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High-Throughput Screening of the Asymmetric Decarboxylative Alkylation Reaction of Enolate-Stabilized Enol Carbonates

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Abstract

The use of high-throughput screening allowed for the optimization of reaction conditions for the palladium-catalyzed asymmetric decarboxylative alkylation reaction of enolate-stabilized enol carbonates. Changing to a non-polar reaction solvent and to an electron-deficient PHOX derivative as ligand from our standard reaction conditions improved the enantioselectivity for the alkylation of a ketal-protected,1,3-diketone-derived enol carbonate from 28% ee to 84% ee. Similar improvements in enantioselectivity were seen for a β-keto-ester derived- and an α-phenyl cyclohexanone-derived enol carbonate.

Keywords

asymmetric catalysis; high-throughput screening; palladium; ligands; solvent effect

New methods for the construction of highly substituted carbocycles with defined stereochemistry are important for the synthesis of natural products and pharmaceutical agents.[1] Although automation is well-established within the pharmaceutical industry for the rapid synthesis of new chemical entities, identification of biological activity via screening, and process optimization,[2] less work has been performed within the academic community utilizing automation.[3] Similarly, the identification of efficient catalysts and their associated optimized reaction conditions, which cannot usually be predicted, often necessitates high-throughput methods to perform the required time- and labor-intensive screening.[4] Herein we report the optimization of the Pd-catalyzed, asymmetric decarboxylative alkylation[5] of enolate-stabilized enol carbonates for the synthesis of all-carbon quaternary stereocenters through automated high-throughput screening of reaction conditions.

Enol carbonate **1**, derived from 2-methyl cyclohexa-1,3-dione, was selected as our substrate for the asymmetric Pd-catalyzed decarboxylative alkylation reaction (Scheme 1). Enol carbonate **1** was synthesized from known mono-ketal **2**[6] via deprotonation with NaH in THF at 60 °C and trapping of the resulting thermodynamic enolate with allyl chloroformate in 69% yield. Interestingly, ketal-opened product **3** was also formed in 12% yield, suggesting that Pd-catalyzed enantioselective formation of the quaternary stereocenter of **4** from **1** may be in competition with ketal-ring opening. Exposure of **1** to our standard decarboxylative alkylation conditions (Pd_2dba_3 and (*S*)-*t*-BuPHOX in THF at 25 °C)[7] resulted in formation of **4**[8] in 62% yield. Allyl ketone **4** required derivatization to ene-dione **5** via Ru-catalyzed metathesis[9] with methyl acrylate and Grubbs' 2nd generation catalyst **6** in order to determine the enantiomeric excess of the product from the asymmetric alkylation reaction.

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Chiral HPLC analysis of **5** showed that the desired quaternary stereocenter-containing product was formed in a poor 28% ee under our standard reaction conditions.

In order to obtain ketone **4** with high levels of enantioselectivity, we conducted high-throughput, parallel screening to determine the required catalyst and reaction conditions. Experiments were conducted in 1 mL vials within 96-well microtiter plates using a Symyx™ Technologies (Santa Clara, CA) Core Module housed in a Braun N_2-filled glovebox. A stock solution of substrate **1** in THF was added to each capped vial charged with Pd_2dba_3 and (*S*)-*t*-BuPHOX in the appropriate solvent(s). After 48 h at 30 °C, the reactions were diluted with hexane and purified via parallel silica gel chromatography using a Code Module housed in a fume hood. The resulting purified alkylated products **4** were subjected to Ru-catalyzed metathesis with excess methyl acrylate to afford **5**, which was then analyzed by chiral SFC for enantiomeric excess. As an initial screen, we investigated enantioselectivity as a function of reaction solvent (Table 1). Modification of our standard reaction conditions to lower catalyst loadings and slightly higher reaction temperature (30 °C) improved enantioselectivity to 40% ee (entry 1) from 28% ee (Scheme 1). Reactions conducted in ethereal and polar solvents (entries 1-6) gave low levels of enantioselectivity. Similarly, polar aromatic solvents gave the poorest ee's (entries 7 and 8). The best enantioselectivities were observed with the use of non-polar aromatic reaction solvents (entries 9 and 10), with the use of hexane as a co-solvent improving enantioselectivity up to 64% ee (entry 12). It is important to note that the use of hexane as the only solvent resulted in no reaction, as the Pd-catalyst precipitated from the reaction mixture.

