Asymmetric Synthesis

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Enantioselective Palladium(0)-Catalyzed Nazarov-Type Cyclization**

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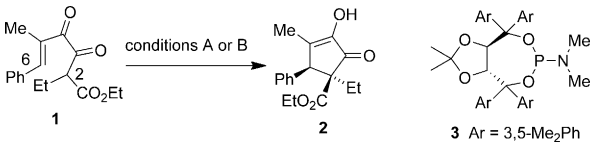
Abstract: *A Pd^0-catalyzed asymmetric Nazarov-type cyclization is described. The optimized ligand for the reaction incorporates a weakly coordinating pyridine ring into a TADDOL-derived phosphoramidite (TADDOL = α,α,α,α-tetraaryl-1,3-dioxolane-4,5-dimethanol). The reaction leads to the formation of cyclopentenones as single diastereoisomers that incorporate two contiguous asymmetric centers, one tertiary and one an all-carbon-atom quaternary stereocenter, in high yield and optical purity. It is noteworthy that the reaction does not require that substrates should be activated by aryl substituents.*

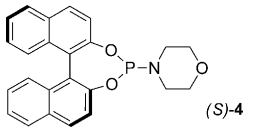
The acid-catalyzed Nazarov cyclization[1] and its asymmetric version[2] are valuable tools for synthesis.[3] Our interest in the variants of this reaction[4] led us to design diketoesters typified by **1** (Scheme 1).[2e] Complementary polarization of the terminal carbon atoms at the C2 and C6 positions is known to accelerate the cyclization.[5] It was therefore not surprising that the enol derivatives of diketoesters related to **1** were excellent substrates for the Brønsted acid catalyzed Nazarov cyclization.[2a,e] It was surprising that **1** also underwent efficient cyclization to form **2** under neutral conditions with a catalytic quantity of Pd^0.[6] Control experiments had excluded the possibility that adventitious Brønsted acid or traces of Pd^{II} had led to the reaction.[4g] We recently described the racemic version of this reaction and one example of the asymmetric case. In the presence of TADDOL-derived phosphoramidite ligand **3** (TADDOL = α,α,α,α-tetraaryl-1,3-dioxolane-4,5-dimethanol), the Pd^0-catalyzed cyclization led to the formation of **2** in 84% yield and 80.5:19.5 e.r.[6] The absolute stereochemistry of **2** was determined by comparison with a sample prepared in earlier work and validated by X-ray crystallographic analysis.[2e]



1 2 3 Ar = 3,5-Me_2Ph

Scheme 1. Pd^0-catalyzed cyclizations. Conditions A: [$Pd_2(dba)_3$] (1 mol%), PPh_3 (4 mol%), DMSO (0.2 M), 60 °C, 4.5 h; 91% yield. Conditions B: [$Pd_2(dba)_3$] (10 mol%), **3** (25 mol%), MeCN (0.06 M), RT, 2.5 h; 84% yield, 80.5:19.5 e.r. DMSO = dimethyl sulfoxide. dba = dibenzylideneacetone.

Our goals were to first optimize the enantioselectivity of the reaction and then to define the reaction scope. Since we lacked a mechanistic hypothesis we initiated our study by screening chiral diphosphine ligands, using the cyclization of **1** to **2** to evaluate catalysts. The results were disappointing. Of nearly 25 diphosphines evaluated, often in several different solvents, none led to the formation of **2** in greater than 23% *ee*.[7] All reactions were slow at RT with half-lives of days or weeks. The first encouraging result was obtained with monodentate phosphoramidite (MonoPhos) (*S*)-**4**, whose use



(*S*)-**4**

as the ligand led to the formation of **2** in 32% *ee*.[8] Significantly, this reaction was complete in less than 24 h with Pd^0 (20 mol%) and a 1:1 P:Pd ratio. In total, nine commercially available, BINOL-derived MonoPhos[9] ligands were evaluated (BINOL = 1,1′-bi-2-naphthol), and although none matched (*S*)-**4** in terms of asymmetric induction, the reactions were rapid in each case. We therefore focused on phosphoramidites.

