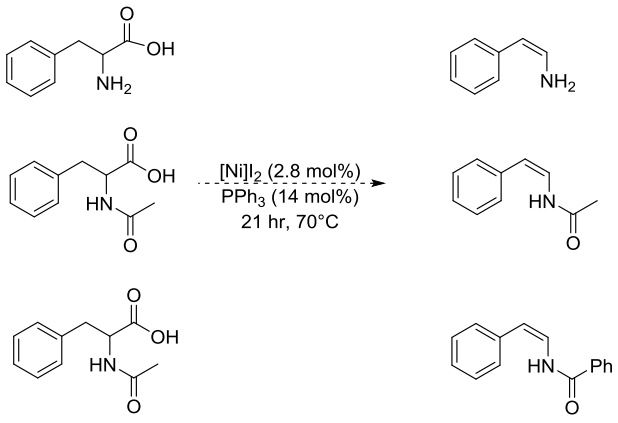
Results and Discussion

Phenylalanine Derivative Screening

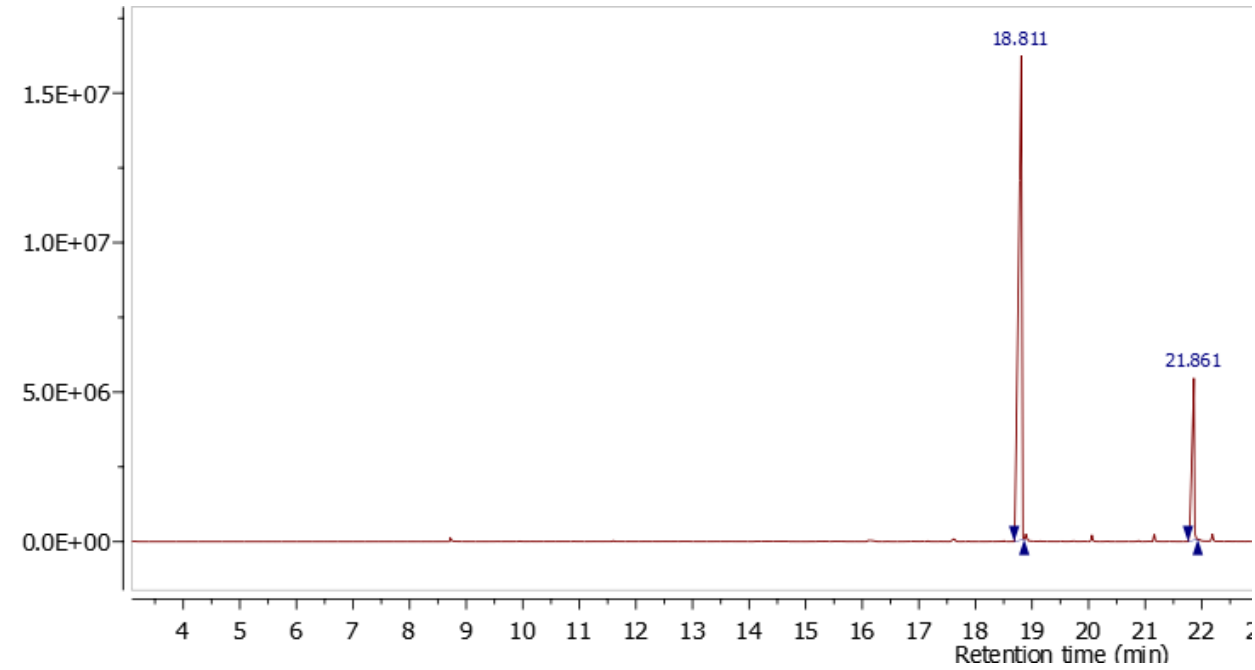
The first phase of our work with Tolman chemistry involved a screening of L-phenylanaline and two derivatives, *N*-acetyl-L-phenylalanine and *N*-benzoyl-L-phenylalanine, through the reported highest yield reaction (94%). All products were analyzed by gas chromatography-mass spectroscopy. All three reactions displayed two prominent peak areas representing triphenylphosphine (19 min) and triphenylphosphine oxide (22 min). Of the three screenings, *N*-acetyl-L-phenylalanine (acetyl-phen) showed the greatest promise based on the mass spectrum obtained at 13.8 min (**Figure 3C)**. As shown in **Figure 4**, the m/z values of 119 and 118 corresponded to the values expected of our desired product. We ruled out the possibility of column contamination on account of the fact that these m/z values were not universal for all three phenylalanine derivatives and due to the fact that these values were clearly derivatives from the start material (161 m/z).