We believe that the use of a non-polar solvent (mixture) produces a higher affinity between the chiral Pd-center and the intermediate enolate than when the reaction is conducted in polar solvents.[10]

In order to improve enantioselectivity in the asymmetric Pd-catalyzed decarboxylative alkylation of **1** to synthetically useful levels, we performed a screen of various ligands. Our ligand search was biased toward the PHOX ligand class, as these have proven especially effective in related reactions and are readily prepared and modified.[11] The ligands employed in the screen are depicted in Figure 1 and the reactions conducted in THF, diethyl ether, toluene, and a 2:1 mixture of hexane and toluene solvents are shown in Figure 2. The highest levels of enantioselectivity were observed with the use of *t*-BuPHOX ligands (**L1**-**L8**) and with the use of a 2:1 hexane and toluene solvent mixture. Ligand **L9**, which does not possess a phosphine, did not yield product. Similarly, PHOX ligands having a third, hetero-atomic chelating group (**L10**-**L12**) resulted in low yields and very low ee's (< 20% ee). Interestingly, ligand **L13**, the silyl-protected derivative of **L12**, afforded product in 61% ee in the opposite enantiomer of that produced with (*S*)-*t*-BuPHOX, **L1**. Cyclohexyldiamine-derived ligands **L23** and **L24**, which have shown great synthetic use in other asymmetric alkylation reactions,[12] afforded **5** in enantiomeric excesses under 10% ee.[13] Although the sterically encumbered naphthyl- and mesityl-derived phosphines **L5** and **L6** decreased enantioselection, electron-deficient *t*-BuPHOX derivatives **L7** and **L8** gave ee's of 82% and 79%, respectively, in 2:1 hexane and toluene as solvent. Interestingly, the monomethoxylated *t*-BuPHOX derivative **L2** afforded product in only 46% ee in the non-polar solvent mixture, suggesting that ligand electronics greatly affect enantioselection. It is hypothesized that, like the less polar solvent(s) in Table 1, the highly electron-deficient phosphine ligands (**L7** and **L8**) create a more-tightly associated Pd-PHOX ligand complex, resulting in higher enantioselectivities.[7d]

We screened other highly electron-deficient PHOX ligands (Figure 3), as well as re-screened the ligands which gave the highest levels of enantioselectivity within the first ligand screen, in order to test whether even more-highly electron-deficient PHOX-derivatives could improve the enantioselectivity of the Pd-catalyzed decarboxylative alkylation reaction of **1** (Table 2).

The highest levels of enantioselection were achieved with the trifluoromethylated *t*-BuPHOX derivative **L25**11,[14] in the 2:1 hexane and toluene mixture (entry 6). It is not too surprising that ligand **L25** was found to be the best ligand with respect to enantioselectivity, as it has been shown to give the highest levels of enantioselection for the asymmetric alkylation of ketones[15] and for an asymmetric alkylation within the our formal synthesis of hamigeran B.[16]

Simultaneous screening of the enantioselective alkylation of enolate-stabilized enol carbonates **7** and **8** revealed improved enantioselectivities from our standard reaction conditions with the use of electron-deficient ligands in the non-polar hexane and toluene solvent mixture (Scheme 2).[17] Exposure of β-keto ester-derived enol carbonate **7** to the decarboylative alkylation catalyst derived from **L8** in 2:1 hexane and toluene improved the enantioselectivity for the formation of **9**[18] to 71% ee from 24% ee when using (*S*)-*t*-BuPHOX in THF.[17] Similarly α-phenyl cyclohexanone-derived enol cabonate **8** afforded allyl ketone **10**[19] in 51% ee when exposed to the catalyst derived from **L31** in the non-polar solvent mixture, an improvement from 11% ee when (*S*)-*t*-BuPHOX is utilized in THF.[17]

In summary, we have used high-throughput screening for the asymmetric, Pd-catalyzed decarboxylative alkylation reaction of enolate-stabilized enol carbonates to afford quaternary stereocenter-containing products with high levels of enantioselection. The high-throughput screening of various solvents and ligands allowed us to improve the enantioselectivities with the use of a non-polar solvent mixture (2:1 hexanes and toluene) and electron-deficient *t*-BuPHOX derivatives.

