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Pyridylalanine (Pal)-Peptide Catalyzed Enantioselective Allenoate Additions to *N*-Acyl Imines

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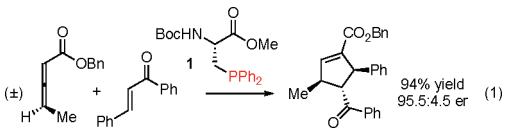
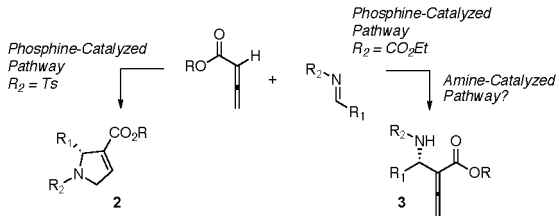
Chiral nucleophiles have emerged as the centerpiece of an explosive movement in the field of asymmetric catalysis that is aptly described as "Lewis Base Catalysis."[1] Among the many types of effective chiral nucleophiles employed as catalysts are a range of naturally occurring catalysts (e.g., the cinchona alkaloids)[2] and, in addition, a virtual anthology of ingeniously designed synthetic catalysts. α-Amino acids occupy a curious place at the interface of these catalyst families, as they possess not only attributes of naturally occurring compounds but also features designed or discovered in the process of catalyst optimization.[3] Among amino acid based catalysts, proline is perhaps best known,[4] but a growing list of other proteinogenic amino acid based catalysts may be used for a broad range of reactions.[5] In addition, unnatural amino acids have been adapted as catalysts, as in the diphenylphosphinylalanine (**1**)-catalyzed asymmetric [3+2]-cycloaddition of allenoate esters and enones,[6] pioneered by Lu and co-workers (eq 1).[7]



As shown in Scheme 1, the expansion of the [3+2] paradigm has included the study of alternative electrophiles. Accordingly, the phosphine-catalyzed cycloaddition of allenoates and imines has resulted in an efficient method for pyrrolidine synthesis (e.g., to make **2**),[8] and striking asymmetric catalytic variants have been reported.[9] Far less precedented is the asymmetric catalytic coupling of allenoates to imines to deliver addition products like **3**. In fact, much less efficient access to addition products had been recorded, even with achiral catalysts. There is some suggestion in the literature that the nature of the imine *N*-substituent could influence the partition of products between **2** and **3** (R_2 = Ts favoring **2**; R_2 = CO_2Et favoring **3**).[8b] However, to optimize for **3**, we chose a different strategy, culminating in unprecedented efficiency for the catalytic production of **3**, with unique catalytic enantioselective variants of this process.

Scheme 1



We had previously found that the nature of the catalyst could lead to orthogonal reactivity in the coupling of allenoates and enones.[10] Whereas phosphines favored a cycloaddition pathway, amines led to alternative reactivity, giving addition products. We thus began a catalyst screen to assess whether the choice of catalyst could lead to efficient coupling of **4a** and **5** to give **3**. As shown in eq 2, we examined *N*-acyl imines with ethoxycarbonyl substituents (e.g., **5a**) to bias the results toward addition products like **3a**, rather than the better established cycloaddition pathway to give **2**. Table 1 summarizes our results. Notably, we found that triphenylphosphine (10 mol%) led to the formation of **3a** in 57% isolated yield (entry 1), although other products could also be detected in the reaction mixture. Venerable nucleophilic catalysts like DMAP, as well as the alkylimidazole core structure found in π-(methyl)-histidine (Pmh) derivative **6**, proved ineffective for the coupling reaction, delivering only trace quantities of **3a** (entries 2 and 3, respectively). On the other hand, pyridine (entry 4) proved a surprisingly good catalyst, forming **3a** in 75% yield in a very clean reaction. Steric hindrance on the pyridine scaffold, however, retarded catalyst performance, with 2-picoline delivering only 14% yield within 24 h (entry 5) and 2,6-lutidine only leading to trace amounts of product (entry 6). 3-Pyridylalanine (Pal) derivative **7** was comparable to pyridine, catalyzing formation of **3a** in 71% yield (with **3a** emerging in racemic form; entry 7).