Scheme 2. Phenylalanine derivative screening

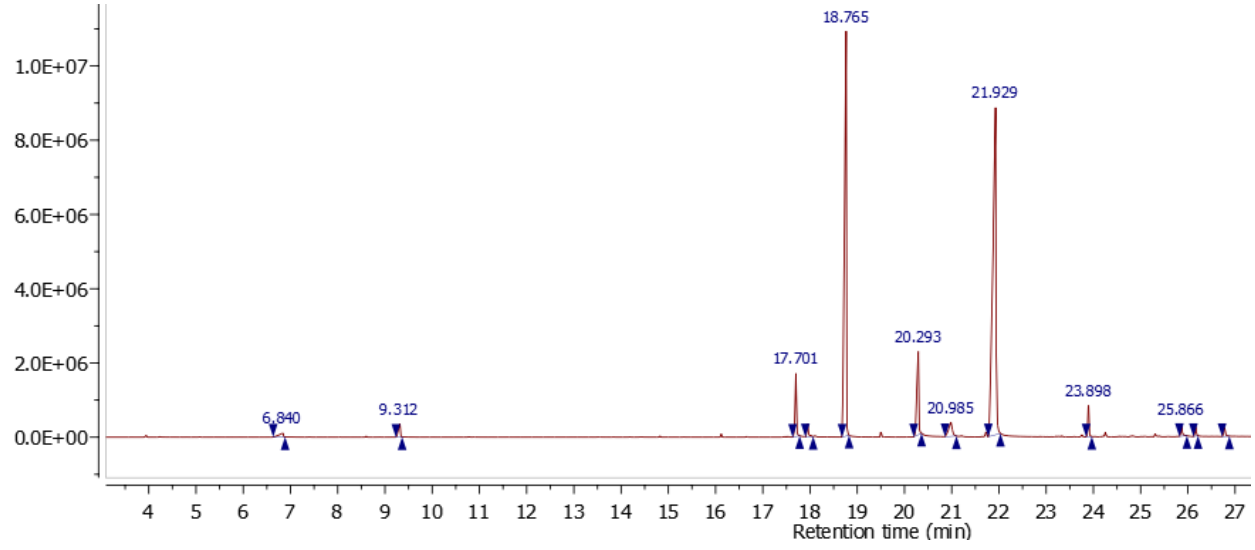


5

A


18.811
21.861
1.5E+07
1.0E+07
5.0E+06
0.0E+00
4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22
Retention time (min)

B


18.765
21.929
20.293
17.701
23.898
6.840
9.312
20.985
25.866
1.0E+07
8.0E+06
6.0E+06
4.0E+06
2.0E+06
0.0E+00
4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27
Retention time (min)

C

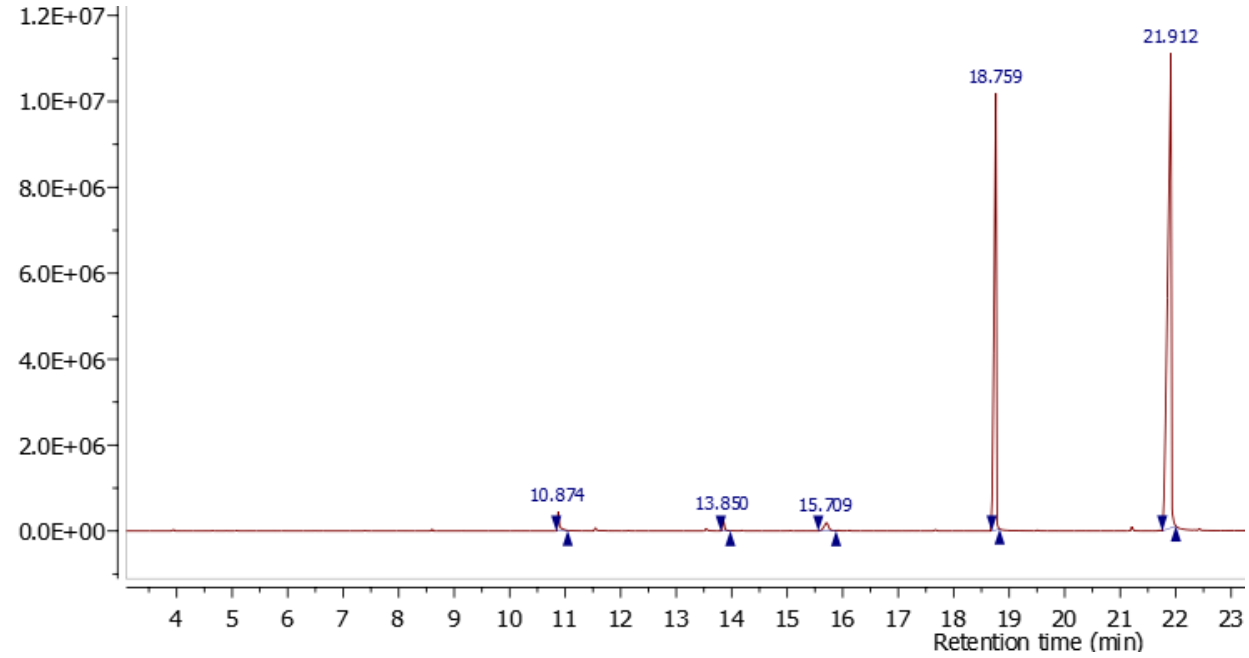


Figure 3. GCMS chromatographs of products of phenylalanine (A), N-benzoyl-L-phenylalanine (B), and N-acetyl-L-phenylalanine screenings.

