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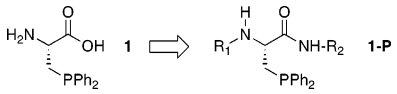
Enantioselective [3 + 2]-Cycloadditions Catalyzed by a Protected, Multifunctional Phosphine-Containing α-Amino Acid

Bryan J. Cowen and Scott J. Miller*

Department of Chemistry, Yale University, P.O. Box 208107, New Haven, Connecticut 06520-8107

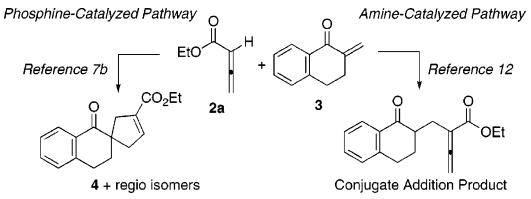
Received May 14, 2007; E-mail: scott.miller@yale.edu

α-Amino acids are receiving explosive attention as catalysts for organic reactions.[1] The catalysis exhibited by proline is perhaps most versatile,[2] although there is now a growing list of reactions that may be catalyzed by other amino acids, including both proteinogenic and nonproteinogenic variants. Concerning the latter, "unnatural" amino acids have also proven important as ligands for metal-catalyzed reactions. In this spirit, the introduction of diphenylphosphinylalanine (**1**) by Gilbertson marked a significant advance both conceptually[3] and in the development of highly selective metal-based catalysts.[4] The dual capacity of phosphines to serve as either ligands or as catalysts in the absence of metals stimulated a study of **1** in this latter context. We wondered if incorporation of **1** into peptides would create a functionality-rich, chiral environment for the Lewis basic P atom that might be tuned as a function of peptide structures (i.e., **1-P**).[5,6]



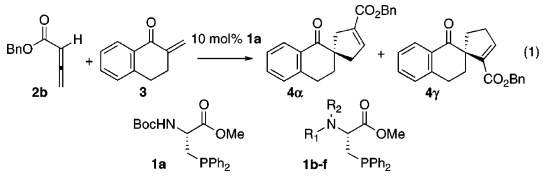
In this context, we examined the formal catalytic [3 + 2]-cycloaddition of allenoate esters and enones pioneered by Lu and co-workers (Scheme 1).[7] Allene **2a** and enone **3** combine to give cycloadduct **4** in the presence of substoichiometric quantities of triphenyl phosphine (PPh_3). From a mechanistic point of view, the reaction is often represented as proceeding through a zwitterionic dipole en route to a formal [3 + 2]-cycloaddition.[8] Notably, significant progress has been reported with chiral catalysts, including important contributions by Zhang,[9] Fu,[10] and Wallace.[11] We noted previously that this coupling reaction may be diverted to give a conjugate addition product when phosphine catalysts are exchanged for amines.[12] We now report that α-amino acids of type **1** lead to substantial enantiocontrol over the phosphine-catalyzed pathway (Scheme 1).

Scheme 1



Our initial experiments established that indeed simple derivatives of **1** are effective catalysts for the cycloaddition of **2b** and **3**, delivering the cycloadducts **4**α and **4**γ in excellent yield and regioselectivity (eq 1, Table 1). For example, with catalyst **1a**, allenoate **2b** and tetralone **3** undergo cycloaddition to form **4**α and **4**γ in a combined yield of 93% (94:6 regioisomeric ratio), with the major adduct **4**α exhibiting 69% ee (entry 1). When the urethane substituent is swapped from *t*-Bu to either benzyl (catalyst **1b**) or methyl (catalyst **1c**), the results are similar (entries 2 and 3). Exchange of the urethane to acetamide (**1d**), however, produces a more dramatic