Experimental Data

^{1}H and ^{13}C NMR spectra were recorded on a Varian Mercury 300 (at 300 MHz and 75 MHz respectively) and are reported relative to residual $CHCl_3$ (δ 7.26 and 77.0 ppm). IR spectra were recorded on a Perkin Elmer Paragon 1000 spectrometer and are reported in frequency of absorption (cm^{-1}). High-resolution mass spectra were recorded on a Agilent 6200 Series Time-of-Flight LC/MS/TOF system with a Agilent G1978A Multimode source in electrospray ionization (ESI) mode. Analytical chiral HPLC for **5** was performed with an Agilent 1100 Series HPLC utilizing a Chiralcel OD-H column with visualization at 254 nm and a 1 mL/min flow rate of 10% *i*-PrOH/90% hexane. Analytical chiral SFC for **5** was performed with a Mettler supercritical CO_2 analytical chromatography system utilizing a Chiralcel AD-H column with visualization at 254 nm and a 3 mL/min flow rate of 2% *i*-PrOH/2% CH_3CN/96% CO_2.

Representative Screening Procedure

To 1 mL vials in a 96-well microtiter plate was added 59 μL of a Pd_2dba_3 solution (0.0025 M in THF) using a Symyx Core Module within a nitrogen-filled glove box. The Pd_2dba_3 solutions were evaporated to dryness under reduced pressure using a Genevac centrifugal evaporator within the glove box. To the dried vials charged with Pd_2dba_3 was added 113 μL of the desired solvent to be screened and 18.8 μL of the desired ligand solution (0.02 M in THF). To the catalyst solutions, which had been stirred at 30°C for 30 min, was added 30 μL of an enol carbonate **1** solution (0.2 M in THF) and 38 μL of the same solvent to be screened. The reactions were stirred at 30 °C for 48 h. The crude reactions were purified via parallel silica gel chromatography, eluted with hexane: ethyl acetate = 5:1, using a Symyx Core Module within a fume hood. The fractions containing purified **4** were evaporated to dryness using using a Genevac centrifugal evaporator.

To each of the 1 mL vials containing purified **4** was added 50 μL of a methyl acrylate solution (0.9 M in CH_2Cl_2) and 50 μL of a Grubbs' 2nd generation Ru-catalyst **6** solution (0.0055 M in CH_2Cl_2) using a Symyx Core Module within a nitrogen-filled glove box. After stirring at 30

°C for 3 h, the crude reactions were again purified via parallel silica gel chromatography, eluted with hexane: ethyl acetate = 3:1, using a Symyx Core Module within a fume hood. The solutions of purified product **5** were directly subjected to chiral SFC analysis to determine % ee.

Selected Spectroscopic Data

Allyl (6-methyl-1,4-dioxaspiro[4.5]dec-6-en-7-yl) carbonate (1)

^{1}H-NMR (300 MHz, $CDCl_3$) δ 5.95 (dddd, *J* = 18.6, 10.5, 5.7, 5.7 Hz, 1H), 5.38 (ddd, *J* = 18.6, 2.7, 1.5 Hz, 1H), 5.29 (ddd, *J* = 10.5, 2.7, 1.5 Hz, 1H), 4.65 (ap dt, *J* = 5.7, 1.2 Hz, 2H), 3.97-4.03 (m, 4H), 2.20-2.27 (m, 2H), 1.70-1.84 (m, 4H), 1.58 (t, *J* = 1.9 Hz, 3H); ^{13}C-NMR (75.0 MHz, $CDCl_3$) δ 152.1, 147.9, 131.2, 122.7, 118.9, 108.4, 68.6, 65.2, 33.0, 26.7, 19.4, 8.4; IR (thin film) 2952, 2884, 1756, 1700, 1442, 1366, 1346, 1235, 1114, 1036, 993; HRMS (ESI) calculated for $C_{14}H_{19}O_5$ $[M+H]^+$ 255.1227, found 255.1240.