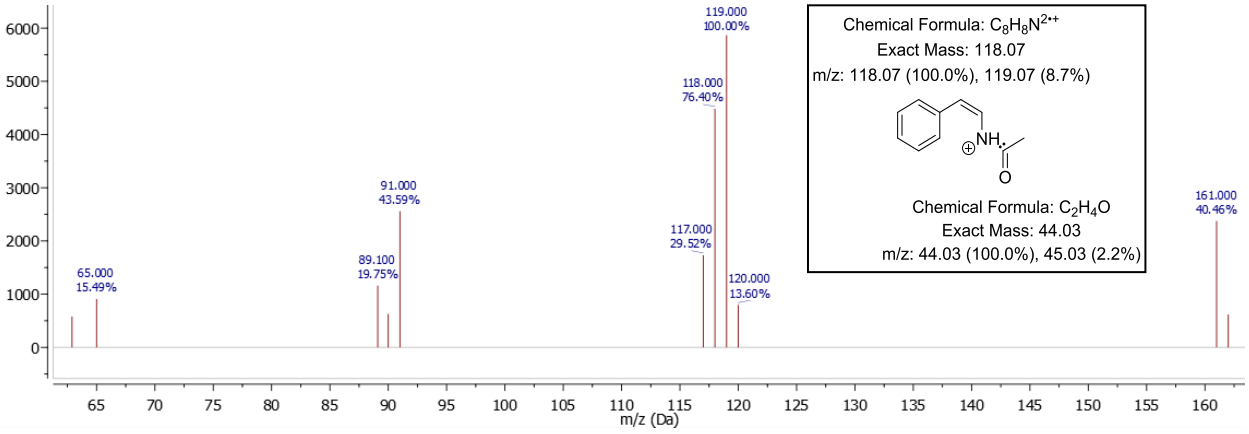


Figure 4. MS of N-acetyl-Lphenylalanine at retention time 13.850 minutes.

Nickel Catalyst and Solvent Screening

To further optimize the reaction for acetyl-phen, we screened all available nickel catalysts inside the lab: nickel(II)iodide, anhydrous; nickel(II)bromide, dimethoxyethane adduct; nickel(II)chloride, anhydrous; nickel(II)bromide, anhydrous; nickel(II)acetylacetonate, anhydrous; nickel(II)hydroxyacetate; nickel(II)trifluoroacetylacetonate dihydrous; bis(triphenylphosphine)nickel(II)chloride; and bis(triphenylphosphine)dicarbonylnickel(II). Of the available catalysts, nickel(II)iodide, anhydrous; nickel(II)bromide, anhydrous; and bis(triphenylphosphine)dicarbonylnickel(II) were the only ones that displayed the expected m/z values at 13.9 min (**Figure 5**).

Based on these results, we decided to optimize the reaction using $[Ni]I_2$ since it had the greatest peak area of our expected product relative to the peak area of the PPh_3 signal and also because it was relatively affordable. We screened five different solvent conditions: ACN, DMSO, HFIP, THF, and toluene (**Table 1**). Following analysis of expected product (ret. time 11.5 and 13.8) signal area relative to PPh_3 (ret. time 1), toluene was identified as the ideal solvent.

Complications

Upon further analysis of the GCMS data, an issue concerning the m/z ratios observed for the expected product was identified. We had identified m/z 161 as evidence for the presence of product and m/z 118 and 119 as primary fragments from the parent. However, these masses could also be derived from the starting material (**Scheme 3A and 3B**). This led us to question the validity of our conclusions that were heretofore solely interpreted from GCMS (yields were too small for NMR analysis). After controlling for solvent and starting reagents we observed the

same splittings from the starting material and concluded that these presumed product signals were most likely alternative fragmentations of the starting amine rather than that of product. Thus, we pursued a different method for decarboxylating amino acids.

Baran Chemistry

Amino acids are among the most abundant chemicals available to us from nature due to their universality throughout all of biology. Because of its ease of access, affordability, and abundance amino acids make for an ideal feedstock for conversion into other useful molecules. Additionally, carboxylic acid groups are very common in bio-active molecules thus making it an abundant handle for future transformation reactions. In 2017 the Baran group published a comprehensive study of redox-active ester (RAE) cross-coupling reactions (**Scheme 4**). Among the reactions reported were pathways that involved amino acid analogues with protected amino groups where the cross-coupling occurred at the carboxylic acid terminus. The Baran group, in this paper, summarized the reactions that allowed them to report Negishi, Kumada, and Suzuki couplings with simple carboxylic acids. The chemistry were especially interesting to our group because of its operational simplicity: The reagents were inexpensive, isolation of the RAEs was not necessary, the reactions were robust enough to tolerate air and moisture, and they were demonstrated to be straightforward for scale-up.[8]

We began to work with this chemistry for the second phase of this research. Our goals were to 1) repeat Baran's RAE chemistry, 2) generate/obtain various protected amino acids, and 3) adapt the RAE procedure for these amino acids (**Scheme 5**).

Replicating Baran's RAE Chemistry

In the first step of the reaction, we activated N-Boc-L-proline with tetrachloro-N-Hydroxyphthalimide (TCNHPI) (**Scheme 6**). The reaction readily proceeded with a 70% yield. H^1NMR analysis of the product matched the Baran group's spectra (**Figure 6**).

Proceeding to the second step, we attempted to cross-couple the activated amine with phenylboronic acid (**Scheme 7**). However, an unexpected issue arose: During TLC analysis, different product spots appeared in our reaction than those in Baran's results (**Figure 7**). As seen in our TLC comparison to Baran's, two novel products not accounted for in Baran's report appeared in our reaction mixture. These impurities persisted even after we controlled for starting reagent purity (save bathophenanthroline), time (strictly 12 hours), and temperature (75°C). Unfortunately, the novel products made separation inherently difficult due to the close RF values of all product spots. The best separation achieved to date has been through a two-part procedure where the product is first separated by 100 ml silica gel in hexanes/ethylacetate 5:1 followed by a small flash column in the same eluent but separated into 1.5 ml fractions. However, there is still contamination of two products in each fraction so it will likely require another one or two sequential flash columns to separate the products enough for characterization.

