ORGANIC LETTERS

2012
Vol. 14, No. 8
2130–2133

# Catalytic α-Allylation of Unprotected Amino Acid Esters

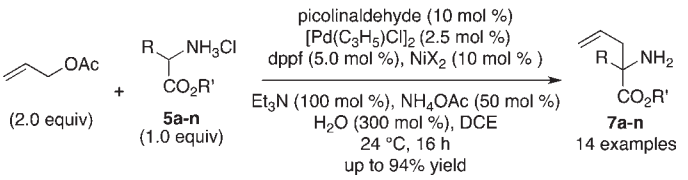
**Ping Fang, Mani Raj Chaulagain, and Zachary D. Aron***

*Department of Chemistry, Indiana University, 800 East Kirkwood Avenue, Bloomington, Indiana 47405-7102, United States*

*zaron@indiana.edu*

**Received March 15, 2012**

## ABSTRACT




**Catalytic α-allylation of unprotected amino acid esters to produce α-quaternary α-allyl amino acid esters is reported. Catalytic loadings of picolinaldehyde and Ni(II) salts induce preferential reactivity at the enolizable α-carbon of amino acid esters over the free nitrogen with electrophilic palladium π-allyl complexes. Fourteen examples are given. Additionally, the use of chiral ligands to access enantioenriched α-quaternary amino acid esters from racemic precursors is demonstrated by the enantioselective synthesis of α-allyl phenylalanine methyl ester from racemic phenylalanine methyl ester.**

Developing protecting-group-free reactions and syntheses streamlines our access to complex chemical entities.[1] Of particular use are carbon−carbon bond forming reactions that occur in the presence of reactive functionalities including alcohols, carboxylates, carbonyls, and basic amines. To date, however, few polar bond-forming reactions selectively occur in the presence of unprotected primary amines, and none produce fully substituted carbon centers.[2,3] This drawback limits access to α-quaternary amino acids that form the core of numerous natural products and pharmaceuticals including inhibitors of sphingolipid biosynthesis (**1**)[4a] and the 20s proteasome (**3**) (Figure 1).[4b−d] Incorporation of α-quaternary amino acids such as aib (**2**) into peptides stabilizes them toward proteolysis[5] and provides a bias for α-helical conformations, controlling peptabiotic- and peptabiol-mediated ion channel formation.[4a,6a] Numerous methods for generating α-quaternary amino acids have been described; however, none of these produce the desired materials in a single transformation.[7] In this communication, we report the first catalytic, enantioselective α-allylation of unprotected

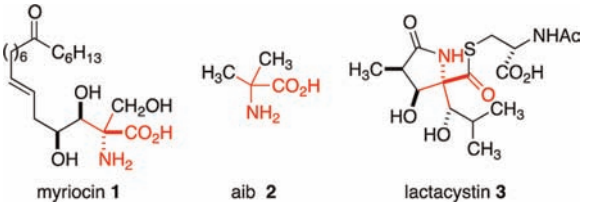



**Figure 1.** α-Quaternary amino acids.

(1) (a) Hoffmann, R. W. *Synthesis* **2006**, *21*, 3531. (b) Young, I. S.; Baran, P. S. *Nat. Chem.* **2009**, *1*, 193.

(2) For examples of enolate alkylation in the presence of primary amines, see: (a) Myers, A. G.; Gleason, J. L.; Yoon, T. *J. Am. Chem. Soc.* **1995**, *117*, 8488. (b) Myers, A. G.; Gleason, J. L.; Yoon, T.; Kung, D. W. *J. Am. Chem. Soc.* **1997**, *119*, 656. (c) Nagula, G.; Huber, V. J.; Lum, C.; Goodman, B. A. *Org. Lett.* **2000**, *2*, 3527. (d) McNeil, A. J.; Toombes, G. E. S.; Gruner, S. M.; Lobkovsky, E.; Collum, D. B.; Chandramouli, S. V.; Vanasse, B. J.; Ayers, T. A. *J. Am. Chem. Soc.* **2004**, *126*, 16559.

(3) For an example of alcohol acylation in the presence of a primary amine, see: Ohshima, T.; Iwasaki, T.; Maegawa, Y.; Yoshiyama, A.; Mashima, K. *J. Am. Chem. Soc.* **2008**, *130*, 2944.