TADDOL-derived phosphoramidites are attractive because of the ease of their synthesis from inexpensive tartrate.[10] We assumed that ligand optimization would be straightforward because the aryl group, amine, and acetal substituents can be varied independently to provide diverse ligands. We quickly discovered that changes in two components of the ligand, each of which improved performance, were not additive. Even though TADDOL ligands have been shown to be exceptionally versatile in catalysis, to date there is little information available to guide their rational design.[11] We ascertained that the amine group was the strongest modulator of asymmetric induction and so we focused attention on it. Preliminary screening revealed that ligand **5** (Table 1) was effective in transferring asymmetry. We designed ligand **6** by hypothesizing that limiting the degrees of rotational freedom about the Pd–P axis in the mono-

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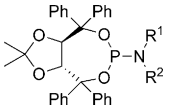
Table 1: Phosphoramidite ligands for the cyclization of **1** to form **2**.[a]



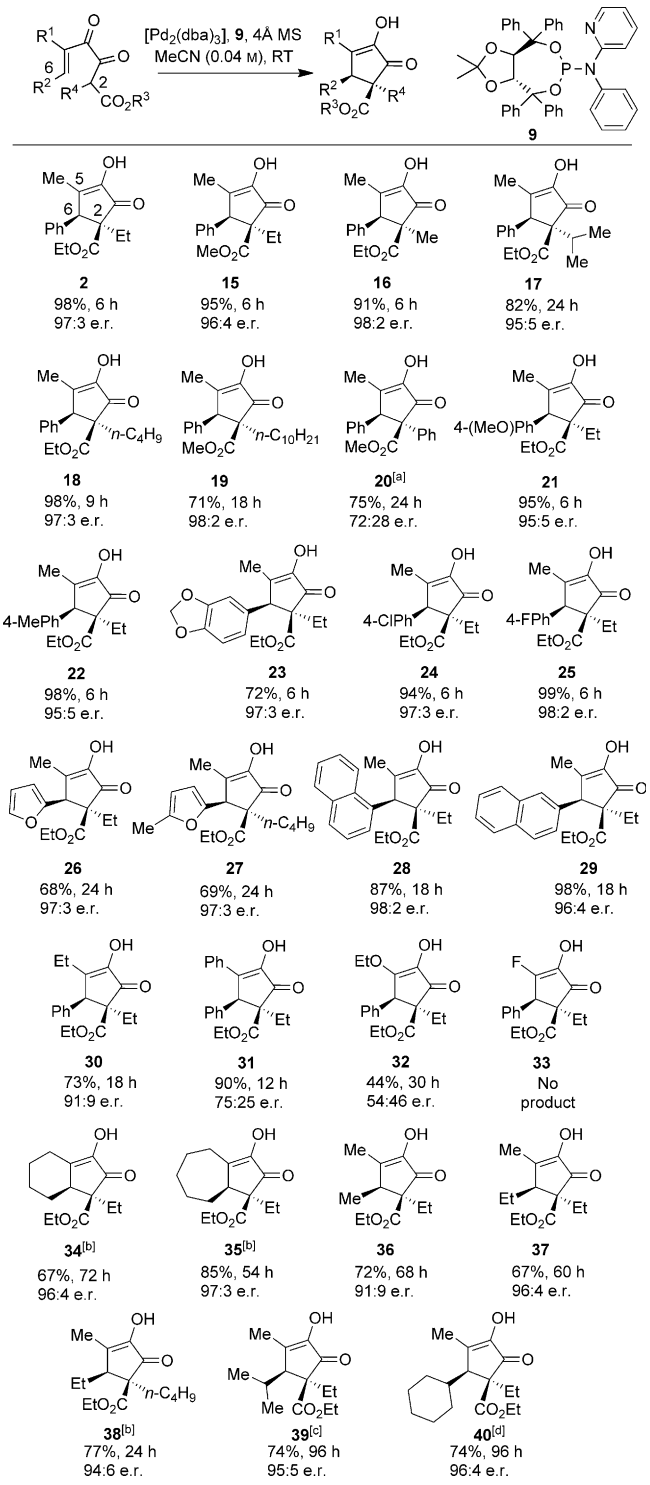
Entry	ligand	R^1	R^2	e.r. of **2**
1	**5**	Me	Me	72:28
2	**6**	Me	2-pyridyl	88:12
3	**7**	Me	Ph	60:40
4	**8**	Ph	Ph	60:40
5	**9**	Ph	2-pyridyl	97:3
6	**10**	2-pyridyl	2-pyridyl	79:21
7	**11**	Me	2-quinolyl	77:23
8	**12**	H	2-pyridyl	73:27[b]
9	**13**	Ph	3-pyridyl	61:39
10	**14**	Ph	4-pyridyl	63:37

