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Intramolecular Palladium-Catalyzed Allylic Alkylation: Enantio- and Diastereoselective Synthesis of [2.2.2] Bicycles

Barry M. Trost,* Karna L. Sacchi, Gretchen M. Schroeder, and Naoyuki Asakawa

Department of Chemistry, Stanford University, Stanford, California 94305-5080

bmtrost@stanford.edu

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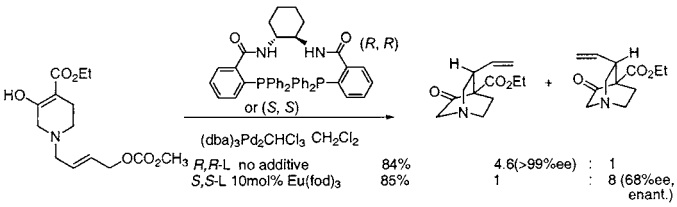
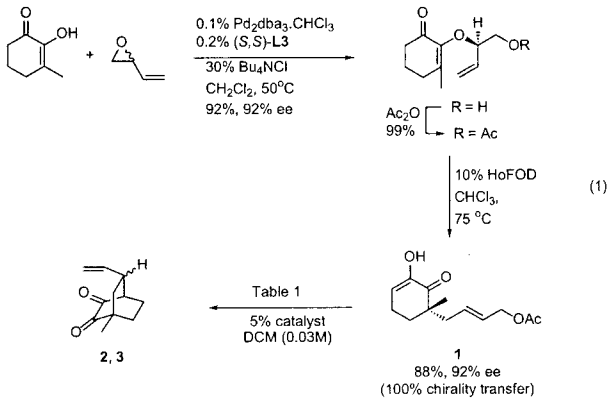
ABSTRACT



Pd-catalyzed asymmetric allylic alkylation provides both enantio- and diastereoselectivity in formation of bicyclo [2.2.2] octan-2,3-diones and quinuclidin-2-ones, the latter potential precursors to quinine alkaloids.

Palladium-catalyzed asymmetric allylic alkylation (AAA) has been shown to be a versatile reaction for generating quaternary chiral centers.[1] Whereas the intermolecular version of this reaction has received much attention, the intramolecular version remains underexplored. Intramolecular palladium-catalyzed asymmetric allylic alkylation has the potential to generate two new stereocenters in a single reaction (at the electrophile and at the nucleophile). Also, this method could allow for a rapid increase in molecular complexity and generate polycycles in a stereospecific manner. Herein, we wish to report the intramolecular palladium-catalyzed asymmetric allylic alkylation to generate [2.2.2] bicycles in good enantio- and diastereoselectivity.

We recently reported the synthesis of chiral cycloalkenones by a palladium-catalyzed AAA/Claisen rearrangement protocol of cyclic α-diketones.[2] The use of vinyl epoxides[3] as the electrophile gives an allylic alcohol after Claisen rearrangement and provides the opportunity for performing a second diastereoselective palladium-catalyzed AAA reaction to generate bicycles (eq 1). This idea was tested with chiral



cycloalkenone **1** (eq 2). The intramolecular alkylation was found to proceed readily in the absence of exogeneous base in the presence of 5 mol % palladium catalyst using methylene chloride as solvent. Only C-alkylated products **2**

(1) For reviews of the palladium-catalyzed asymmetric allylic alkylation, see: Trost, B. M. *Chem. Pharm. Bull.* **2002**, *50*, 1. Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **1999**, *121*, 4545. Trost, B. M. *Acc. Chem. Res.* **1996**, *29*, 355. Trost, B. M.; Van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395. Heumann, A.; Reglier, M. *Tetrahedron* **1995**, *51*, 975. Hayashi, T. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH Publishers Inc.: New York, 1993. Sawamura, M.; Ito, Y. *Chem. Rev.* **1992**, *92*, 857. Fiaud, J. C. In *Metal-Promoted Selectivity in Organic Synthesis*; Graziani, M., Hubert, A. J., Noels, A. F., Eds.; Kluwer Academic Publishers: Dordrecht, 1991. Consiglio, G.; Waymouth, R. M. *Chem. Rev.* **1989**, *89*, 257.