Table 1. Amino Acid Catalyst Survey for [3 + 2]-Cycloadditions[a]



entry	catalyst	temp/time	yield α+γ (%)[b]	α:γ[c]	ee α (%)[d]
1	**1a**	23 °C/3 h	93	94:6	69
2	**1b**, R_1 = Cbz, R_2 = H	23 °C/3 h	88	95:5	68
3	**1c**, R_1 = CO_2Me, R_2 = H	23 °C/3 h	96	93:7	66
4	**1d**, R_1 = Ac, R_2=H	23 °C/3 h	86	93:7	51
5	**1e**, R_1 = Ts, R_2 = H	23 °C/3 h	40	88:12	rac
6	**1f**, R_1 = Boc, R_2 = Me	23 °C/3 h	60	93:7	rac
7	**1a**	−25 °C/30 h	95	>99:1	80
8	**1a**	−40 °C/24 h	16	>99:1	84

[a] Reactions were run in $PhCH_3$ with 1.5 equiv of allenic ester and 10 mol % of **1**. [b] Isolated yield after silica gel chromatography. [c] Determined from the ^{1}H NMR spectrum of purified product. [d] All ee's were measured using chiral HPLC.

difference. Catalyst **1d** delivers the product with less selectivity (α:γ = 93:7; **4**α exhibiting 51% ee; entry 4). Replacement of the Boc group in **1a** with the tosyl group (catalyst **1e**) leads to a total loss of enantioselectivity (entry 5). Likewise, replacement of the NH function in catalyst **1a** with an *N*-Me group (catalyst **1f**; entry 6) leads to racemic products, suggesting that subtle H-bonding effects may be important in the transition state. Notably, each catalyst in the series provides reasonable reaction rates, although the urethanes are the most active, delivering >88% yield of **4** within 3 h (23 °C).

Lowering the reaction temperature leads to an increase in selectivity. For example, when the reaction is run at −25 °C, regioselectivity improves, with essentially exclusive formation of **4**α (α:γ >99:1); the major product under these conditions exhibits 80% ee (entry 7). At −25 °C, 30 h is required for the reaction to reach completion (95% isolated yield). Further lowering of the temperature leads to a modest increase in selectivity (84% ee; entry 8), but the rate is slow under these conditions (entry 8).

An examination of the substrate scope reveals that catalyst **1a** tolerates a range of substrates (Table 2). Methoxy-substituted case **5** affords **6** with slightly enhanced selectivity (entry 1, 84% ee). Heteroatom-substituted cases, along with heteroaromatic substrates, also afford products with excellent regioselectivity, although enantiomeric ratios are somewhat lower. For example, heterocycle **8** is formed from **7** with an α:γ ratio of 94:6 and 65% ee (entry 2). Furanoid enone **9** leads to spirocycle **10** with total regiocontrol and 76% ee (entry 3). Pyrrole derivative **11** exhibits a similar reaction profile, with **12** formed with >99:1 α:γ selectivity, and 71% ee (entry 4). Acyclic substrates also participate, with somewhat lower selectivity. α-Methylated enone **13** gives **14** with 85:15 regioselectivity and 70% ee (entry 5). Chalcone (**15**) leads to compound

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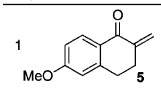
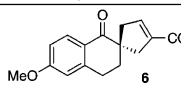
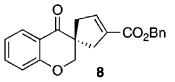
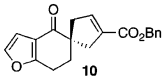
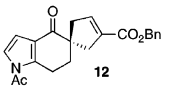
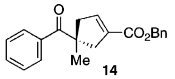
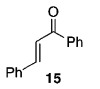
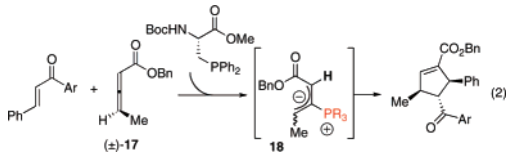
Table 2. Substrate Scope for [3 + 2]-Cycloadditions[a]

entry[i]	substrate	product (α)[h]	time (h)	yield α+γ (%)[b]	α:γ[c]	ee α (%)[d]
1	 5	 6	30	95	>99:1	84
2[e]	 7	 8	24	68	94:6	65
3[f]	 9	 10	43	75	>99:1	76
4[g]	 11	 12	24	53	>99:1	71
5[e,f]	 13	 14	43	75	85:15	70
6[e]	 15	 16	43	81	44:56	82