Protection of amino acid wit Pthalic anhydride

To fulfill goal 2, we attempted to protect leucine with pthalic anhydride (**Scheme 8**). We adapted our procedure by downscaling a Chinese patent that utilized a Dean-Stark apparatus. Once we attempted to isolate product from the solidified gel the reaction had formed we immediately ran into a problem of separation. No matter how polar the eluent (including a

solution of {10% NH_3OH in MeOh}:DCM 1:9) the product would not move off the baseline. This indicated the presence of a highly polar substance, with the most likely explanation being that the reaction failed and the leucine left over was stuck strongly to the TLC plate.

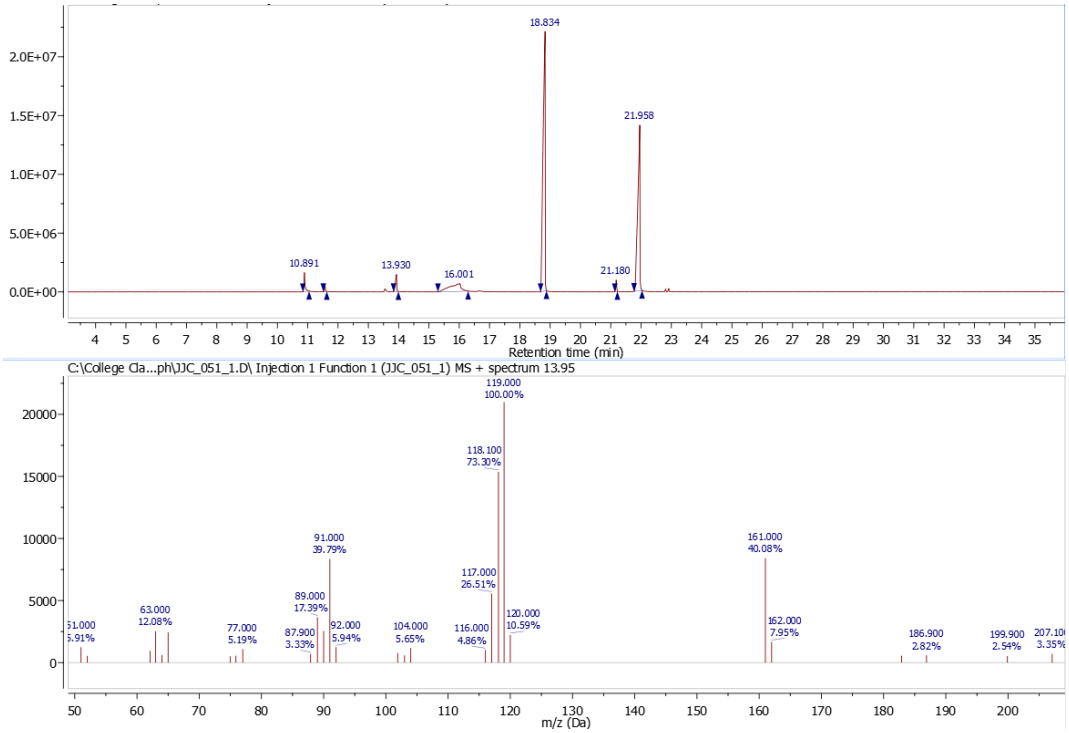
Conclusions

Though many obstacles have thus far stymied our progress, the generation of peptoid start materials from an inexpensive feedstock remains a promising direction of research. If a successful pathway is discovered it would have powerful implications on the field of organic chemistry as a whole. Amino acids are highly abundant, inexpensive, and their modification is well understood; if we can then simply decarboxylate customized amino acids we would have developed a dependable method to quickly generate customized hetero-substituted olefins.