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Table 1. Palladium-Catalyzed Cyclization of α-Diketone[a]

entry	ligand	additive	% yield (major diastereomer)	dr (**2**:**3**)[b]
1	**L1**		66	1:2.4
2	(*S*,*S*)-**L2**		69	3.5:1
3	(*R*,*R*)-**L2**		75	1:4.9
4	(*S*,*S*)-**L3**		58	2.3:1
5	(*R*,*R*)-**L4**		20	1:4.4
6	(*S*,*S*)-**L5**		no reaction	
7	(*R*,*R*)-**L2**	Bu_4NCl (0.3 equiv)	no reaction	
8	(*R*,*R*)-**L2**	TBAT (0.1 equiv)	60	1:3

[a] All experiments were run in refluxing methylene chloride at 0.03 M with 2.5 mol % Pd_2dba_3·$CHCl_3$ and 5 mol % ligand. [b] Determined by GC.

and **3** were observed. When an achiral ligand, triphenylphosphine (**L1**, Figure 1), was used, the major diastereomer of

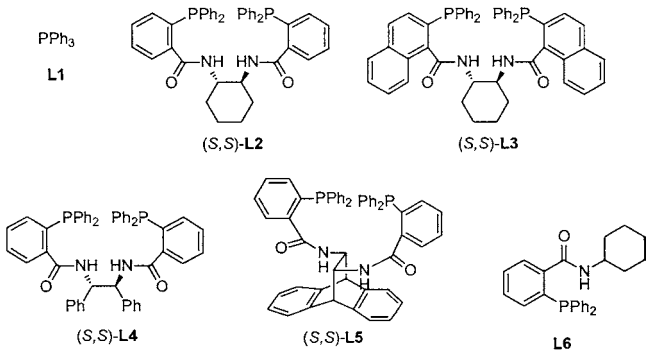
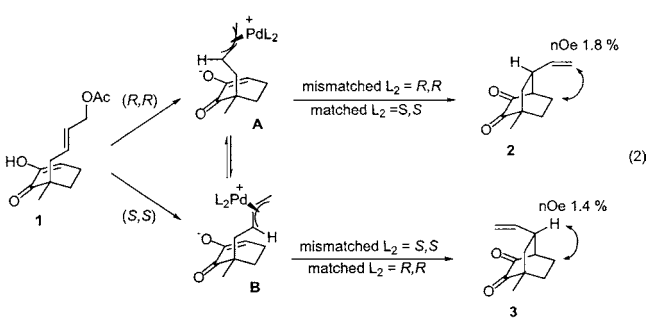
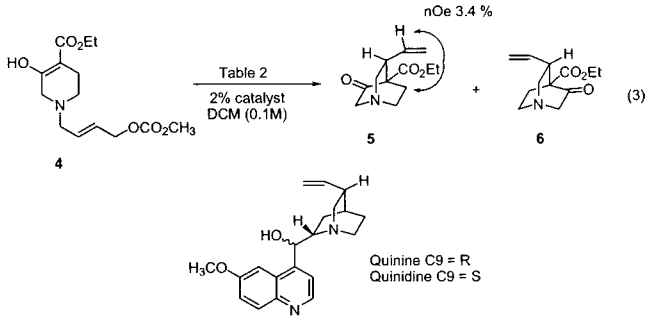


Figure 1. Ligands.