(4) (a) Horn, W. S.; Smith, J. L.; Bills, G. F.; Raghoobar, S. L.; Helms, G. L.; Kurtz, M. B.; Marrinan, J. A.; Frommer, B. R.; Thornton, R. A.; Mandala, S. M. *J. Antibiot.* **1992**, *45*, 1692. (b) Omura, S.; Fujimoto, T.; Otoguro, K.; Matsuzaki, K.; Moriguchi, R.; Tanaka, H.; Sasaki, Y. *J. Antibiot.* **1991**, *44*, 113. (c) Omura, S.; Matsuzaki, K.; Fujimoto, T.; Kosuge, K.; Furuya, T.; Fujita, S.; Nakagawa, A. *J. Antibiot.* **1991**, *44*, 117. (d) Feling, R. H.; Buchanan, G. O.; Mincer, T. J.; Kauffman, C. A.; Jensen, P. R.; Fenical, W. *Angew. Chem., Int. Ed.* **2003**, *42*, 355.

(5) Adessi, C.; Soto, C. *Curr. Med. Chem.* **2002**, *9*, 963.

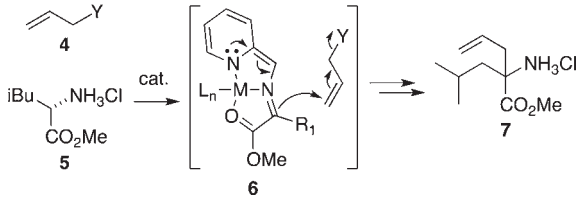
(6) Peggion, C.; Formaggio, F.; Crisma, M.; Epand, R. F.; Epand, R. M.; Toniolo, C. *J. Peptide Sci.* **2003**, *9*, 679.

10.1021/ol300665n 
**Published on Web 04/09/2012**

amino acid esters to produce enantioenriched α-quaternary amino acid esters in a single transformation.

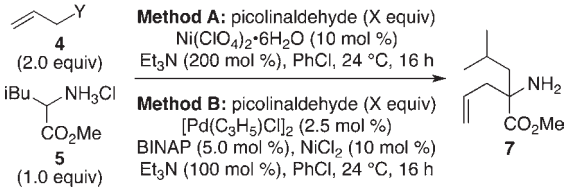
Recently, we reported the intermediate presence of azomethine ylides in picolinaldehyde/metal-mediated amino acid racemizations and condensations.[8] This work demonstrated that azomethine ylide formation is facilitated by metal chelation, allowing racemization to occur under mild conditions. We report here an important extension of this chemistry showing that nickel chelates of picolinaldehyde, in concert with palladium complexes, catalyze the Tsuji–Trost allylation of unprotected amino acid esters in excellent yields and demonstrate the potential for excellent enantioselectivities (Scheme 1).[9]

**Scheme 1.** Picolinaldehyde-Catalyzed Amino Acid Allylation




Quinonoid intermediates are effective nucleophiles in biological systems,[10] suggesting that intermediates such as **6** should react well with appropriate electrophiles. Similar intermediates are well established in the work of O'Donnell and co-workers who use deprotonated amino acid imines as nucleophiles in a variety of carbon–carbon bond forming reactions.[11] These intermediates are further established to react with metal π-allyl complexes.[12] However, in the preceding examples, stoichiometric imine formation or complex enzymatic systems are required to control the competing reactivity of the quinonoid and the nucleophilic nitrogen of the starting material **5**.

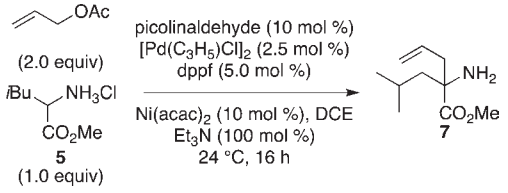
**Table 1.** Initial Screens




| entry | -Y | X | method | yield (%)[a] |
|---|---|---|---|---|
| 1 | -Br | 1.0 | A | 11% |
| 2 | -Br | 0.1 | A | trace |
| 3 | -OAc | 1.0 | B | 47% |
| 4 | -OAc | 0.1 | B | 43% |

[a] Yields were determined by $^1$H NMR using an internal standard.

