On the Question of Asymmetric Induction with Acyclic Allylic Substrates. An Asymmetric Synthesis of (+)-Polyoxamic Acid

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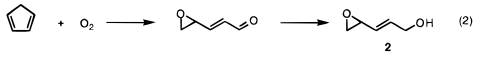
In the development of asymmetric catalysts for allylic alkylation, the introduction of the 1,3-diphenylallyl system has led to its becoming the "standard" test system (eq 1).[1] Unfortunately, in all cases to date, as the size of the 1,3-allyl substituents decreases so does the ee. For example, whereas reactions of **1** (R = Ph) can give products whose ee exceeds 99% with chiral 2-diphenylphosphinobenzoxazolines,[2,3] the reported ee's for **1** (R = CH_3) with these same ligands range between 50% and 75%.[3,4] The source of the poorer ee's as the size of R decreases may derive from the ambiguity created by the presence of interconverting syn and anti π-allylpalladium intermediates with small R groups, whereas when R is large, the syn,syn complex will be strongly favored. While our modular ligands have proven successful for the geometrically defined cyclic cases,[5a] their effectiveness with acyclic substrates is subject to the same isomeric uncertainty as above. On the other hand, if our working concept of a chiral pocket[5b,c] has merit, it may inhibit such interconversions and thereby achieve higher levels of asymmetric induction. Herein we report the unexpected results of this study which led to the development of a novel deracemization of the vinyl epoxide **2** which is atom economically available from cyclopentadiene and singlet oxygen as shown in eq 2 according to known procedures.[6]



Initial efforts focused on **1a** using the ligand **3** with π-allylpalladium chloride dimer **4** as the catalyst precursors as shown in eq 3. Surprisingly, the alkylation proceeded very slowly. Using sodium hydride as base in THF as solvent, a reaction time of 24 h gave only a 29% yield of **5** and a 53% recovery of starting material. More importantly, the alkylated product had an ee of only 12%. Switching to cesium carbonate in methylene chloride, a reaction system that gave excellent

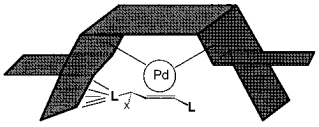


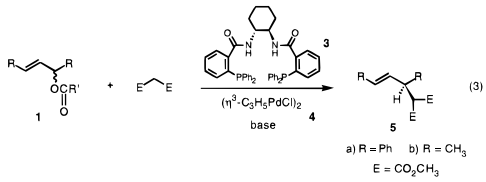
Figure 1. Representation of the catalytic active site.

Table 1. Asymmetric Alkylations Involving 1,3-Dimethylallyl Substrate **1b**

entry	base	solvent	yield (%)	ee[a] (%)
1	NaH	THF	63	29
2	Cs_2CO_3	THF	62	84
3	NaH	CH_2Cl_2	86	81
4	Rb_2CO_3	CH_2Cl_2	92	91
5	Cs_2CO_3	CH_2Cl_2	98	92

[a] Determined by ^{1}H NMR chiral shift with Eu(hfc)$_3$ in C_6D_6.

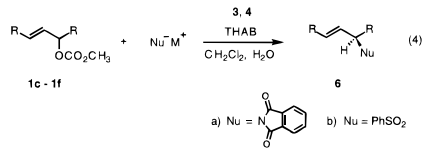
results in cyclic cases,[5] increased the ee to 52% but saw the conversion plummet−after 24 h, the yield of **3** was only 9% and the recovered **1a** was 79%.



A possible explanation is depicted in the cartoon shown in Figure 1. Using a chiral pocket as a working model, if the 1,3-substituents are too big, they may encounter steric hindrance both in forming the alkene−palladium complex as well as in the molecular motion in going from a η^2 to η^3 complex during ionization. Such a rationale suggests that this series of catalysts will have a limit in terms of what substrates will fit into the chiral pocket.[7]

We, therefore, turned to the substrate with small substituents, the 1,3-dimethyl series **1b**, as shown in eq 3, with the results of the alkylation with dimethyl malonate to give **5b**[3,8,9] summarized in Table 1. Two important features stand out from this data. First, solvent choice is important; switching from THF to methylene chloride (entries 1 vs 3) dramatically increased ee. Second, choice of alkali metal base matters with the larger metal giving higher ee in both THF (entry 1 vs 2) and methylene chloride (entries 3−5). For the first time, satisfactory ee has been obtained for the dimethyl case.

For the diethyl substrate **1c**, the most extensive studies were performed with potassium phthalimide as the nucleophile to give imide **6a** (R = C_2H_5) (eq 4).[10] The reaction is slower than for the dimethyl substrate **1b** and favored by use of a more polar solvent. For example, after 48 h reaction time at ambient temperature, the yield went from 33% in methylene chloride to



86% in DMSO but the ee plummeted from 80% to 35%. Phase

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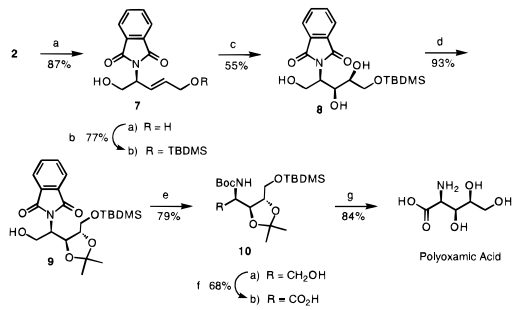
Scheme 1. Synthesis of (+)-Polyoxamic Acid[a]