the cyclized material was isolated in 66% yield (Table 1) in modest diastereoselectivity (1:2.4). Thus, the intrinsic bias for substrate **1** is to form diketone **3**. Switching to the chiral (*S*,*S*)-**L2** gave the cyclized product **2** in 69% yield and 3.5:1 dr (entry 2); thus the chiral catalyst is able to overcome the intrinsic bias of the substrate. (*R*,*R*)-**L2** gave an improved yield (75%) and dr (1:4.9). Importantly, the major diastereomer was reversed from that using the (*S*,*S*) ligand, indicating catalyst control in the stereoselectivity of formation of the new stereogenic center. The question arises: What is the diastereo determining event in this transformation? As eq 2 illustrates, matched ionization of α-diketone **1** with the (*R*,*R*) ligand would result in intermediate **A** in which ionization has taken place from the bottom side of the allylic acetate as drawn.[4] Conversely, the (*S*,*S*) ligand ionizes preferentially from the top face of **1** as drawn and results in intermediate **B**. Keeping in mind that ionization and nucleophilic addition are the microscopic reverse, matched nucleophilic attack on intermediate **A** using the (*R*,*R*) ligand would take place at the carbon that was previously substituted by the acetate. However, these terminal addition products are not observed. The major diastereomer generated from the reaction with the (*R*,*R*) ligand gives α-diketone **3**, the result of a matched attack by the nucleophilic enol on intermediate **B** (L_2 = *R*,*R* ligands). Thus, the intermediate generated from matched ionization (**A**) must equilibrate to give **B**, as attack of the nucleophile directly on intermediate **A** would generate mismatched compound **2**. In short, a Curtin−Hammett situation is operating in this reaction.[5] A variety of chiral ligands were tried, all of which consistently gave the product resulting from a matched nucleophilic attack on the rapidly equilibrating intermediates **A** and **B** (Table 1, entries 4−6). Additives were also tried in an attempt to increase the rate of π-allyl equilibration, thereby increasing the dr; however, improved results were not obtained (entries 7 and 8).





Intramolecular palladium-catalyzed AAA of allylic carbonate **4** presents the fascinating dual challenge of diastereo- and enantiocontrol (eq 3). Given our recent success using prochiral nucleophiles in the palladium-catalyzed AAA, in particular β-ketoesters,[6] we thought this challenge could be met.[7] This reaction would allow for an asymmetric synthesis of quinuclidinones, important building blocks for the synthesis of quinoline *Cinchona* alkaloids.[8] Quinine[9] and qui-

(2) Trost, B. M.; Schroeder, G. M. *J. Am. Chem. Soc.* **2000**, *122*, 3785.
(3) For examples of butadiene monoepoxide as an electrophile in the Pd-cat. AAA, see: Trost, B. M.; Jiang, C. *J. Am. Chem. Soc.* **2001**, *123*, 12907. Trost, B. M.; McEachern, E.; Toste, F. D. *J. Am. Chem. Soc.* **1998**, *120*, 12702. Trost, B. M.; Bunt, R. C. *Angew. Chem., Int. Ed. Eng.* **1996**, *35*, 99.
(4) For a discussion of "matched" and "mismatched" ionization and nucleophilic attack, see the reviews in ref 1.
(5) Eliel, E. L. *Stereochemistry of Carbon Compounds*; McGraw-Hill: New York, 1962.
(6) Trost, B. M.; Radinov, R.; Grenzer, E. M. *J. Am. Chem. Soc.* **1997**, *119*, 7879.
(7) For examples of prochiral nucleophiles in the palladium-catalyzed AAA, see: Trost, B. M.; Schroeder, G. M. *J. Am. Chem. Soc.* **1999**, *121*, 6759. Trost, B. M.; Ariza, X. *J. Am. Chem. Soc.* **1999**, *121*, 10727. Kuwano, R.; Ito, Y. *J. Am. Chem. Soc.* **1999**, *121*, 3236. Kuwano, R.; Nishio, R.; Ito, Y. *Org. Lett.* **1999**, *1*, 837. Trost, B. M.; Ariza, X. *Angew. Chem., Int. Ed. Eng.* **1997**, *36*, 2635. Hayashi, T.; Kanehira, K.; Hagihara, T.; Kumada, M. *J. Org. Chem.* **1988**, *53*, 113.