(*E*)-Methyl 4-(6-methyl-7-oxo-1,4-dioxaspiro[4.5]decan-6-yl)but-2-enoate (5)

^{1}H-NMR (300 MHz, $CDCl_3$) δ 6.92 (ddd, *J* = 15.3, 6.9, 6.9 Hz, 1H), 5.80 (d, *J* = 15.3 Hz, 1H), 3.91-3.98 (m, 4H), 3.70 (s, 3H), 2.66 (dd, *J* = 14.7, 6.9 Hz, 1H), 2.39-2.53 (m, 2H), 2.36 (dd, *J* = 14.7, 6.9 Hz, 1H), 1.89-1.94 (m, 2H), 1.73-1.84 (m 2H), 1.16 (s, 3H); ^{13}C-NMR (75.0 MHz, $CDCl_3$) δ 210.8, 166.5, 145.9, 113.1, 65.1, 64.9, 58.1, 51.3, 36.9, 35.8, 29.5, 19.1, 17.1; IR (thin film) 2954, 2890, 1714, 1654, 1436, 1335, 1273, 1177, 1072, 1030; HRMS (ESI) calculated for $C_{14}H_{21}O_5$ $[M+H]^+$ 269.1384, found 269.1382. Chiral HPLC t_{Rmajor}: 25.3 min. $t_{R\ minor}$: 34.6 min. Chiral SFC $t_{R\ major}$: 10.8 min. $t_{R\ minor}$: 11.8 min.

Acknowledgments

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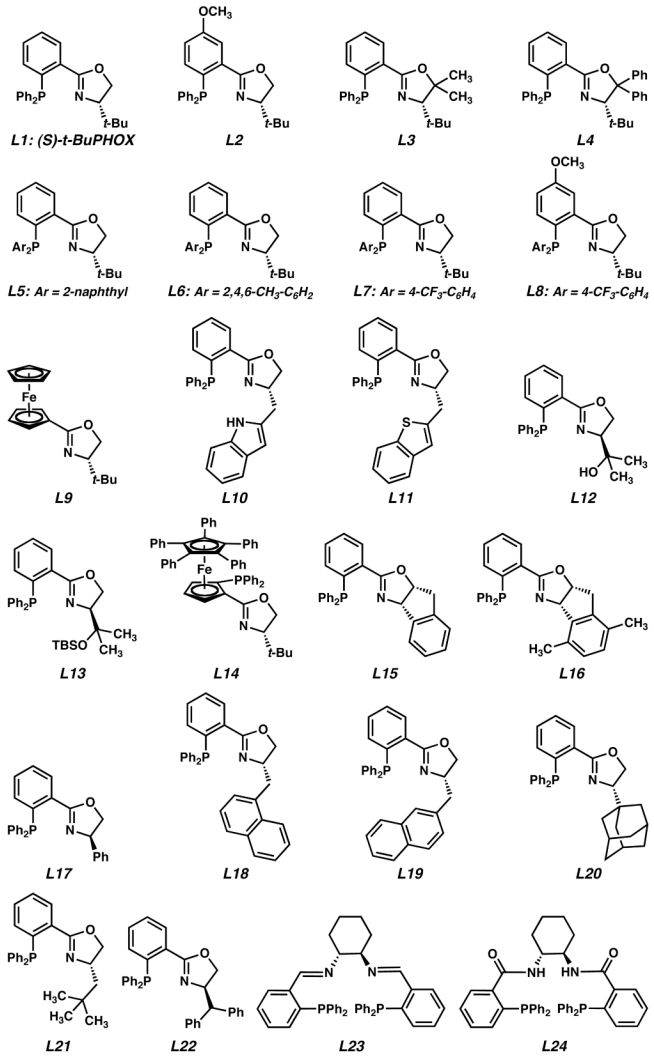


Figure 1.
Ligands screened in the Pd-catalyzed decarboxylative alkylation reaction of **1**

