe)	58

Wasserman, H. H.; Ho, W. B. *J. Org. Chem.* **1994**, *59*, 4364-4366.

Synthesis of Hydroxylamine



Entry	Amine	Cyanomethyalation[a]			Overall Yield
		Conditions	Time (h)	Yield (%)	
1	$PhCH_2NH_2$	A	24	95	82
2	$PhCH_2CH_2NH_2$	A	24	96	75
3	$PhCH_2CH_2CH_2NH_2$	A	24	93	74
4		B[b,c]	22	97	79
5	Ph_2CHNH_2	B	15	98	55
6		C	1	89	76
7	$BnO_2CCH_2NH_2$	B[d]	18	91	62
8		B[b,e]	26	92	61

[a]Conditions A. $ClCH_2CN$ (1.5 eq), K_2CO_3 (2.0 eq), CH_3CN, 60°C; Conditions B. $BrCH_2CN$ (1.5 eq), i-Pr_2NEt (2.0 eq), CH_3CN, rt; Conditions C. ICH_2CN (2.0 eq), K_2CO_3 (2.5 eq), DMF, rt.
[b]HCl salt of amine was used.
[c]$BrCH_2CN$ (1.3 eq), i-Pr_2NEt (3.0 eq).
[d]$BrCH_2CN$ (1.2 eq), i-Pr_2NEt (2.0 eq).
[e]$BrCH_2CN$ (2.0 eq), i-Pr_2NEt (3.0 eq).

Tokuyama, H.; Kuboyama, T.; Fukuyama, T. *Org. Syn.* **2003**, *80*, 207 – 218.

Summary

- A powerful and chemoselective amide bond formation reaction that proceeds in the presences of reactive functional groups is developed.
- No reagents or catalysts are needed.
- Water and CO_2 are the only by-products.
- Unprotected amino acids or peptides can be coupled directly.
- Preparation of the reactive α-ketoacids is the major draw-back.