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Synthesis of Novel Quaternary Amino Acids Using Molybdenum-Catalyzed Asymmetric Allylic Alkylation

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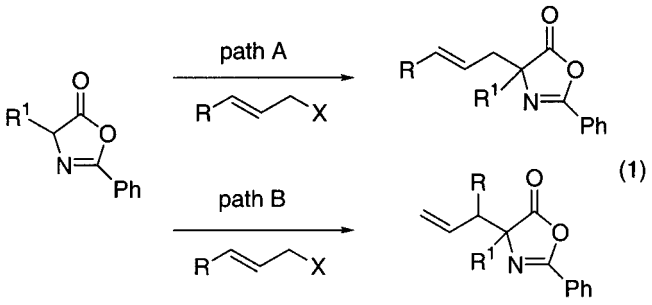
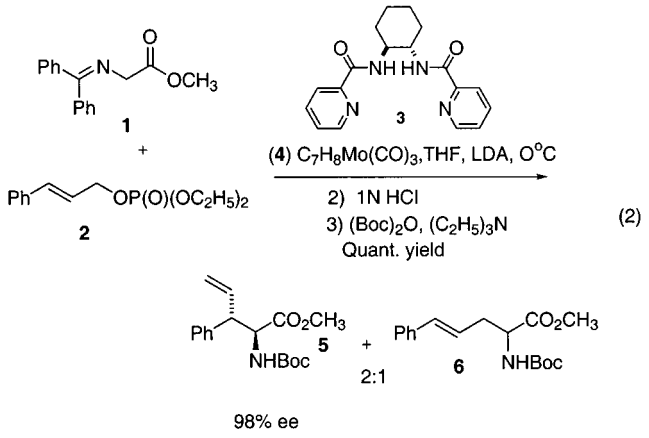
The growing importance of unusual amino acids in the design of drugs stimulates the development of new synthetic methods. Among the most challenging for asymmetric synthesis are quaternary amino acids since they cannot be made by asymmetric catalytic hydrogenation. We previously disclosed the ability to synthesize such systems using the palladium asymmetric allylic alkylation[1] (AAA) reaction (eq 1, path A) with azlactones with good enantio-



(1)

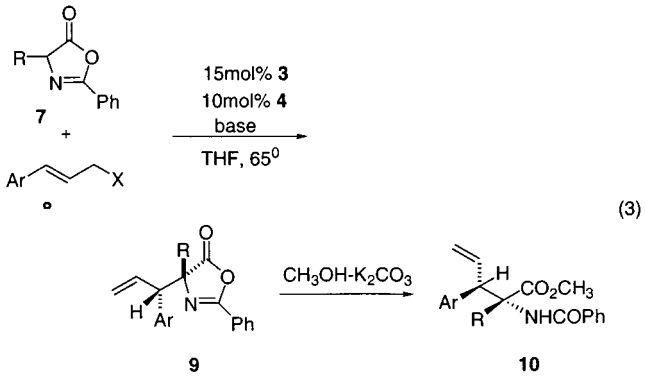
selectivity. An even more challenging task is shown in eq 1, path B. For such regioselectivity, Mo-[2,3] and W-catalyzed[2,4] allylic alkylations are preferred. However, the Mo AAA reaction did not seem promising since the use of more stabilized anions such as those derived from 1,3-diketones or β-ketoesters reacted significantly more poorly compared to malonate anion which did not bode well for a rather highly stabilized anion like that derived from an azlactone. As a result, we turned to the examination of a glycine ester **1** as in eq 2. Indeed, the lithium enolate of **1** reacted rapidly



(2)

with cinnamyl phosphate **2** in the presence of the chiral Mo catalyst derived from ligand **3** and precatalyst **4** to give a 2:1 ratio of the branched (**5**) and linear (**6**) products.[5] Gratifyingly, the dr (20:1) and ee (98%) of **5** was excellent. However, the modest regioselectivity did not bode well for an even more sterically demanding nucleophile that would be required to make quaternary amino acids. Thus, despite our misgivings regarding reactivity issues, we chose to explore the use of azlactones as reported herein (eq 1, path b).

Initial studies examined the reaction shown in eq 3 with Ar =



(3)

Ph and R = CH_3. Because the cleanliness of the generation of the enolate of **7** with sodium hydride was poor, we examined the use of the hexamethyldisilamide base. Whereas the use of sodium or potassium hexamethyldisilamide gave some linear product as well as the desired branched product **9** (Ar = Ph, R = CH_3), employment of the lithium base gave only the branched product in 83% yield and excellent diastereoselectivity (dr = 96:4) using the *tert*-butylcarbonate leaving group. Switching to the diethyl phosphate leaving group, the product was formed as a single diastereomer (dr > 98:2) also in 80% yield. The azlactone was solvolyzed in basic methanol to give the aminoester **10** (Ar = Ph, R = CH_3) quantitatively. Analysis by chiral HPLC showed the ee in both cases to be 99%. An improved procedure avoids the isolation of the alkylated azlactone. Directly adding basic methanol to the initial reaction mixture using **8** (Ar = Ph, X = OCO_2Boc) produced a 90% yield of **10** instead of 83% for the two step protocol. Using the one pot protocol with **8** (Ar = Ph, X = OCO_2CH_3) gave 92% yield of **10** having a 97:3 dr wherein the major diastereomer had a 99% ee.