**Table 2.** Reaction Optimization




| entry | additive (equiv) | yield[a] |
|---|---|---|
| 1 | N/A | 24–73% |
| 2 | $H_2O$ (3.0) | 75% |
| 3 | $H_2O$ (3.0), $NH_4Cl$ (0.5) | 70% |
| 4 | $H_2O$ (3.0), $NH_4OAc$ (0.5) | 82%[b] |
| 5 | $H_2O$ (3.0), $Me_4NOAc$ (0.5) | 58% |
| 6 | $H_2O$ (3.0), HOAc (0.5) | 52% |

[a] Yields were determined by $^1$H NMR using an internal standard. [b] Isolated yield.

We hypothesized that the delocalization seen in quinonoid **6** would cause it to react as a "soft" nucleophile in contrast to the competing "hard" nitrogen nucleophile, suggesting a mechanism for chemoselectivity. Early attempts at the condensation using allyl bromide did not bear this hypothesis out (Table 1, entries 1 and 2). Stoichiometric loadings of picolinaldehyde were necessary to minimize reaction at nitrogen, yet even these conditions gave poor conversions. Accordingly, we turned our attention to softer metal π-allyl complexes. To our gratification, reactions involving palladium π-allyl species gave improved yields and exhibited multiple turnovers with respect to the aldehyde-based catalyst (Table 1, entries 3 and 4). It should be noted that the pH of these systems was critical to selectivity, as superstoichiometric quantities of base led

(7) (a) Seebach, D.; Sting, A. R.; Hoffmann, M. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2708. (b) Cativiela, C.; Diaz-de-Villegas, M. D. *Tetrahedron: Asymmetry* **1998**, *9*, 3517. (c) Cativiela, C.; Diaz-de-Villegas, M. D. *Tetrahedron: Asymmetry* **2000**, *11*, 645. (d) Najera, C.; Sansano, J. M. *Chem. Rev.* **2007**, 4584. (e) Maruoka, K. *Org. Process Res. Dev.* **2008**, *12*, 679. (f) Cativiela, C.; Mario, O. *Tetrahedron: Asymmetry* **2009**, *20*, 1.

(8) (a) Felten, A.; Zhu, G.; Aron, Z. D. *Org. Lett.* **2010**, *12*, 1916. (b) Chaulagain, M. R.; Aron, Z. D. *J. Org. Chem.* **2010**, *75*, 8271.

(9) (a) Tsuji, J.; Takahashi, H.; Morikawa, M. *Tetrahedron Lett.* **1965**, *6*, 4387. (b) Trost, B. M.; VanVranken, D. L. *Chem. Rev.* **1996**, *96*, 395. (c) Tsuji, J.; Minami, I. *Acc. Chem. Res.* **1987**, *20*, 140.

(10) (a) Eliot, A. C.; Kirsch, J. F. *Annu. Rev. Biochem.* **2004**, *73*, 383. (b) Richard, J. P.; Amyes, T. L.; Crugeiras, J.; Rios, A. *Biochim. Biophys. Acta* **2011**, *1814*, 1419.

(11) (a) O'Donnell, M. J. *Acc. Chem. Res.* **2004**, *37*, 506. (b) O'Donnell, M. J.; Boniece, J. M.; Earp, S. E. *Tetrahedron Lett.* **1978**, 2641. (c) O'Donnell, M. J.; Eckrich, T. M. *Tetrahedron Lett.* **1978**, 4625.