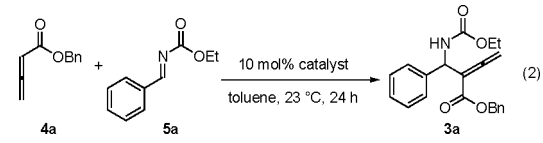
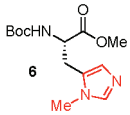
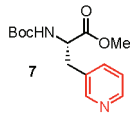


Table 1. Catalyst Screen for Imine−Allenoate Coupling[a]

Entry	Lewis Base Catalyst	Yield (%)[b]
1	Triphenylphosphine	57
2	4-(Dimethylamino)pyridine (DMAP)	trace[c]
3	 **6**	trace
4	Pyridine	75
5	2-Picoline	14
6	2,6-Lutidine	trace
7	 **7**	71 (racemic)

[a] Reactions were run at 23 °C in toluene with 1.5 equiv of allenic ester. [b] Isolated yield after silica gel chromatography. [c] Significant decomposition of allenic ester observed.

The emergence of a Pal-based catalyst (**7**) as effective while a Pmh-based catalyst (**6**) was ineffective for the catalytic formation of **3a** is intriguing mechanistically and not presently understood. From a practical standpoint, however, in turning our attention to enantioselective catalysis, we then assembled a set of Pal-based peptides (**8a**−**e**) in an effort to achieve the first enantioselective variants of this reaction

(eq 3). We began by embedding the Pal residue in familiar chiral frameworks that have proven effective in our study of unrelated families of asymmetric reactions.[11] Rather amazingly, the choice of scaffolds biased to adopt β-turn conformations proved beneficial.[12] Thus, as shown in Table 2, we tested a number of tetrapeptide catalysts with the Pro-Aib sequence inserted between Boc-Pal and a C-terminal amino acid of varying stereochemical identity at the i+3 position, relative to Boc-Pal. As shown in entries 1 and 2, L-Pro-Aib catalysts **8a** and **8b** led to efficient formation of **3a** in terms of yield, but with quite modest enantiomer ratios (er; 56:44; 58:42, respectively). Use of D-Pro in the i+1 position (catalyst **8c**) led to a modest improvement in selectivity with a D-residue at the i+3 position (62.5:37.5 er, entry 3). But, the combination of D-Pro-Aib with L-Phe at the i+3 position led to a dramatic improvement in rate and selectivity (catalyst **8d**: 86% yield of **3a**, 78:22 er, entry 4). Alteration of the C-terminal functional group from a methyl ester to a *N*,*N*-dimethylamide (catalyst **8e**) led to further improvements, with **3a** now isolated in 90% yield, and with 83.5:16.5 er (entry 5).

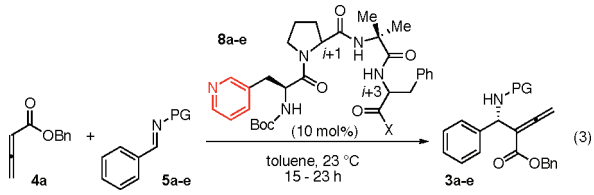


Table 2. Imine and Peptide Variations for Catalytic Imine−Allenoate Coupling[a]