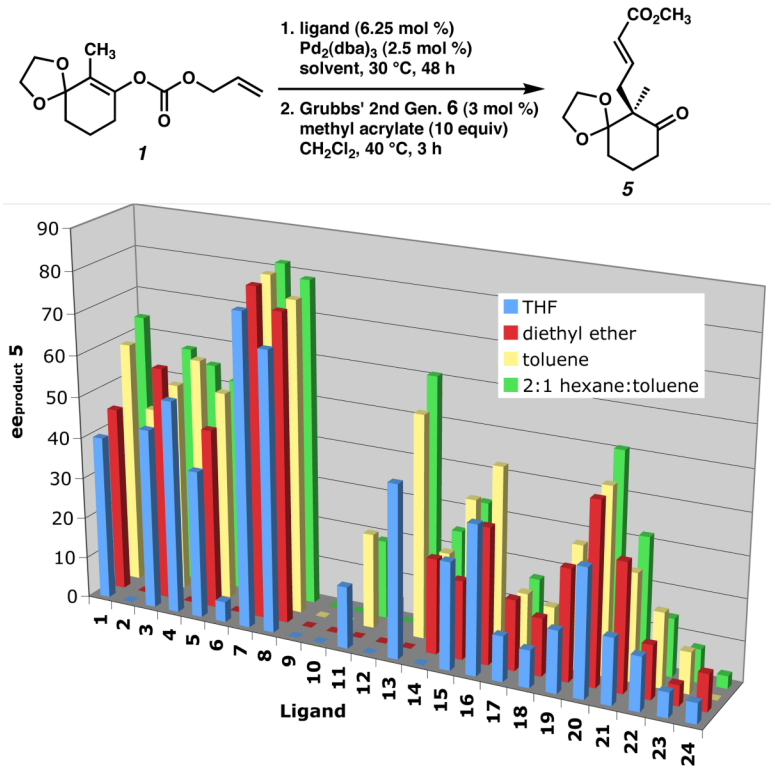


Figure 2.
Dependence of enantiomeric excess of **5** on ligand structure and solvent in the decarboxylative alkylation reaction of **1**

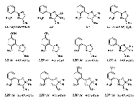
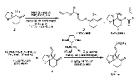
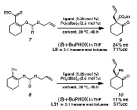


Figure 3.
Ligands screened in the Pd-catalyzed decarboxylative alkylation reaction of **1**



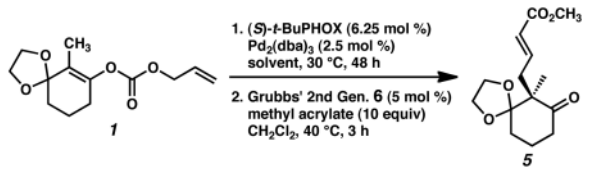
Scheme 1.
Preparation of **5** from **2** via asymmetric decarboxylative alkylation



Scheme 2.
Asymmetric Pd-catalyzed decarboxylative alkylation reactions of enolate-stabilized enol carbonates **7** and **8**

Table 1

Evaluation of Reaction Solvent

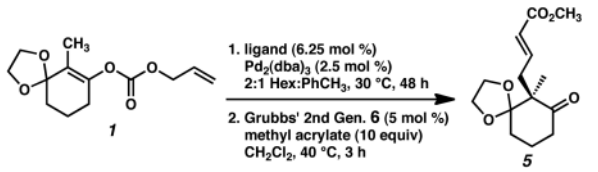


Entry	Solvent	ee (%)[a]
1	THF	40
2	Et_2O	45
3	*t*-$BuOCH_3$	49
4	DME	30
5	*p*-dioxane	21
6	EtOAc	27
7	PhF	19
8	PhCl	19
9	PhH	55
10	$PhCH_3$	59
11	Hex:$PhCH_3$ (1:1)	61
12	Hex:$PhCH_3$ (2:1)	64

[a] Enantiomer excesses determined via chiral SFC analysis of chromatographically-purified product **5**.

Table 2

Evaluation of Reaction Ligands



Entry	Ligand	ee (%)[a]
1	**L1**	64
2	**L3**	58
3	**L4**	55
4	**L7**	82
5	**L8**	79
6	**L25**	84
7	**L26**	72
8	**L27**	74
9	**L28**	72
10	**L29**	58
11	**L30**	74
12	**L31**	70

[a]Enantiomer excesses determined via chiral SFC analysis of chromatographically-purified product **5**.