(12) (a) Kanayama, T.; Yoshida, K.; Miyabe, H.; Kimachi, T.; Takemoto, Y. *J. Org. Chem.* **2003**, *68*, 6197. (b) Kanayama, T.; Yoshida, K.; Miyabe, H.; Takemoto, Y. *Angew. Chem., Int. Ed.* **2003**, *42*, 2054. (c) Nakoji, M.; Kanayama, T.; Okino, T.; Takemoto, Y. *J. Org. Chem.* **2002**, *67*, 7418. (d) Nakoji, M.; Kanayama, T.; Okino, T.; Takemoto, Y. *Org. Lett.* **2001**, *3*, 3329. (e) Chen, G.; Deng, Y.; Gong, L.; Mi, A.; Cui, X.; Jiang, Y.; Choi, M. C. K.; Chan, A. S. C. *Tetrahedron: Asymmetry* **2001**, *12*, 1567. (f) Kazmaier, U.; Maier, S.; Zumpe, F. L. *Synlett* **2000**, 1523. (g) You, S.-L.; Hou, X.-L.; Dai, L.-X.; Cao, B.-X.; Sun, J. *Chem. Commun.* **2000**, 1933. (h) Trost, B. M.; Ariza, X. *J. Am. Chem. Soc.* **1999**, *121*, 10727. (i) Kazmaier, U.; Zumpe, F. L. *Angew. Chem., Int. Ed.* **1999**, *38*, 1468. (j) Hiroi, K.; Hidaka, A.; Sezaki, R.; Imamura, Y. *Chem. Pharm. Bull.* **1997**, *45*, 769. (k) Baldwin, I. C.; Williams, J. M. J.; Beckett, R. P. *Tetrahedron: Asymmetry* **1995**, *6*, 1515. (l) Genet, J.-P.; Juge, S.; Achi, S.; Mallart, S.; Montes, J. R.; Levif, G. *Tetrahedron* **1988**, *44*, 5263.

to predominant *N*-allylation. These results established that catalytically generated picolinaldehyde quinonoid intermediates can act as nucleophiles in carbon−carbon bond forming reactions and indicated a viable route for the direct synthesis of α-quaternary amino acid esters.

Variation of the Lewis acid, solvent, ligand, and additives were used to optimize the reaction (Tables 2 and S1). Lewis acid screens revealed that Ni(II) salts provided optimal reactivity (Table S1, entries 1−5). Interestingly, anhydrous $Zn(OTf)_2$ proved a poor cocatalyst for the reaction, whereas $Zn(OAc)_2 \cdot 2H_2O$ was more efficacious, suggesting that water and/or acetate might prove to be important additives in the reaction (Table S1, entries 4 and 5). The reaction proceeds well in noncoordinating solvents, with moderately polar, aprotic solvents such as chlorobenzene and dichloroethane providing optimal results (Table S1, entries 6−10). Both mono- and bidentate ligands effectively promote the reaction, with good reactivity observed using trifurylphosphine in the monodentate series, and an overall preference for dppf (Table S1, entries 11−15). Unfortunately, reactions with dppf alone proved inconsistent, requiring the addition of small quantities of water to achieve reproducibility (Table 2, entries 1 and 2). As the reaction involves several cationic species, we examined various ammonium salt additives, identifying ammonium acetate as key to improving overall yields (Table 2, entries 2−6). It is noteworthy that both the ammonium and acetate components of the salt proved important for overall reactivity as seen by examining entries 3−6 in Table 2.

Following reaction optimization, we sought to explore the substrate scope (Figure 2). The reaction works well with a variety of simple amino acid esters, providing the desired products in excellent yields. Additionally, the reaction shows broad functional group tolerance, with substrates bearing indole, phenol, ester, thioether, carbamate, and amides providing the corresponding products in high yields (Figure 2, entries **7d** and **7g**−**7m**). Reactions with glutamate esters gave the pyroglutamate derivative, although use of glutamine methyl ester prevented this cyclization (**7n**). The reaction exhibits sensitivity to branching at the *β*-carbon, requiring the use of an alternative ligand with phenylglycine and exhibiting poor yields in the case of valine. Histidine and cysteine bearing a free thiol appear to be outside of the scope of the reaction, likely due to either disruptive chelation between the side chain and the Lewis acid or reactivity at the *β*-carbon.

Having developed an efficient α-allylation protocol, we turned our attention to enantioselectivity (Table 3). Using the well-developed ligands reported by Trost and co-workers, these efforts focused on ligating the palladium *π*-allyl complex.[13] Variation of base proved to have a notable impact on both yield and enantioselectivity (Table 3, entries 1−3). These results suggest that the base plays a direct role in the transformation, consistent with our observations on the