Adopting the one-pot protocol as our standard, variation of the Ar and R substituents, as in eq 3, was examined using the methyl carbonate leaving group. Table 1 summarizes the results. In nearly all cases, only a single diastereomer was detected (entries 3−12). Using the methyl- and benzyl-substituted azlactones, only the branched regioisomer was formed using allyl substrates such as **8** (entries 1−4, 6−8). Employing the chiral racemic substrate as the allylating partner as in entry 5 did see some deterioration in the regio- and enantioselectivity as we noted in our earlier work.[2] In this case, two diastereomeric complexes must form when the reactions are run to 100% conversion. Apparently, their rate of

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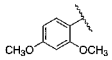
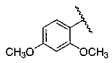
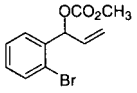
Table 1. Catalyzed AAA to Quaternary Amino Acids

Entry	Ar[a]	R	time, h	isolated yields branched	isolated yields linear[a]	ee	dr
1	Ph	CH_3-	3	92%	N.D	99%	97:3
2		CH_3-	3	84%	N.D.	91%	96:4
3		CH_3-	4	84%	4%	92%	>98:2
4		CH_3-	3	89%	N.D.	90%	>98:2
5[c]		CH_3-	4	82%	9%	85%	>98:2
6	Ph	$PhCH_2$-	3	92%	N.D.	96%	>98:2
7		$PhCH_2$-	3	86%	N.D.	94%	>98:2
8		$PhCH_2$-	3	90%	N.D.	94%	>98:2
9	Ph	$CH_3S(CH_2)_2$-	4	86%	6%	92%	>98:2
10	Ph	$(CH_3)_2CHCH_2$-	4	85%	5%	96%	>98:2
11	Ph	CH_2CHCH_2-	3	82%	6%	97%	>98:2
12	Ph	$(CH_3)_2CH$-	6	76%	11%	96%	>98:2

[a] In all cases, X = OCO_2CH_3. [b] N.D. = not detected. [c] Substrate was



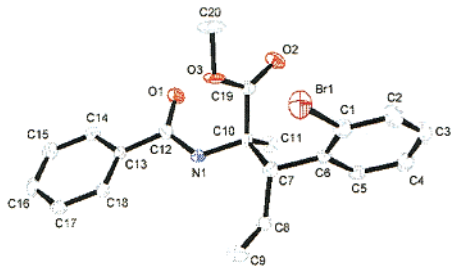


Figure 1.

equilibration, although reasonably fast, is still somewhat competitive with the rate of nucleophilic attack. Curiously, using longer alkyl substituents than methyl (entries 9 and 11) or branched alkyl groups (entries 10 and 12) also led to some linear regioisomers. Nevertheless, in every case, the branched product was isolated in excellent yields and stereoselectivities.

The impact of catalyst loading was examined in the reaction of entry 6. Dropping the Mo to 5 mol % and 7.5 mol % ligand gave quite comparable results after 7 h—86% isolated yield of product as a single diastereomer of 95% ee—albeit with 6% of the linear product observed. Further reduction to 2 mol % Mo and 3.5 mol % ligand gave only a 52% isolated yield of a 4:1 branched:linear product wherein the branched product still was only one diastereocomer of 93% ee.

The relative and absolute stereochemistry was established by X-ray crystallographic analysis of the product of entry 5 as shown in Figure 1. The stereochemistry of all the remaining examples are then assumed by analogy. The facial selectivity with respect to the allyl is the same as with malonate.[2] Figure 2 depicts the two different diastereomeric transition states that minimize steric hindrance. The crystal structure shows the approach in A to be favored. Simple MM2 calculation on the products resulting from A and B gave energy differences of 2−10 kcal/mol in favor of

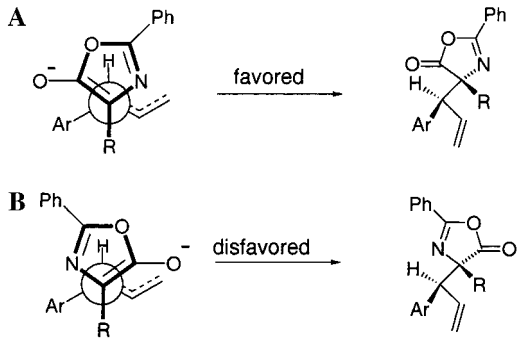
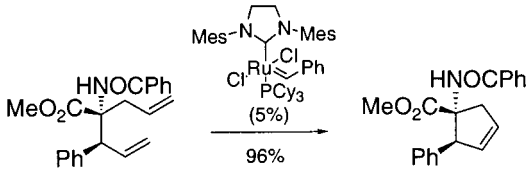


Figure 2.

that resulting from A. This correlation suggests that the product derives from a late transition state which reflects the relative thermodynamic stability of the two possible diastereomers.

The Mo-catalyzed AAA reaction leads to an unprecendented high level of regio-, diastero-, and enantioselectivity in the reactions of azlactones as nucleophiles. Thus, access to highly unusual quaternary amino acids result. The products may also serve as sources of additional novel amino acids. For example, using ring-closing metathesis as in eq 4 (product of entry 11), a cyclic amino ester of



(4)

high diastereo- and enantioselectivity is generated. This represents the first examples of control of stereochemistry at a nucleophile in a Mo-catalyzed AAA.

The ability of these ligands to provide such exquisite control even at 65 °C is noteworthy. Providing an understanding must await more details of the structure of the catalytically active species. Nevertheless, at present, they show increasing promise as an important tool for asymmetric synthesis of important building blocks. This process complements the Pd AAA which provides only the linear product with cinnamyl substrates.

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Supporting Information Available: Experimental procedure and characterization data for compound in Table 1 (PDF). X-ray crystallographic file in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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