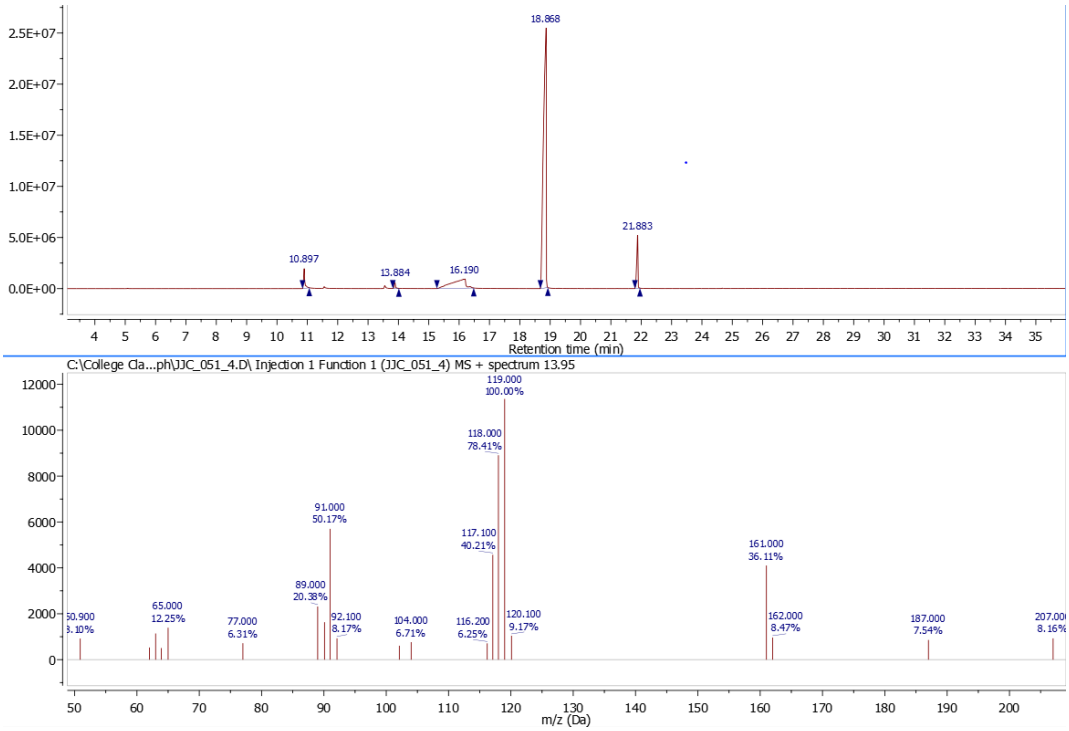
Future Work

To continue this work, we will need to determine the sensitivity of Baran RAE chemistry and then fine-tune these conditions for amino acids and their derivatives. Additionally, we will generate Boc-protected/phthalamido-leucine TCNHPI adducts (compounds A and B from **Scheme 9**) for cross-coupling in RAE chemistry. Until another procedure for protecting leucine with phthalic anhydride is found, we will continue to fine-tune the reaction and test the current product with ninhydrin staining to determine if the reaction had proceeded.

A


18.834
21.958
10.891
13.930
16.001
21.180
Retention time (min)
C:\College Cla...ph\JJC_051_1.D\ Injection 1 Function 1 (JJC_051_1) MS + spectrum 13.95
119.000
100.00%
118.100
73.30%
91.000
39.79%
161.000
40.08%
117.000
26.51%
89.000
17.39%
63.000
12.08%
120.000
10.59%
162.000
7.95%
77.000
5.19%
87.900
3.33%
92.000
5.94%
104.000
5.65%
116.000
4.86%
186.900
2.82%
199.900
2.54%
m/z (Da)

B


18.868
21.883
10.897
13.884
16.190
Retention time (min)
C:\College Cla...ph\JJC_051_4.D\ Injection 1 Function 1 (JJC_051_4) MS + spectrum 13.95
119.000
100.00%
118.000
78.41%
91.000
50.17%
117.100
40.21%
161.000
36.11%
89.000
20.38%
65.000
12.25%
120.100
9.17%
92.100
8.17%
162.000
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187.000
7.54%
m/z (Da)

C

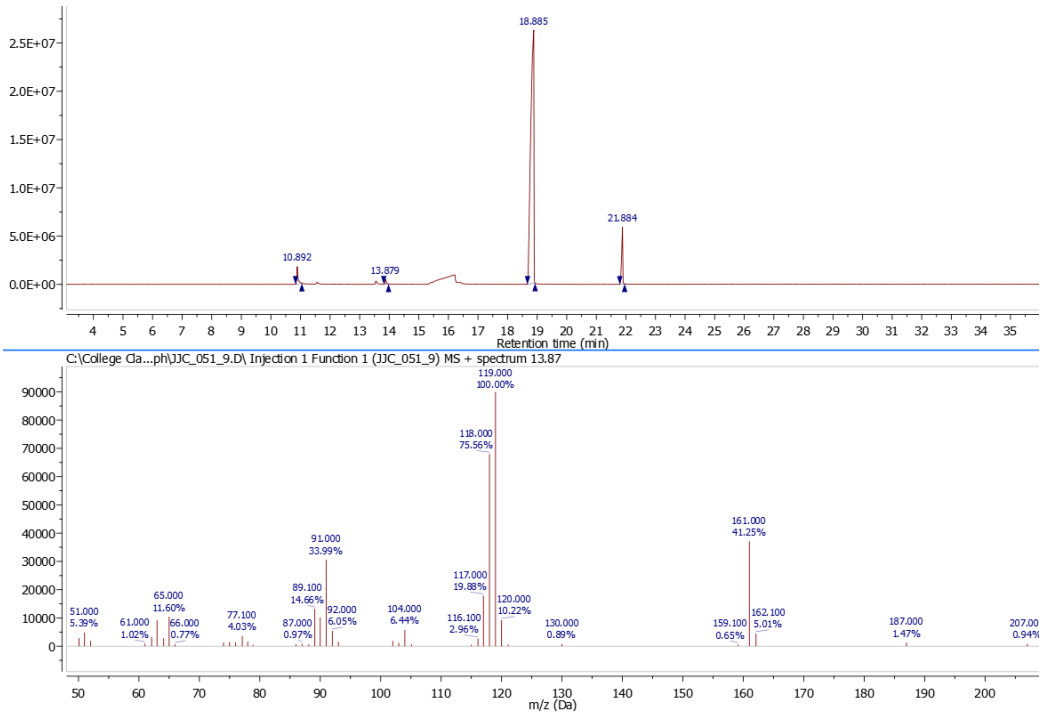


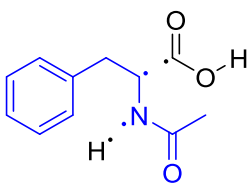
Figure 5. GCMS chromatograms and spectrum at 13.9 for $[Ni]I_2$ (A), $[Ni]Br_2$ (B), and bis(triphenylphosphine)dicarbonylnickel (C).