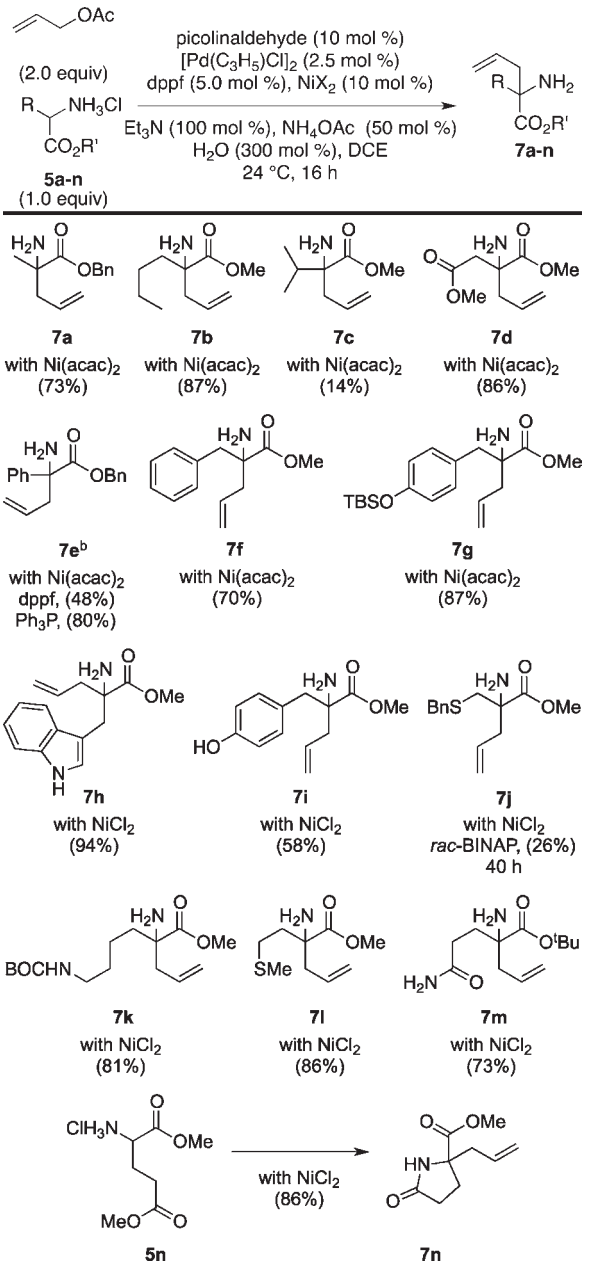


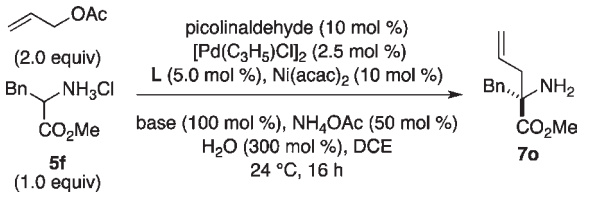

**Figure 2.** Reaction scope. [a]Yields given are isolated yields. [b]Reaction run using the tosylate salt of phenylglycine methyl ester.

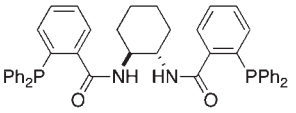
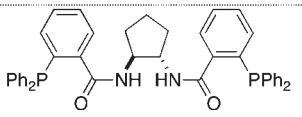
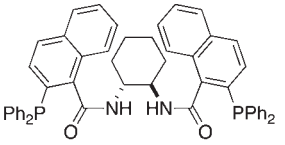
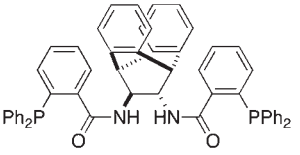
effect of ammonium acetate. The reaction is sensitive to the structure of the chelating ligand, with yield and enantioselectivity varying widely with minor structural variations (Table 3, entries 3−7).[13] Under optimized conditions, the reaction produces (*S*)-α-quaternary phenylalanine derivative **7o** in 95% yield and 91% ee from the corresponding racemic methyl ester (Table 3, entry 3).[14] This one step dynamic kinetic resolution protocol dramatically simplifies

(13) (a) Trost, B. M.; Van Vranken, D. L. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 228. (b) Trost, B. M.; Van Vranken, D. L.; Bingel, C. *J. Am. Chem. Soc.* **1992**, *114*, 9327. (c) Trost, B. M. *Acc. Chem. Res.* **1996**, *29*, 355.