Table 2. Palladium-Catalyzed Cyclization of β-Keto Ester **4**

entry	ligand	additive	% yield[b]	dr (**5**:**6**)[c]	% ee **5**[d] (% ee **6**[d])
1	**L6**		81	1:2.2	
2	(*S*,*S*)-**L2**		82	3.6:1	93
3	(*R*,*R*)-**L2**		74	3.8:1	−96
4	(*S*,*S*)-**L3**		74	1.5:1	78
5	(*S*,*S*)-**L4**		48	3.4:1	88
6	(*S*,*S*)-**L5**		68	1:1.1	58
7	(*S*,*S*)-**L2**	Bu_4NCl (0.3 equiv)	78	2.9:1	91 (6)
8	(*S*,*S*)-**L2**	$Ho(fod)_3$ (0.1 equiv)	55	1:6.1	48 (62)
9	(*S*,*S*)-**L2**	$Yb(fod)_3$ (0.1 equiv)	39	1:5.2	56 (55)
10	(*S*,*S*)-**L2**	$Eu(fod)_3$ (0.1 equiv)	85	1:8	50 (68)
11[e]	(*R*,*R*)-**L2**		84	4.6:1	>99

[a] All experiments were run in methylene chloride (0.1 M) at room temperature with 1 mol % Pd_2dba_3·$CHCl_3$ and 3 mol % ligand unless otherwise noted. [b] Combined yield of both diastereomers. [c] Determined by crude ^1H NMR. [d] Determined by chiral HPLC. [e] The reaction was run at 0.01 M in methylene chloride.

nidine are particularly important members of this family of molecules, as they have found use as pharmaceuticals[10] and have themselves been employed in asymmetric catalysis.[11]

As with the previous case, the intramolecular allylic alkylation was found to proceed in the absence of exogenous base in the presence of 2 mol % catalyst at room temperature, using methylene chloride as the solvent. Cyclization of β-keto ester **4** was first optimized by variation of the ligand (Table 2). Achiral ligand **L6** gave the cyclized quinuclidinone in good yield (81%) as a 1:2.2 mixture of diastereomers favoring ester **6**. Like the α-diketones, the standard cyclohexyl diamine ligand **L2** gave the best results. Thus with ligand (*S*,*S*)-**L2**, the product was isolated in good yield (82%) as a 3.6:1 mixture of diastereomers favoring ester **5**. Once again, the chiral catalyst was able to overcome the intrinsic bias of the substrate. Gratifyingly, the enantioselectivity of the reaction was excellent (93%). As illustrated in Table 2, the naphthyl-, stilbene-, and anthracene-derived ligands (**L3**−**L5**, Figure 1) gave poorer ee and de (entries 4−6).

Various additives were found to have a dramatic effect on the reaction. While the addition of tetrabutylammonium chloride gave the cyclized product in slightly diminished ee and de, lanthanum fod reagents had a profound impact on the reaction and reversed the diastereoselectivity. Thus, with $Eu(fod)_3$ the diastereoselectivity increased dramatically to 1:8 in favor of ester **6** (entry 10). Unfortunately, the ee was not maintained (68%). Considering the transition states possible for this reaction, we expected a bulky Lewis acid such as $Eu(fod)_3$ to favor transition states **C** and **D** as a result of steric factors. Instead it appears that the lanthanum fod reagents exert an electronic effect, enhancing the interactions between the enolate and π-allyl, thus favoring transition states **E** and **F** (Figure 2).

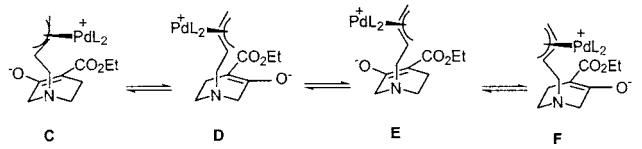


Figure 2. Possible transition states for the cyclization of β-keto ester **4**.

Variation of the reaction solvent (THF, toluene, dioxane, acetonitrile) gave no improvement. Dichloroethane gave results comparable to those with methylene chloride. Performing the reaction under more dilute conditions did give improved results (entry 11). Thus, at 0.01 M in methylene chloride, the cyclized product **5** could be isolated in 84% yield as a 4.6:1 mixture of diastereomers in remarkable ee (>99%). These conditions give the best results for this substrate to date.

