Asymmetric Catalysis

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Enantioselective Synthesis of 2,2-Disubstituted Tetrahydrofurans: Palladium-Catalyzed [3+2] Cycloadditions of Trimethylenemethane with Ketones**

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Found throughout nature and in synthetic products, tetrahydrofurans are a ubiquitous structural motif with wide-reaching biological activity. Among the many approaches towards their synthesis,[1] cycloaddition represents a powerful and attractive strategy,[2] but catalytic enantioselective variants remain rare.[3,4] We recently disclosed one such approach involving the palladium-catalyzed cycloaddition of trimethylenemethane (TMM) with aldehydes.[4c] Herein, we describe the surprising success of this method in reactions with aromatic ketones, a substrate class which was previously unknown in Pd/TMM reactions using achiral ligands.

First discovered over 30 years ago,[5] the palladium-catalyzed TMM cycloaddition is a versatile method for the synthesis of five-membered rings.[6] The recent discovery that bulky phosphoramidites are effective chiral ligands has stimulated a fresh examination of Pd/TMM chemistry, thus leading to highly enantio- and diastereoselective cycloadditions with olefins,[7] imines,[8] and tropones.[9] A hallmark of the phosphoramidites used in these studies is an improved catalytic activity when compared to the achiral ligands used previously, thus allowing reactions with highly substituted acceptors such as tetrasubstituted olefins[7b] and ketimines[8b,c] under mild reaction conditions. However, these substrates required a TMM precursor bearing a cyano group to obtain high *ee* values.[10] Given our earlier success with cycloadditions of aldehydes, we wondered whether more complex and less reactive carbonyl groups might also function in the asymmetric TMM cycloaddition, despite the fact that racemic reactions with ketones are relatively challenging and quite limited.[11,12] The reduced reactivity of the ketone coupled with the presence of relatively acidic protons[13] undoubtedly prevents a more general synthetic scope. Further, aliphatic aldehydes were not tolerated under the asymmetric reaction conditions, presumably because of the presence of α protons. An additional challenge involves enantioselectivity, since enantioface differentiation of ketones was expected to be more difficult than with the corresponding aldehydes. Nevertheless, such a reaction would provide rapid access to enantioenriched 2,2-disubstituted tetrahydrofurans, an important structural component[14] that is found, for example, in the antifungal drug posaconazole (**1**, Figure 1).[15]

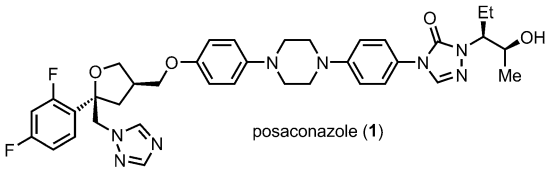
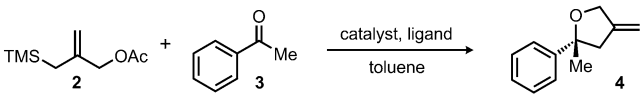


Figure 1. Structure of the antifungal agent posaconazole (**1**).

Despite these concerns, initial tests using acetophenone under our previously optimized reaction conditions[4c] were encouraging, thus giving the desired cycloadduct **4** in moderate yield but with a reasonable *ee* value (Table 1, entry 1; see Figure 2 for ligand structures). Notably, the enantioselectivity was roughly equivalent to that obtained in the reaction of benzaldehyde, although the yield was significantly lower. Also consistent with our earlier study, a Lewis acid cocatalyst was not required (entry 2). While the product obtained from these reactions was qualitatively clean as judged by ^{1}H NMR

Table 1: Initial optimization of reaction conditions with acetophenone.



Entry[a]	Catalyst	Ligand	*T* [°C]	Yield [%]	*ee* [%]
1[b]	[Pd(dba)$_2$]	**L1**	50	48	80[c]
2	[Pd(dba)$_2$]	**L1**	50	60	84[c]
3	[CpPd(η^3-C$_3$H$_5$)]	**L1**	50	91	78
4	[CpPd(η^3-C$_3$H$_5$)]	**L1**	23	70	80
5[d]	[CpPd(η^3-C$_3$H$_5$)]	**L1**	50	50	78
6	[CpPd(η^3-C$_3$H$_5$)]	**L2**	50	$<$20	71
7	[CpPd(η^3-C$_3$H$_5$)]	**L3**	50	$<$20	55
8	[CpPd(η^3-C$_3$H$_5$)]	**L4**	50	0	–

