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

Prof. Barry M. Trost and Dr. Dustin A. Bringley

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

Barry M. Trost: bmtrost@stanford.edu

Abstract

An approach to 2,2-disubstituted 4-methylenetetrahydrofurans has been developed utilizing a cycloaddition of trimethylenemethane with aryl ketones, with formation of the products in up to 96% yield and 95% ee. The reaction is catalyzed by palladium in the presence of a phosphoramidite ligand possessing a stereogenic phosphorus, where only a single epimer at phosphorus yields the active catalyst. The identity of this epimer and the origin of its effect on reactivity are discussed.

Keywords

trimethylenemethane cycloaddition; tetrahydrofuran synthesis; asymmetric catalysis; phosphoramidite

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] In this Communication, we describe the surprising success of this method in reactions with aromatic ketones, a substrate class that 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 5-membered rings.^[6] The recent discovery that bulky phosphoramidites are effective chiral ligands has stimulated a fresh examination of Pd-TMM chemistry, 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

Correspondence to: Barry M. Trost, bmtrost@stanford.edu.

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previously, allowing for reactions with highly substituted acceptors such as tetrasubstituted olefins^[7b] and ketimines^[8b,c] under mild conditions. However, these substrates required a TMM precursor bearing a cyano group in order to obtain high ee.^[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 conditions, presumably due to 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]

Despite these concerns, initial tests using acetophenone under our previously optimized conditions^[4c] were encouraging, giving the desired cycloadduct **4** in moderate yield but with reasonable ee (Table 1, entry 1). 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 co-catalyst was not required (entry 2). While the product obtained from these reactions was qualitatively clean as judged by ¹H NMR, the HPLC traces contained a small impurity that prevented an accurate determination of ee. Reasoning that this impurity might stem from competitive cycloaddition with dibenzylideneacetone (dba), we explored alternative palladium sources. Gratifyingly, CpPd(η^3 -C₃H₅) 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), although a slight loss in yield and no significant improvement in ee 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 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, 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 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 than the corresponding acetophenone derivatives. Chemoselective reaction with the carbonyl group of an enone was also possible. Reaction of 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 under these 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 multi-step syntheses of the 2,2,4-trisubstituted tetrahydrofuran core of posaconazole (**2**),^[16] rapid access was obtained by employing commercially available triazolyl derivative **11** (entry 5). While the selectivity was modest, the ee could be improved to 87% after a single recrystallization, providing cycloadduct **12** in 31% overall yield from ketone **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 (entries 6–12). Heterocycles were also tolerated (entry 13). An X-ray crystal structure of **22** unambiguously allowed the determination of 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]

The unique efficiency of ligand **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 conditions,^[4] we were able to synthesize **L1** in <1:>20 dr; the major (and active) diastereomer appears to possess the *R,R,R,S_P* configuration based on its ³¹P NMR spectrum, since the major signal (at δ 144.2 ppm) appears upfield of the minor signal (at δ 148.0 ppm).^[17] Although we were unsuccessful in crystallizing **L1** directly, this assignment is corroborated by X-ray crystal analysis of ligand **L4** (see supporting information), which clearly depicts the *S_P* configuration and also shows the major diastereomer (at δ 148.9) upfield of the minor diastereomer (at δ 149.6) in the ³¹P 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 that 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 that demonstrates uniquely high activity under these 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)

To an argon-purged vial of 4-acetyl-4'-bromobiphenyl (41.3 mg, 0.15 mmol), $\text{CpPd}(\eta^3\text{-C}_3\text{H}_5)$ (1.6 mg, 0.0075 mmol) and **L1** (10.2 mg, 0.015 mmol) was added toluene (1.0 ml) and the solution stirred for 2 minutes 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 hours. It was then purified directly by flash chromatography (4% ethyl acetate in hexanes) to give a white solid (42.7 mg, 87% yield). ^1H NMR (400 MHz, CDCl_3): δ 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 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3): δ 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. IR (thin film): 3074, 2911, 2857, 1662, 1429, 1384 cm^{-1} . $[\alpha]_{23}^{\text{D}} = -43.2$ (c 1.70, CHCl_3). Chiral HPLC: Chiralpak AD-H, 0.8 mL/min, 1% i-PrOH in heptane, $\lambda = 254$ nm, $t_{\text{R, minor}} = 9.1$ min, $t_{\text{R, major}} = 12.4$ min. EA: calcd for $\text{C}_{18}\text{H}_{17}\text{BrO}$: 65.67% C, 5.20% H, 24.27% Br; found 65.42% C, 5.47% H, 24.37% Br.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1.
Structure of the antifungal agent posaconazole.

Figure 2.
Ligands used during optimization.

Figure 3.
X-ray-based ORTEP drawing of cycloadduct **19**. Spheres are drawn at the 50% probability level.

Table 1

Initial optimization 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 isolated values; ee's were determined by chiral HPLC.

^[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 ee.

^[d] Used only 5 mol% **L1**.

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

Entry ^[a]	Substrate	Product	% yield	% ee
9			68	88
10			87	83
11			71	78
12			77	92
13			62	87

^[a] All reactions were conducted using for 3 hours at 0.15 M in toluene at 50 °C with 1.6 equivalents **1**, 5 mol% CpPd(η^3 -C₃H₅) and 10 mol% **L1** unless stated otherwise. Yields are isolated values; ee's were determined by chiral HPLC.

^[b] Reaction conducted at 23 °C for 24 hours.

^[c] Used 3.0 equivalents of **1**.

^[d] Ee obtained after a single recrystallization, in 31% overall yield from **11**.