[a] All reactions were performed according to conditions B, Scheme 1. [b] The ligand was poorly soluble in neat MeCN and was screened in 5:1 $MeCN:CH_2Cl_2$.

dentate metal–ligand complex would result in improved asymmetry transfer. Since strongly coordinating diphosphines were poorly reactive catalysts, a pyridyl nitrogen atom in ligand **6** provides a second weak coordination site.[12,13] Ligand **6** led to a large improvement in asymmetric induction, leading to the formation of **2** in 88:12 e.r., whereas **7** and **8** were not promising, both leading to the product in 60:40 e.r (Table 1, entries 2–4). These results suggested that the pyridyl nitrogen atom rather than the aromatic ring was important. Phosphoramidite **9** proved to be even better than **6**, leading to **2** in 97:3 e.r., and was chosen for all work. A few of the other ligands that were screened are shown in Table 1. Ligands **13** and **14** in which R^2 is a 3- or a 4-pyridyl group, respectively, gave results that were similar to **8** in which R^2 is phenyl which, like **13** and **14**, does not provide a second coordination site, lending support to our hypothesis for the role of the pyridine nitrogen atom.

The reaction solvent exerted a large influence on both the enantioselectivity as well as the reaction rate.[14] Acetonitrile was shown to be the best solvent whereas propionitrile was poor. Modest amounts of water were deleterious to both yield and enantioselectivity. In the presence of 2 g mmol^{-1} powdered 4 Å molecular sieves (MS) a nearly quantitative yield of **2** was formed with 97:3 e.r. in less than 6 h. In the absence of the sieves the reaction was complete in 20 h and led to the formation of **2** in 66% yield with 97:3 e.r. Other dehydrating agents did not lead to rate acceleration or to improvement of the yield.[15] The catalyst load was decreased to Pd^0 (5 mol%) and **9** (7.5 mol%), and the scope of the cyclization was examined (Scheme 2).[16]

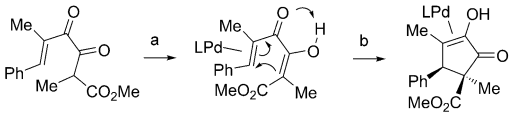
Large aliphatic groups at the C2 position were well tolerated (**17**–**19**), although the time to completion increased with the size of the C2 substituent. A phenyl group at the C2 position (**20**) resulted in a long reaction time and 72:28 e.r. Also, the use of ligand **6** in place of **9** led to the formation of **20** in 90:10 e.r., which suggests an unfavorable competing π-stacking interaction between one of the phenyl groups of the ligand with the C2-phenyl substituent. Cyclization was successful in the case of electron-rich (**21**–**23**, **26**, **27**) as well as electron-poor (**24**, **25**) aromatic moieties at the C6 position. The preparation of α- and β-naphthyl derivatives **28** and **29**, respectively, indicates that steric bulk at C6 is well tolerated.



Scheme 2. Cyclization products with yields, completion times, and e.r. values. Unless otherwise noted, reaction conditions were as described in the Experimental Section. [a] Using ligand **5**, 82:18 e.r. (91%). With ligand **6**, 90:10 e.r. (77%). [b] $[Pd_2(dba)_3]$ (5 mol%) and **9** (15 mol%). [c] $[Pd_2(dba)_3]$ (15 mol%) and **9** (40 mol%). [d] $[Pd_2(dba)_3]$ (20 mol%) and **9** (50 mol%).