Solvent	Retention Time (min)		Ratio of Signal Area to PPh_3
	11.5	13.85	
Control	0.00988	0.02061	
ACN	0.01115	0.02903	
DMSO	0.01801	0.06091	
HFIP	0.44528*	0.01891	
THF	0.00938	0.01891	
Toluene	0.01406	0.04229	

Table 1. Comparison of relative product signal from solvent screening

*outlier due to the presence of a new molecule with the same retention time

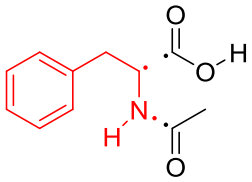
A



Chemical Formula: $CHO_2^{\bullet}$
Exact Mass: 45.00
m/z: 45.00 (100.0%), 46.00 (1.1%)

Chemical Formula: $C_{10}H_{11}NO^{2\bullet}$
Exact Mass: 161.08
m/z: 161.08 (100.0%), 162.09 (10.8%)

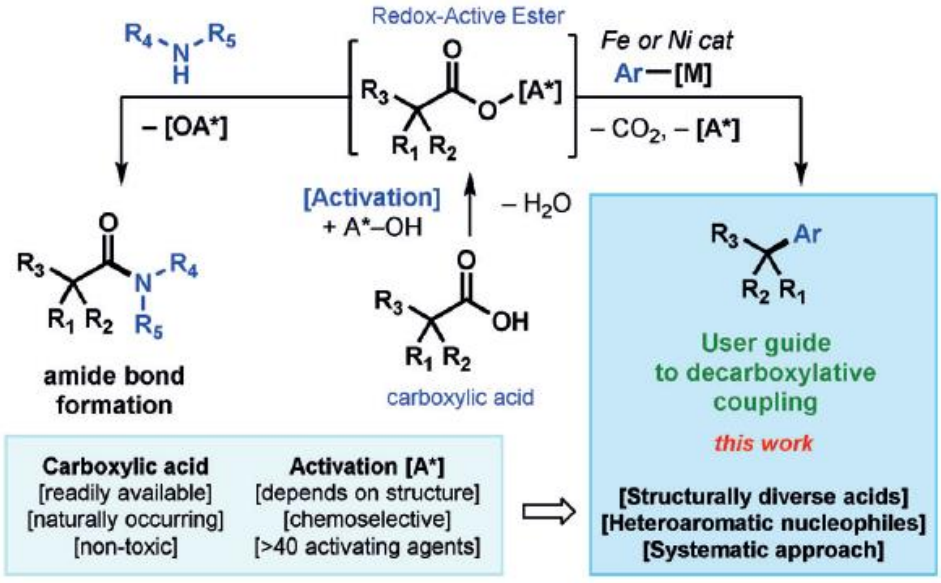
B



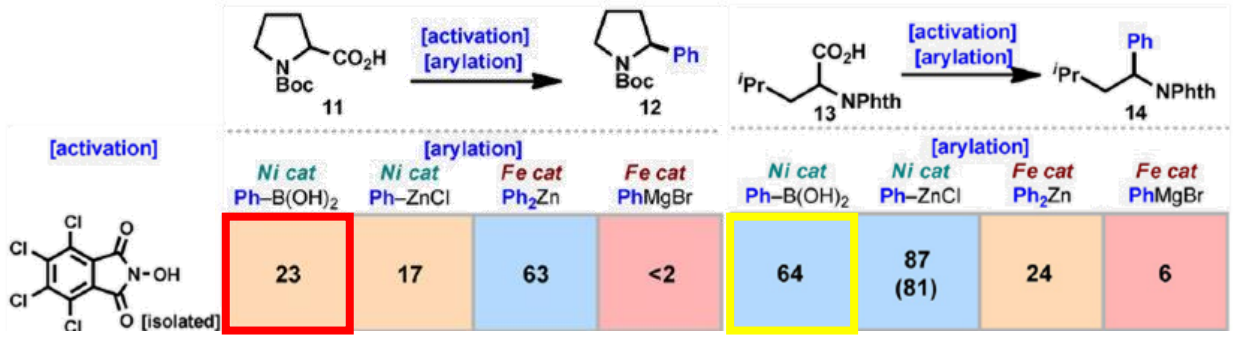
Chemical Formula: $C_2H_3O^{\bullet}$
Exact Mass: 43.02
m/z: 43.02 (100.0%), 44.02 (2.2%)

Chemical Formula: $C_8H_9N^{2\bullet}$
Exact Mass: 119.07
m/z: 119.07 (100.0%), 120.08 (8.7%)

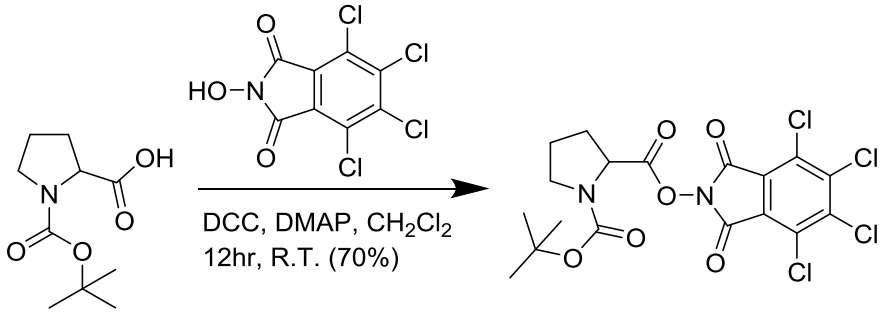
Scheme 3: Expected m/z ratios of two different *N*-acetyl-L-phenylalanine splittings.