(14) The identity of the major enantiomer was determined by comparison with the literature optical rotation of the known product. Dolbeare, K.; Pontoriero, G. F.; Gupta, S. K.; Mishra, R. K.; Johnson, R. L. *J. Med. Chem.* **2003**, *46*, 727.

**Table 3.** Enantioselective Variant




| entry | L | base | yield[a] | ee[b] |
|---|---|---|---|---|
| 1 |  | $Et_3N$ | 60% | 80% |
| 2 | | DBU | 72% | 86% |
| 3 | | KOAc | 95%[c] | 91% |
| 4 |  | KOAc | 93% | 78% |
| 5 |  | KOAc | 70% | -27% |
| 6 |  | KOAc | 44% | 8% |
| 7 | (*R*)-BINAP | KOAc | 62% | -20% |

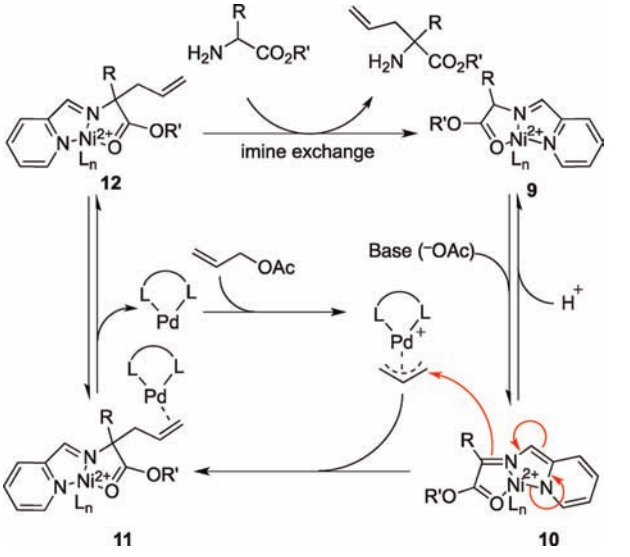
[a] Yields were determined by $^1$H NMR using an internal standard. [b] Enantioselectivities were determined by chiral HPLC of isolated products. [c] Isolated yield.

access to enantioenriched α-quaternary amino acids. Additionally, as the HCl salts of product esters are highly crystalline, enantioselectivities can potentially be upgraded through simple recrystallization.

A plausible mechanistic rationale for this reaction is shown below (Scheme 2). Schiff base formation and nickel association result in tridentate complex **9**, which stabilizes deprotonation at the amino acid α-carbon.[8a] The resultant quinonoid/enolate intermediate **10** reacts with a palladium $\pi$-allyl complex to produce complex **11**. Subsequent decomplexation produces Schiff base **12**. An imine exchange regenerates imine **9** and releases the final product to

(15) (a) Cordes, E. H.; Jencks, W. P. *J. Am. Chem. Soc.* **1962**, *84*, 826. (b) Dirksen, A.; Hackeng, T. M.; Dawson, P. E. *Angew. Chem., Int. Ed.* **2006**, *45*, 7581. (c) Dirksen, A.; Dirksen, S.; Hackeng, T. M.; Dawson, P. E. *J. Am. Chem. Soc.* **2006**, *128*, 15602.

**Scheme 2.** Proposed Allylation Mechanism




complete the cycle. It is likely that the added water and/or ammonium salts catalyze this step by acting as sterically unencumbered nucleophiles through a mechanism parallel to that proposed by Jencks in their work with aniline-catalyzed Schiff base exchange.[15] Additionally, the anions of these salts likely solubilize or otherwise interact beneficially with one or more of the many cationic intermediates in this pathway, suggesting a potential role for the acetate in the enantioselective variant.

In conclusion, we have developed a catalytic one step synthesis of α-allylated α-quaternary amino acid esters and demonstrated its potential for application as a dynamic kinetic resolution. The reaction exhibits broad substrate scope with moderate functional group sensitivity. This chemistry simplifies access to an important family of compounds and provides an attractive alternative to existing multistep methods.[7] Further studies of the dynamic kinetic resolution are currently underway.

**Acknowledgment.** We acknowledge the financial support of Indiana University.

**Supporting Information Available.** Experimental procedures and spectral data for all new compounds generated through this work. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.