[a] (a) 2.5% $(dba)_3Pd_2{\cdot}CHCl_3$, 7.5% **3**, 10% Cs_2CO_3, THF, rt. (b) Imidazole, TBDMS−Cl, CH_2Cl_2, rt. (c) $(DHQ)_2PYR$, NMO, OsO_4, CH_2Cl_2, H_2O, rt. (d) $(CH_3)_2C(OCH_3)_2$, TsOH, THF, rt. (e) (i) NH_2NH_2, C_2H_5OH, reflux; (ii) $(Boc)_2O$, $(C_2H_5)_3N$, CH_2Cl_2, rt. (f) cat. $RuCl_3$, H_2O, $NaIO_4$, CH_3CN, CCl_4, H_2O. (g) TFA, H_2O.

transfer conditions balanced the opposing effects. Using 5 mol % tetrahexylammonium bromide with potassium phthalimide in methylene chloride−water, a 78% yield of **6a** ($R = C_2H_5$)[10] of 94% ee was obtained. These same conditions using sodium benzenesulfinate gave the allylic sulfone **6b** ($R = C_2H_5$)[10] of 91% ee in 92% yield. Extending the size of the alkyl groups to the *n*-propyl substrate **1d** and even the *n*-pentyl substrate **1e** with sodium benzenesulfinate as nucleophile gave comparable results [**6b** ($R = n\text{-}C_3H_7$),[10] 99% yield, 97% ee, and **6b** ($R = n\text{-}C_5H_{11}$),[10] 78% yield, 95% ee]. On the other hand, branching at the allylic position as in **1f** saw a diminishment in the ee of **6b** ($R = c\text{-}C_6H_{11}$) to 31% (68% yield). In these cases, the ee's were determined with a chiral HPLC column (Chiralpak AD). The absolute configuration of **6a** was established by conversion to the *O*-methylmandelamide[11] and agrees with that predicted by extrapolation of the mnemonic established for the cyclic cases assuming reaction proceeds via the syn,syn complex.[5] The absolute configurations for all the remaining examples are assigned by analogy.

To test the effect of a functionalized substituent, a hydroxymethyl group, the vinyl epoxide **2** was examined. As shown in Scheme 1, the best conditions employed $(dba)_3Pd_2{\cdot}CHCl_3$ as the Pd(0) source and cesium carbonate as a cocatalyst. In this way, phthalimide **7a**[10] of 82% ee[12,13] was isolated in 87% yield.[14] This five carbon building block in which each carbon can be differentially elaborated can provide entry to a plethora of targets. In conjunction with a program on a de novo asymmetric synthesis of the antifungal agents, polyoxins and nikkomycins,[15] we targeted polyoxamic acid, the novel amino acid substituent of these antifungal agents.[16] Chemoselective silylation of the less hindered allyl alcohol to give **7b**[10] (selectivity of 28:1) occurred by slow addition of the silylating agent to a mixture of imidazole and the diol **7a**. In agreement with earlier work with similar systems,[17,18] dihydroxylation of **7b** gave excellent yields (86%) but modest selectivity (∼2:1) favoring diastereomer **8**[10] even with chiral catalysts.[19] Fortunately, the excellent crystallinity of the diol **8** allowed it to be obtained diastereo- and enantiomerically pure in 55% yield. After protection as the acetonide (**9**),[10] oxidation of the primary alcohol directly to the corresponding acid proceeded normally using catalytic ruthenium chloride. However, the physical properties of polyoxamic acid made its isolation from the reaction of removal of the phthalimide group difficult. As a result, the phthalimide group was exchanged for the Boc (**10a**) which was oxidized as above to the acid **10b**, a known precursor of polyoxamic acid.[20] Following the literature protocol, trifluoroacetic acid frees polyoxamic acid, identical in every respect with spectra of an authentic sample.[21]

The modular ligands based upon 2-diphenylphosphinobenzoic acid and chiral diamines provide catalysts that induce high ee with acyclic substrates that fare poorly with all other reported ligands. At the same time, the 1,3-diphenyl substrate, whose reactions almost universally give excellent ee, gives quite unsatisfactory results herein. The steric hindrance caused by branching appears to be the source of this effect as the 1,3-dicyclohexyl ligand exhibits similar behavior, but straight chains appear tolerated. The fact that the catalyst imposes a size restriction on the substrate is in accord with a chiral pocket concept. Thus, there exists a nice complementarity between our ligands and virtually all others, thereby allowing asymmetric allylic alkylations to be practiced quite broadly. The unprecedented dependence of ee on metal cation reveals that the structure of the ion pair that constitutes the nucleophile is critical for good molecular recognition. It is curious that the asymmetric induction appears to depend more upon the escort ion (i.e., the cation) than the ion that actually bonds in the enantiodetermining event (i.e., the anion).[5] The participation of the epoxide **2** readily derived from a cheap starting material, cyclopentadiene, in two steps in such reactions provides a particularly flexible asymmetric building block to numerous targets. Access to polyoxamic acid in this way realizes just one such potential. Further work exploring such routes is underway.

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Supporting Information Available: Spectral characterization and high-resolution mass spectrometry or combustion analysis results for **6a,b**, **7a,b**, **8**, **9**, and **10a** (3 pages). See any current masthead page for ordering and Internet access instructions.

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(10) All new compounds have been fully characterized spectrally, and elemental composition has been established by high-resolution mass spectroscopy and/or combustion analysis (see the supporting information).

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(13) The absolute configuration was established by conversion of the phthalimide group to an *O*-methylmandelamide (see ref 11).

(14) The ee values of 88% and 89%, respectively, were obtained using succinimide.

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