Scheme 4. Redox-Active Ester (RAE) reaction pathway reported by Baran et.al.[2]

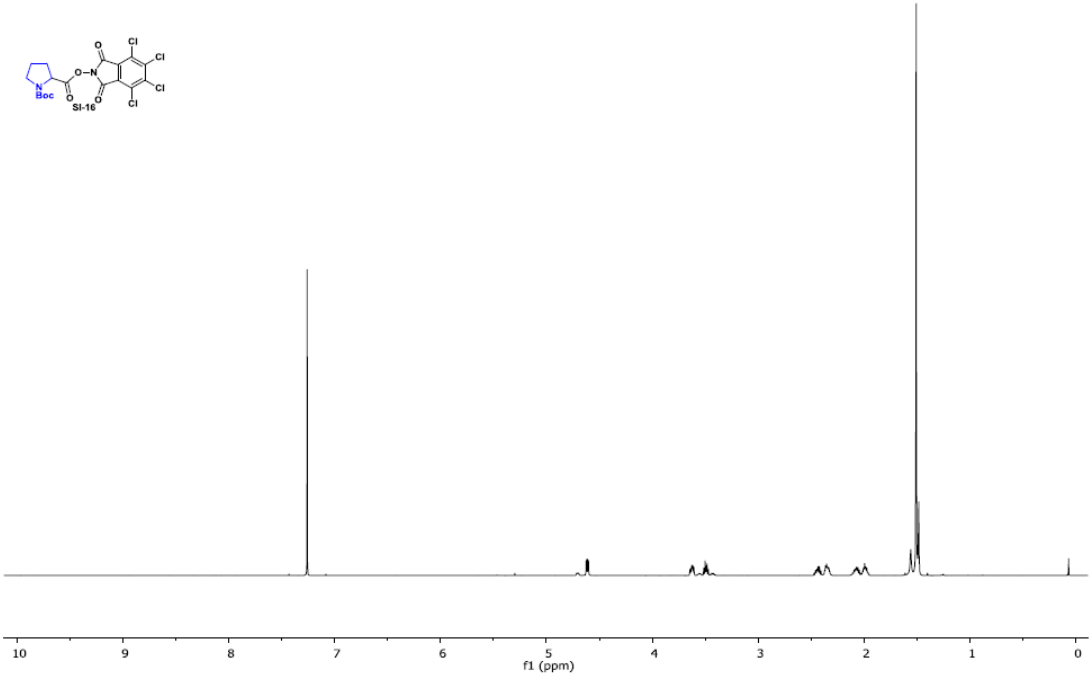


Scheme 5. Reported yield of Baran RAE reactions. Red box indicates test reaction for repetition of RAE reaction. Yellow box indicates goal reaction for use on amino acids.



Scheme 6. Activation of Boc-protected proline

A



B

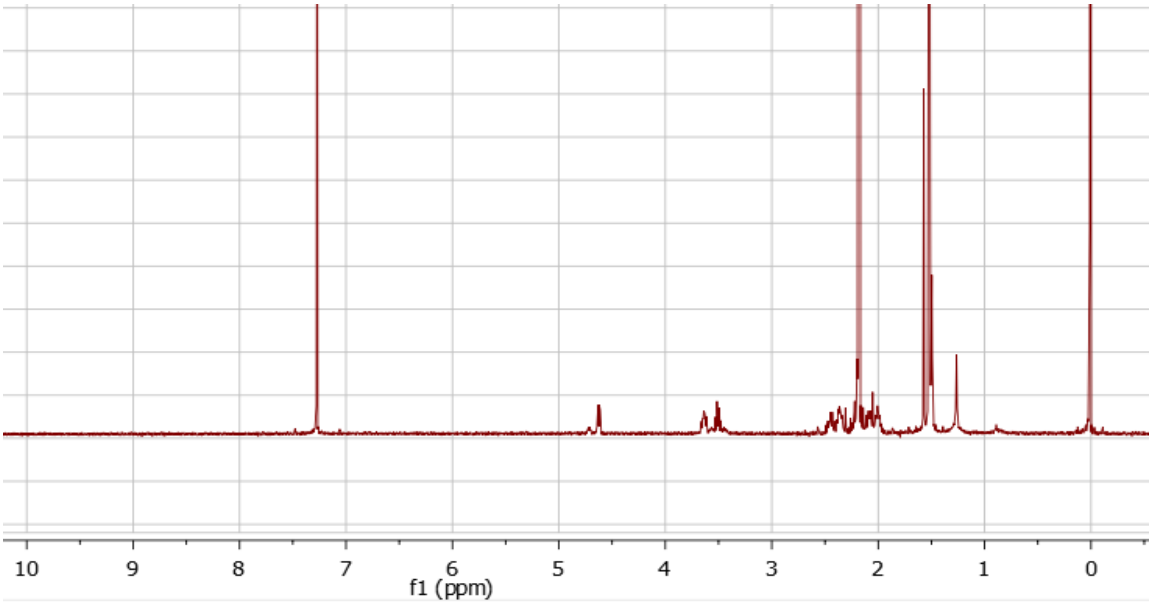
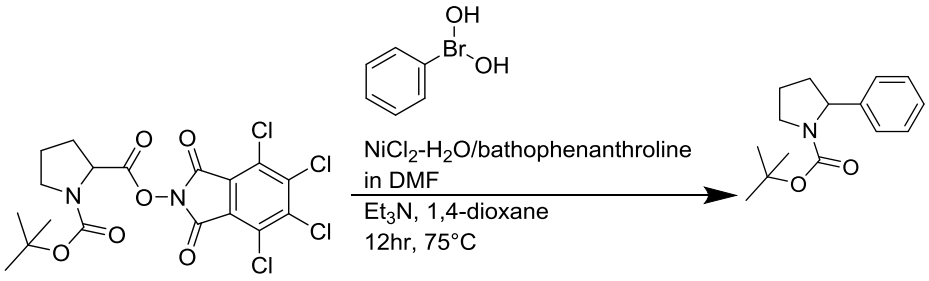