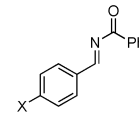
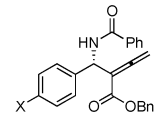
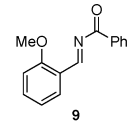
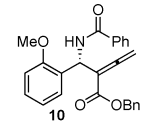
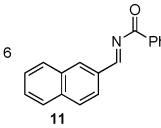
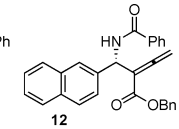
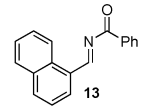
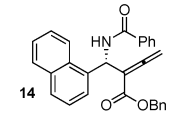
entry	PG, compd	i+1	i+3	X, catalyst	yield (%)[b]	er[c]
1	CO_2Et, **5a**	L-Pro	L-Phe	OMe, **8a**	57, **3a**	56.0:44.0
2	CO_2Et, **5a**	L-Pro	D-Phe	OMe, **8b**	71, **3a**	58.0:42.0
3	CO_2Et, **5a**	D-Pro	D-Phe	OMe, **8c**	76, **3a**	62.5:37.5
4	CO_2Et, **5a**	D-Pro	L-Phe	OMe, **8d**	86, **3a**	78.0:22.0
5	CO_2Et, **5a**	D-Pro	L-Phe	NMe_2, **8e**	90, **3a**	83.5:16.5
6	Ts, **5b**	D-Pro	L-Phe	OMe, **8d**	71, **3b**	60.0:40.0
7	Bn, **5c**	D-Pro	L-Phe	OMe, **8d**	NR[d]	--
8	$POPh_2$, **5d**	D-Pro	L-Phe	OMe, **8d**	NR	--
9	Bz, **5e**	D-Pro	L-Phe	OMe, **8d**	94, **3e**	84.0:16.0
10	Bz, **5e**	D-Pro	L-Phe	NMe_2, **8e**	80, **3e**	92.0:8.0

[a] Reactions were run at 23 °C in toluene with 1.5 equiv of allenic ester. [b] Isolated yield after silica gel chromatography. [c] All enantiomer ratios (er's) were measured using chiral HPLC. [d] No reaction.

As shown in Table 2 (entries 6−10), we then evaluated the *N*-protecting group on the imine (**5b**−**e**). Notably, swapping the ethoxycarbonyl group for tosyl (**5b**) led to diminished yield and selectivity (71% yield, 60:40 er, entry 6). *N*-Substitution as either benzyl (**5c**) or diphenyl phosphinoyl (**5d**) led to a loss of reactivity altogether (entries 7 and 8). The benzoyl group (as in **5e**) proved to be a useful substituent, however, with catalyst **8d** delivering the product in 94% yield (84:16 er; entry 9) and catalyst **8e** affording the product in 80% yield, with an er of 92:8 (entry 10).

Having identified a catalyst capable of efficient production of compounds like **3** with unprecedented enantioselectivity (up to 92:8, 84% ee), we then turned our attention to substrate scope with respect to the imine (Table 3). Electron-rich substrates participate in the reaction with comparable efficiency. As shown in entries 2 and 3, *p*-methoxy and *o*-methoxy products **3f** and **10** may be achieved catalytically (**8e**, 10 mol%) with comparable er's (92:8, and 90.5:9.5, respectively). Interestingly, after a single recrystallization product **3f** is isolated from the mother liquor in near optical purity (98.5:1.5 er, 81% isolated yield). *p*-*t*-Bu-substituted product **3g** may be achieved with comparable efficiency (91.5: 8.5 er, entry 4). *p*-Bromo-substituted product **3h** is accessed in a slightly reduced 56% yield with an er of 88.5:11.5 (96.5:3.5 after recrystallization; entry 5). Naphthyl-substituted imines participated in the coupling reaction delivering products **12** and **14** (62% yield, 90.5:9.5 er and 81% yield, 88.5:11.5 er respectively; entries 6−7). *p*-Trifluoromethyl-substituted imine **5i** also participates in the reaction, albeit with reduced yield and enantioselectivity (45% yield, 84.5:15.5 er; 94.0:6.0 er after recrystallization; entry 8).