[a] All reactions were conducted using 5 mol% Pd catalyst, 10 mol% ligand, and 1.6 equiv of **2** at 0.15 M in toluene unless stated otherwise. Yields are for isolated products. The *ee* values were determined by HPLC using a chiral stationary phase. [b] Reaction conducted in the presence of 10 mol% [In(acac)$_3$]. [c] A minor impurity in the HPLC trace prevented an accurate determination of the *ee* value. [d] Used only 5 mol% **L1**. acac = acetylacetonate, Cp = cyclopentadiene, TMS = trimethylsilyl.

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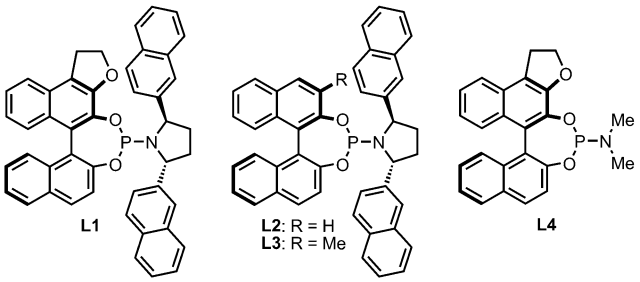


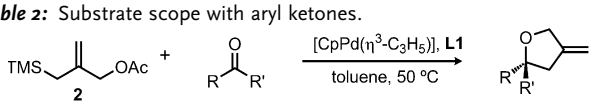
Figure 2. Ligands used during optimization of reaction conditions.

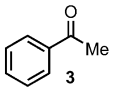
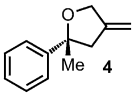
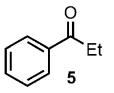
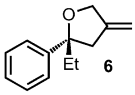
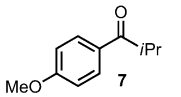
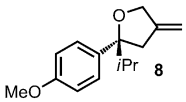
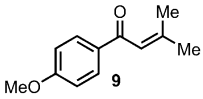
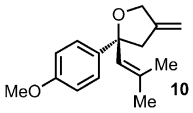
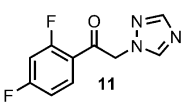
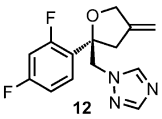
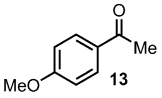
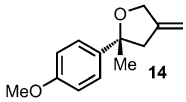
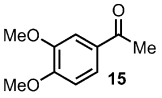
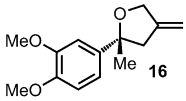
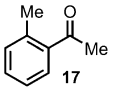
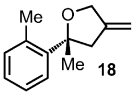
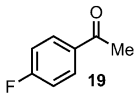
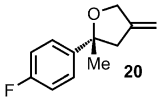
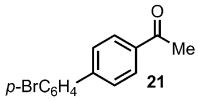
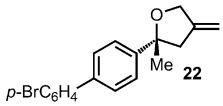
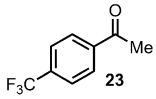
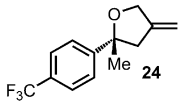
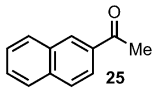
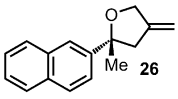
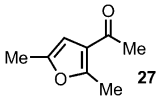
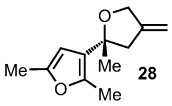
spectroscopy, the HPLC traces contained a small impurity which prevented an accurate determination of the *ee* value. Reasoning that this impurity might stem from competitive cycloaddition with dibenzylideneacetone (dba), we explored alternative palladium sources. Gratifyingly, [CpPd(η^3-C_3H_5)] not only gave an improved purity profile, but also provided the desired product in 91% yield (entry 3). The reaction temperature could be reduced to 23°C (entry 4), and a slight loss in yield and no significant improvement in the *ee* value indicated that reaction at 50°C would be preferred. Finally, cutting the amount of ligand in half produced a commensurate reduction in yield (entry 5). While the yield was modest, the observation that the selectivity remained unchanged provides the first experimental evidence that the Pd/ligand ratio in the active catalyst may be 1:1.