Figure 6. Comparison of Baran's NMR spectrum (A) to ours (B) of TCNHPI-activated Boc-L-proline. Very similar except for signal in our product at 2.2 ppm and 1.3 ppm (likely water contamination).



Scheme 7. Cross-coupling of RAE with phenylboronic acid

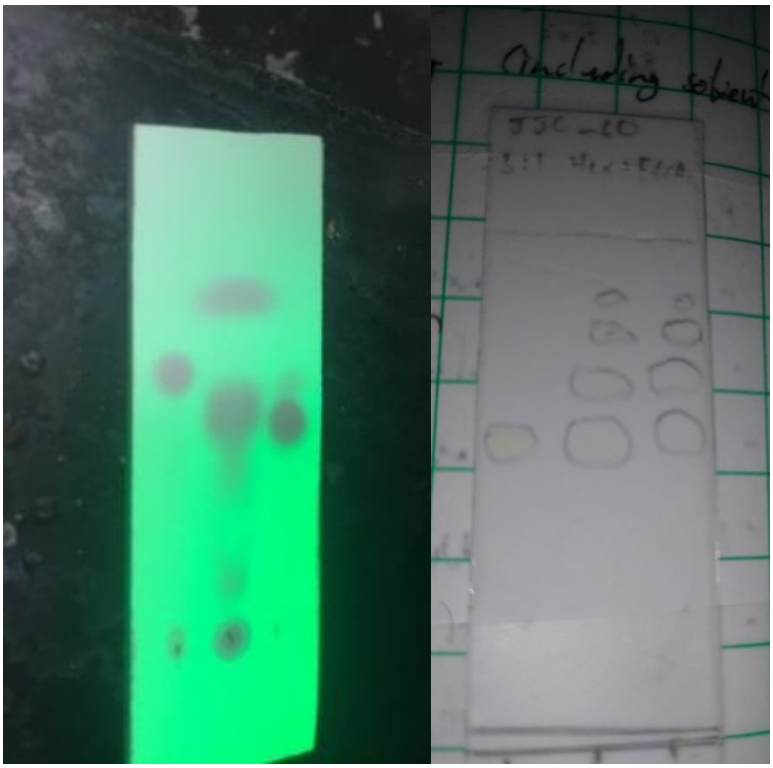
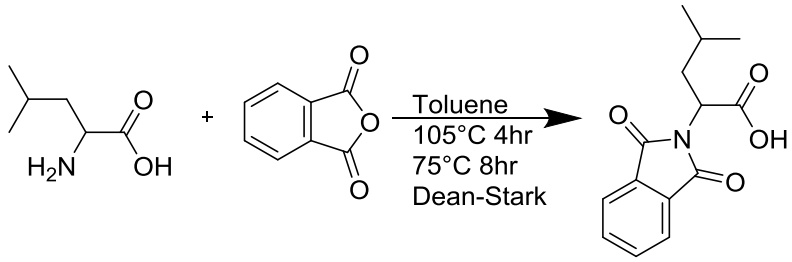
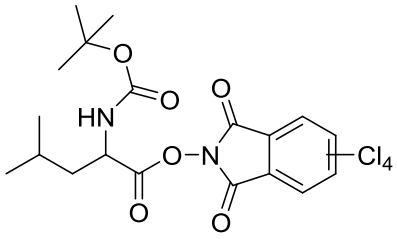


Figure 7. TLC under UV (hexanes/ethylacetate 3:1). (Left) Baran, Lane 1: starting material, RAE; Lane 2: reaction mixture; Lane 3: pure product. (Right) Ours, Lane 1: starting material, RAE; Lane 3: reaction mixture; Lane 2: co-spot.

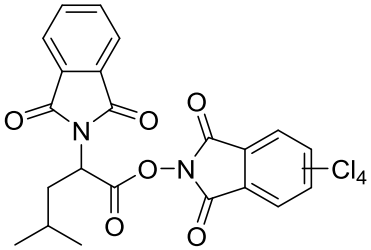


Scheme 8. Protection of leucine with phthalic anhydride.

A)



B)



Scheme 9. Boc-protected (A) and pthalic anhydride protected (B) TCNHPI-activated leucine.

Literature Cited

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