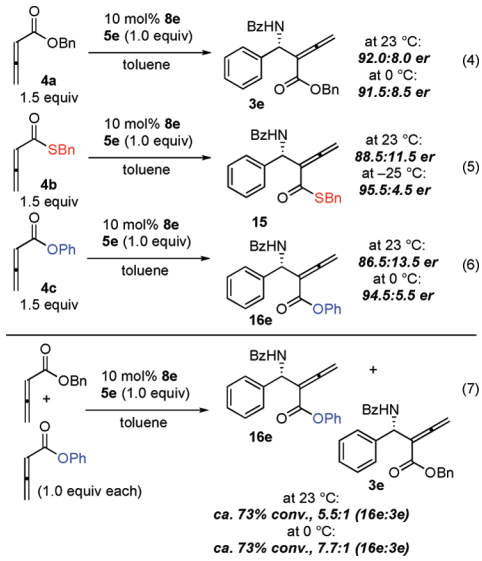
Table 3. Substrate Scope for *N*-Acyl Imine−Allenoate **4a** Coupling[a]

Entry	Substrate	Product[b]	Yield (%)[c]	er[d]
1	 X = H, **5e**	 X = H, **3e**	80 0 °C: 67 −25 °C: 17	92.0:8.0 91.5:8.5 88.0:12.0
2	X = MeO, **5f**	X = MeO, **3f**	88 (81)[e]	92.0:8.0 (98.5:1.5)[f]
3	 **9**	 **10**	79	90.5:9.5
4	X = *t*-Bu, **5g**	X = *t*-Bu, **3g**	65	91.5:8.5
5	X = Br, **5h**	X = Br, **3h**	56 (46)[e]	88.5:11.5 (96.5:3.5)[f]
6	 **11**	 **12**	62	90.5:9.5
7	 **13**	 **14**	81	88.5:11.5
8	X = CF_3, **5i**	X = CF_3, **3i**	45 (36)[e]	84.5:15.5 (94.0:6.0)[f]

[a] All data are the average of two experiments. Reactions were run at 23 °C in toluene with 1.5 equiv of allenic ester and 10 mol% catalyst **8e** for 16−24 h. [b] See Supporting Information for the determination of absolute stereochemistry. [c] Isolated yield after silica gel chromatography. [d] All enantiomer ratios (er's) were measured using chiral HPLC. [e] Parenthetical value refers to % yield of material collected from the mother liquor after racemate crystallizes out. [f] Parenthetical value refers to er of material collected from the mother liquor after racemate crystallizes out.

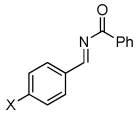
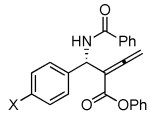
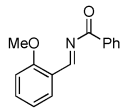
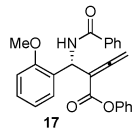
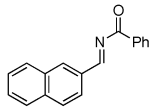
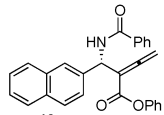
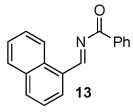
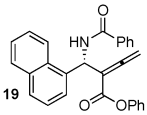
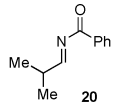
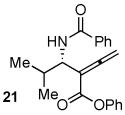
While reactions were efficient and delivered products with substantial enantioselectivity for the first time, we wished to optimize the catalysis further. As shown in Table 3 (entry 1, above) reduced reaction temperatures led to inconveniently slow reactions (and little change in enantioselectivity). We therefore elected to identify more reactive substrates such that low temperature reactions could be studied more thoroughly and with convenient reaction times. We hypothesized that more electrophilic allenoate esters might engage in more rapid reactions. We thus elected to assess the behavior of allenothioate esters (e.g., **4b**) and phenyl allenoate esters (e.g., **4c**) as potential partners in the **8e**-catalyzed coupling reaction. As shown in eqs 4−6, we were pleased to find that both **4b** and **4c** allowed for more rapid reactions. Indeed, both substrates allowed reactions to take place to high levels of conversion at reduced temperatures, and excellent levels of selectivity were observed. While thioester **4b** led to the production of **15** exhibiting a 95.5:4.5 er (−25 °C; eq 5), phenyl ester **4c** led to the formation of **16e** with 94.5:5.5 er (0 °C; eq 6).[13] In direct competition experiments (eq 7), **4c** was found to be substantially more reactive

than **4a** at room temperature (**16e/3e**, 5.5:1); at 0 °C, the difference in reactivity was amplified (**16e/3e**, 7.7:1).[14]