We briefly examined other ligands under these optimized reaction conditions, but found that **L1** is remarkably unique in both catalytic activity and enantioselectivity. For example, while the parent phosphoramidite **L2** gave a slight decrease in *ee* value, the product was formed in very poor yield, with unreacted starting material as the predominant species (entry 6). Simple 3-substituted binol derivatives such as **L3** are likewise insufficient (entry 7). Finally, employing the dimethylamine-derived phosphoramidite **L4** gave a completely inactive catalyst (entry 8).

Having identified optimized reaction conditions, we next evaluated the scope of the transformation (Table 2). Surprisingly, reactions of ketones with larger aliphatic substituents, such as propiophenone (entry 2) and 4′-methoxyisobutyrophenone (entry 3), gave slightly better *ee* values than the corresponding acetophenone derivatives. Chemoselective reaction with the carbonyl group of an enone was also possible. Reaction of the isobutenyl ketone **9** at 50°C provided a 16:47:25 mixture of the bis(cycloadduct), tetrahydrofuran, and cyclopentane, respectively. Since the bis(cycloadduct) necessarily arises by initial cycloaddition with the olefin, this result constitutes only a slight preference for cycloaddition with the carbonyl group under these reaction conditions. However, the tetrahydrofuran was isolated in 60% yield and 82% *ee* when the reaction was conducted at room temperature (entry 4), along with the cyclopentane in 20% yield and 79% *ee* and no detectable presence of the bis(cycloadduct). The chemoselectivity in this example, while relatively modest, is impressive considering that reactions of enones employing **L2** provided exclusive reaction with the olefin.[7c] Compared to previously reported multistep synthe-

Table 2: Substrate scope with aryl ketones.



Entry[a]	Substrate	Product	Yield [%]	*ee* [%]
1[b]			70	80
2			71	86
3			88	95
4[b,c]			60	82
5			69	47 (87)[d]
6			74	89
7			96	94
8			60	86
9			68	88
10			87	83
11			71	78
12			77	92
13			62	87

[a] All reactions were conducted for 3 h at 0.15 M in toluene at 50°C with 1.6 equivalents **1**, 5 mol% [CpPd(η^3-C_3H_5)], and 10 mol% **L1** unless stated otherwise. Yields are for isolated products. The *ee* values were determined by HPLC using a chiral stationary phase. [b] Reaction conducted at 23°C for 24 h. [c] Used 3.0 equivalents of **1**. [d] The *ee* value obtained after a single recrystallization. The overall yield after recrystallization was 31% from **11**.

ses of the 2,2,4-trisubstituted tetrahydrofuran core of posaconazole (**1**),[16] rapid access was obtained by employing the commercially available triazolyl derivative **11** (entry 5). While the selectivity was modest, the *ee* value was improved to 87% after a single recrystallization, thus providing the cycloadduct **12** in 31% overall yield from **11**.

The reaction also proved to be relatively insensitive to the aromatic portion of the ketone, including substitution pattern and electronic nature of the substituent (Table 2, entries 6–12). Heterocycles were also tolerated (entry 13). An X-ray crystal structure of **22** unambiguously allowed the determination of the absolute stereochemistry (Figure 3). It should be noted that the sense of chirality is consistent with that observed in both aldehyde and nitroalkene cycloadditions.[4,7d]

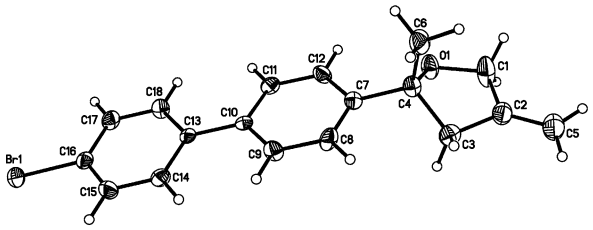


Figure 3. X-ray-based ORTEP drawing of cycloadduct **22**. Thermal ellipsoids are drawn at the 50% probability level.