Replacing the methyl group in **2** at the C5 position by an ethyl group (giving **30**) resulted in small decreases in optical purity and yield and an increase in the time to completion. Placement of a phenyl group at the C5 position led to a further decrease of the optical purity of product **31**. An ethoxy substituent at C5 led to nearly racemic product **32** whereas no cyclization was detected when a fluorine substituent was placed at the C5 position (**33**). Aryl substitution at C6 is not necessary to activate the cyclization, as cyclopentenones **34**–**40** demonstrate. The times to completion are, however, much longer for the all-aliphatic products, necessitating a heavier catalyst load (**34**–**35** and **38**–**40**).

Based on our preliminary results from ongoing mechanistic studies using DFT calculations,[17,18] we propose the following mechanistic pathway: a) coordination of Pd to the alkene group of the substrate[19] followed by enol tautomerization of the diketoester; b) concerted proton transfer from the enol to the carbonyl with the formation of a Pd–π-allyl complex and intramolecular nucleophilic attack to form the C–C bond (Scheme 3). The stereochemistry determining step



Scheme 3. Proposed mechanism.

is the one in which the initial coordination of Pd takes place to one of the two enantiofaces of the alkene. The P atom and the pyridyl N atom of the ligand occupy the remaining two coordination sites on the Pd center.

The points of closest contact between catalyst and bound substrate are between the pyridyl group of the ligand and the C6 Ph and the C5 Me groups, and also between one Ph group of the TADDOL ligand and the C2 Me group (Figure 1).[18]

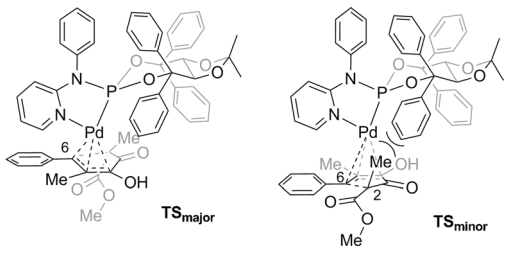


Figure 1. The key steric interactions between the TADDOL phosphoramidite ligand, the metal, and the substrate.

The latter point of contact is essential for controlling the stereochemical outcome as one Ph group of the ligand gets in the way of the Me group at the C2 position during the cyclization leading to formation of the minor enantiomeric product. To the best of our understanding, chirality transfer from the ligand/metal complex to the product can be rationalized by this interaction between the Me group at the C2 position and one of the Ph groups on the ligand.

The solvation-corrected energy of the transition state leading to the major enantiomer was calculated to be 3.2 kcal mol^{-1} lower than that leading to the formation of the minor enantiomer. Further mechanistic studies will be reported in a separate manuscript.

We have described a catalytic asymmetric Nazarov-type cyclization that takes place under neutral conditions. The products are formed in 44–99% yield with up to 98:2 e.r. Yields and optical purities are generally high. Two contiguous asymmetric centers, one tertiary and one an all-carbon-atom quaternary stereocenter, are formed. All products were isolated as single diastereoisomers. Activation of the substrate through aryl substitution at the C6 position is not required but is beneficial to the rate of the reaction. We expect that the reaction described herein will be part of a larger family of metal-mediated Nazarov-type cyclizations. For example, when [Ni(cod)$_2$] (cod = 1,5-cyclooctadiene) was used in place of [Pd$_2$(dba)$_3$] in the reaction described in the Experimental Section, racemic **2** was formed as a single diastereoisomer.

Experimental Section

A mixture of [Pd$_2$(dba)$_3$] (6 mg, 6 μmol, 2.5 mol%), phosphoramidite **9** (12 mg, 18 μmol, 7.5 mol%), and activated 4 Å MS (480 mg, 2 g mmol^{-1}) in MeCN (5 mL) was stirred for 10 min at RT under argon. To this mixture was added a solution of diketoester **1** (69 mg, 0.24 mmol) in MeCN (1 mL). After stirring for 6 h at RT, the mixture was filtered through celite and the volatiles were removed under vacuum. The product was purified by silica-gel column chromatography (hexane:EtOAc = 85:15) to produce **2** (68 mg, 98%, 97:3 e.r.) as a colorless oil.[2e]

Keywords: asymmetric synthesis · cyclization · enantioselectivity · palladium · TADDOLs

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