Notably, product **15** was found to be somewhat sensitive to silica gel, rendering isolation of good yields of **15** difficult. On the other hand, phenyl ester **16e** is better behaved. Therefore, we elected to explore the scope of the chemistry with **4c** more thoroughly (Table 4). In general, catalytic coupling reactions of **4c** (employing 10 mol% **8e**) required only 1 h at 0 °C to reach full conversion.[15] In addition, enantioselective reactions of **4c** generally lead to products with higher selectivity than the analogous reactions of **4a** at reduced temperature. *p*-Methoxy-, *o*-methoxy-, and *t*-Bu-substituted imines reacted smoothly with **4c** furnishing products **16f**, **17**, and **16g** with identical enantiomer ratios (92.5:7.5 er; entries 2−4). *p*-Bromo-substituted imine **5h** delivers product **16h** with good enantioselectivity (43% yield, 94:6 er; entry 5). Naphthyl-substituted imines participate in quite efficient reactions (**18**: 56% yield, 92.5:7.5 er; **19**: 66% yield, 92:8 er respectively; entries 6−7). Aliphatic imines participate in the reactions, albeit with reduced efficiency. Isopropyl imine **20** engaged in coupling with **4c** to give **21** in 42% yield with an er of 80.5:19.5 (entry 8). Expansion of the substrate scope of this new catalytic process is now a component of future studies.

Table 4. Substrate Scope for *N*-Acyl Imine−Allenoate **4c** Coupling[a]

Entry	Substrate	Product[b]	Yield (%)[c]	er[d]
1	 X = H, **5e**	 X = H, **16e**	64 23 °C: 48 –25 °C: 34[e]	94.5:5.5 86.5:13.5 94.0:6.0
2	X = MeO, **5f**	X = MeO, **16f**	49	92.5:7.5
3	 **9**	 **17**	67	92.5:7.5
4	X = *t*-Bu, **5g**	X = *t*-Bu, **16g**	55	92.5:7.5
5	X = Br, **5h**	X = Br, **16h**	43	94.0:6.0
6	 **11**	 **18**	56	92.5:7.5
7	 **13**	 **19**	66	92.0:8.0
8[f]	 **20**	 **21**	42	80.5:19.5

[a] All data are the average of two experiments. Reactions were run at 0 °C in toluene with 1.5 equiv of allenic ester, 1 equiv of 2,3-dimethylnaphthalene (internal standard), and 10 mol% catalyst **8e** for 1 h. [b] See Supporting Information for the determination of absolute stereochemistry. [c] Isolated yield after silica gel chromatography. [d] All enantiomer ratios (er's) were measured using chiral HPLC. [e] Conversion after 20 h as determined by ^{1}H NMR of the crude reaction mixture using an internal standard. [f] Reaction was run using 20 mol% catalyst **8e**.

In conclusion, we have presented entirely unique examples of asymmetric catalytic additions of allenoates to *N*-acyl imine derivatives. In so doing, we have identified a new catalyst type based on pyridylalanine. These findings expand the reach of amino acid and peptide-based catalysis in new ways. Moreover, these findings raise intriguing questions about the nature of Lewis base catalysis. Understanding the differences between the imidazole-based catalysis of naturally occurring histidine and pyridine-based catalysis of the nonproteinogenic amino acid pyridylalanine is among our current goals.

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Supporting Information Available: Experimental procedures and characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) Lowering the temperature to −25 °C with substrate **4c** did not improve the er.
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(15) Isolated yields of the phenyl esters in Table 4 are somewhat lower than the analogous benzyl esters in Table 3 due to a modest sensitivity to silica gel.

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