The unique efficiency of **L1** in this transformation remains impressive. Because the binol derivative in **L1** is unsymmetric, the ligand is chiral at phosphorus (R_P and S_P). In our previous work,[4] we found that only a single diastereomer of **L1** was active. Thus, the chirality at phosphorus serves as a unique control element for the reactivity of the catalyst, a phenomenon which to the best of our knowledge has not been previously described in the chemical literature. By appropriate selection of the reaction conditions,[4] we were able to synthesize **L1** in $<1:>20$ d.r., and the major (and active) diastereomer appears to possess the R,R,R,S_P configuration based on its ^{31}P NMR spectrum, since the major signal (at $\delta =$ 144.2 ppm) appears upfield of the minor signal (at $\delta =$ 148.0 ppm).[17] Although we were unsuccessful in crystallizing **L1** directly, this assignment is corroborated by X-ray crystal analysis of **L4** (see the Supporting Information), which clearly depicts the S_P configuration and also shows the major diastereomer (at $\delta = 148.9$) upfield of the minor diastereomer (at $\delta = 149.6$) in the ^{31}P NMR spectrum.

For a possible explanation as to why only the S_P isomer of **L1** is catalytically active, we performed AM1 semi-empirical calculations using Spartan to determine the lowest-energy conformations for the respective diastereomers. The results suggest that the ground-state geometries are substantially different, and that only the S_P isomer is poised to achieve secondary bonding interactions between the palladium metal and a naphthyl group from the pyrrolidine,[18] as has been previously observed in π-allylpalladium/phosphoramidite complexes.[19] The need for such interactions would be in accordance with the observation that **L4** is unreactive in the present system. The models also suggest that the oxygen atom of the dihydrofuran may form a secondary interaction with the palladium, which may help explain the improved catalytic performance of **L1** relative to **L2**. These secondary interactions should also favor the formation of a monoligated palladium/phosphoramidite complex, as was hypothesized from the optimization studies (Table 1).

In summary, we have demonstrated a novel palladium-catalyzed [3+2] cycloaddition of trimethylenemethane with ketones. This reaction demonstrates novel reactivity which has not been previously observed and provides access to highly enantioenriched tetrahydrofurans bearing a tetrasubstituted stereocenter. An example utilizing an α,β-unsaturated ketone also demonstrates a modest preference (3:1) for reaction with the carbonyl group. A critical factor enabling this reaction was the development of a C_1-symmetric phosphoramidite which demonstrates uniquely high activity under these reaction conditions, wherein the epimer at phosphorus relative to the chiral scaffold that was uniquely reactive was identified as the R,R,R,S_P isomer.

Experimental Section

Representative procedure for the synthesis of (*R*)-2-(4′-bromobiphenyl-4-yl)-2-methyl-4-methylenetetrahydrofuran (**22**): Toluene (1.0 mL) was added to an argon-purged vial of 4-acetyl-4′-bromobiphenyl (41.3 mg, 0.15 mmol), [CpPd(η^3-C_3H_5)] (1.6 mg, 0.0075 mmol), and **L1** (10.2 mg, 0.015 mmol) and the solution stirred for 2 min before 2-[(trimethylsilyl)methyl]allyl acetate (50 μL, 0.24 mmol) was added. The vial was immediately immersed in an oil bath set to 50 °C and stirred for 3 h. It was then purified directly by flash chromatography (4% ethyl acetate in hexanes) to give a white solid (42.7 mg, 87% yield). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.55$–7.43 (m, 8H), 4.97 (quintet, $J = 2.2$ Hz, 1H), 4.87 (quintet, $J = 2.2$ Hz, 1H), 4.51 (d, $J = 13.4$ Hz, 1H), 4.39 (d, $J = 13.4$ Hz, 1H), 2.94 (d, $J =$ 15.3 Hz, 1H), 2.77 (d, $J = 15.3$ Hz, 1H), 1.57 ppm (s, 3H). ^{13}C NMR (100 MHz, CDCl3): $\delta = 148.2$, 146.4, 140.1, 138.7, 132.2, 128.9, 127.1, 125.8, 121.7, 105.1, 84.8, 70.4, 46.4, 29.4 ppm. IR (thin film): $\tilde{\nu} =$3074, 2911, 2857, 1662, 1429, 1384 cm^{-1}. $[\alpha]_{23}^{D} = -43.2$ ($c = 1.70$, $CHCl_3$). HPLC: Chiralpak AD-H, 0.8 mL min^{-1}, 1% *i*PrOH in heptane, $\lambda =$ 254 nm, $t_{R,minor} = 9.1$ min, $t_{R,major} = 12.4$ min. Elemental analysis (%): calcd for $C_{18}H_{17}BrO$: C 65.67, H 5.20, Br 24.27; found: C 65.42, H 5.47, Br 24.37.

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