The absolute configuration of the product was determined by X-ray analysis of the hydrochloride salt of ester **5**. The X-ray crystal structure also confirmed the relative configuration assigned initially by NOE experiments. Like with α-diketones, the major diastereomer is a result of matched ionization followed by $\pi-\sigma-\pi$ equilibration to allow matched nucleophilic attack. The absolute configuration can be rationalized by the cartoon depicting the chiral pocket in Figure 3. Thus, (*R*,*R*)-**L2** gives the stereochemistry shown.

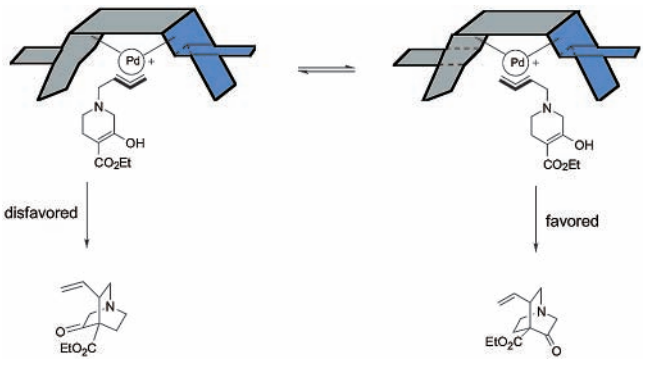


Figure 3. Rationalization of the absolute stereochemistry using (*R*,*R*)-**L2**.

To conclude, the intramolecular palladium-catalyzed allylic alkylation has been achieved and gives the cyclized products

(8) For the synthesis of enantiopure quinuclidones, see: Da Silva Goes, A. J.; Cave, C.; d'Angelo, J. *Tetrahedron Lett.* 1998, *39*, 1339. Frackenpohl, J.; Hoffman, H. M. R. *J. Org. Chem.* **2000**, *65*, 3982. Hoffmann, H. M. R.; Plessner, T.; von Riesen, C. *Synlett* **1996**, *7*, 690.

(9) The first stereoselective total synthesis of quinine was recently reported: Stork, G.; Niu, D.; Fujimoto, A.; Koft, E. R.; Balkovec, J. M.; Tata, J. R.; Dake, G. R. *J. Am. Chem. Soc.* **2001**, *123*, 3239.

(10) Jarco, S. *Quinine's Predecessor*: *Francesco Torti and the Early History of Cinchona*; Johns Hopkins University Press: Baltimore, 1993. Molyneux, M. In *Conn's Current Therapy*; Rakel, R. E., Ed.; W. B. Saunders Co.: Philadelphia, 1998. McHale, D. *The Biologist* **1986**, *33*, 45. Smit, E. H. D. *Acta Leidnesia* **1987**, *55*, 21. Warhurst, D. C. *Acta Leidnesia* **1987**, *55*, 53. White, N. J. *Acta Leidnesia* **1987**, *55*, 65. Wernsdorfer, W. H. *Acta Leidnesia* **1987**, *55*, 197. L'Estrange Orme, M. *Acta Leidnesia* **1987**, *55*, 77. Malcolm, A. D.; David, G. K. *Acta Leidnesia* **1987**, *55*, 87.

(11) Wijnberg, H. In *Topics in Stereochemistry*; Eliel, E. L., Wilen, S. H., Allinger, N. L., Eds.; Wiley: New York, 1986; Vol. 16, p 87. Kolb, H. C.; Van Nieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483.

in good diastereo- and enantioselectivity. The mechanism of this reaction was elucidated and found to consist of matched ionization, π-allyl equilibration, and then matched nucleophilic attack. This method provides the first catalytic enantioselective synthesis of quinuclidinones.

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Supporting Information Available: Experimental procedures and spectroscopic characterization (IR, ^{1}H, ^{13}C NMR, HRMS) of all key compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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