[a] All data are the average of two experiments. Reactions were run at −25 °C in $PhCH_3$ with 1.5 equiv of allenic ester and 10 mol % of **1a**. [b] Isolated yield after silica gel chromatography. [c] Determined from the ^1H NMR spectrum of purified product. [d] All ee's were measured using chiral HPLC. [e] Reaction was run at 4 °C. [f] Reaction was run with 5 equiv of enone. [g] Reaction was run at 23 °C with 20 mol % of **1a**. [h] See Supporting Information for the determination of absolute stereochemistry. [i] Benzyl allenoates were selected for their ease of handling and optimal performance.

16 with 82% ee, although regioselectivity is reduced to a nearly statistical level (entry 6).

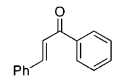
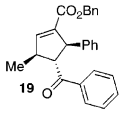
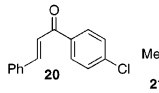
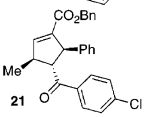
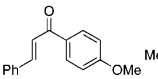
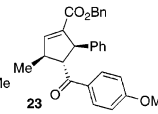
Chalcone, however, provided an opportunity to observe a unique "deracemization" reaction upon cycloaddition with racemic γ-substituted allene **17**. In these cases, we were particularly interested in whether or not racemic allene substrates could be subjected to "dynamic kinetic asymmetric transformations," as the initial adducts of catalyst−allene reaction are intermediates such as **18**, in which the element of planar chirality has been erased (eq 2).



Indeed, we were pleased to find that when (±)-**17** is exposed to chalcone in the presence of a full equivalent of catalyst **1a**, a 94% yield of cyclopentene **19** is formed within 7 h and that the product exhibits 91% ee (Table 3, entry 1). Furthermore, when a substoichiometric amount of the catalyst is employed, a similar result is observed, although the reaction rate is diminished (entry 2, 38% yield within 24 h, 93% ee). These effects are maintained through a set of chalcones. For example, *p*-chloro-substituted chalcone **20** may be converted to **21** in 96% yield with the product exhibiting 87% ee (entry 3). *p*-Methoxy-substituted chalcone **22** delivers its corresponding cycloadduct **23** in 89% yield, with 90% ee (entry 4). In each of these cases, these highly substituted cycloadducts are formed as single regio- and diastereomers. These examples constitute unique cases of allenoate deracemizations via chiral phosphine-catalyzed [3 + 2]-cycloaddition.[13]

Our current thinking on the basis of asymmetric induction is stimulated by recent observations of Yu[14] and Kwon[15] concerning mechanism. Transition state **24** is consistent with the identity of

Table 3. Substrate Scope for [3 + 2]-Cycloadditions Employing γ-Substituted Allenic Ester (±)-**17**[a]

entry	substrate	product	cat. loading (mol%)	time (h)	yield (%)[b]	ee (%)[c]
1		 19	100	7	94	91
2			20	24	38	93
3	 20	 21	100	3	96	87
4	 22	 23	100	12	89	90

[a] Reactions were run with 1.5 equiv of allenic ester. [b] Isolated yield after silica gel chromatography. [c] All ee's were measured using chiral HPLC.

the major enantiomer that is formed. Ensemble **24** may assume transition state organization via the illustrated H-bond and requires

One of Several Possible Transition State Structures (Tetralone Approaches from Bottom)

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that the dipolarophile approach the zwitterion from the π-face opposite one of the Ph rings of the catalyst. Of course, alternatives are possible, and detailed studies of mechanism are now ongoing.

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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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