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

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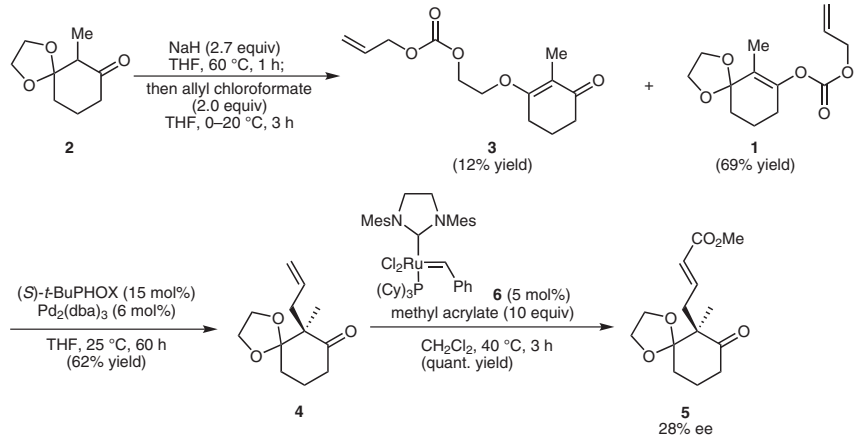
Abstract: The use of high-throughput screening allowed for the optimization of reaction conditions for the palladium-catalyzed asymmetric decarboxylative alkylation reaction of enolate-stabilized enol carbonates. Changing to a nonpolar reaction solvent and to an electron-deficient PHOX derivative as 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.

Key words: 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 monoketal **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 second-generation catalyst **6** in order to determine the enantiomeric excess of the product from the asymmetric alkylation reaction. 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.



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

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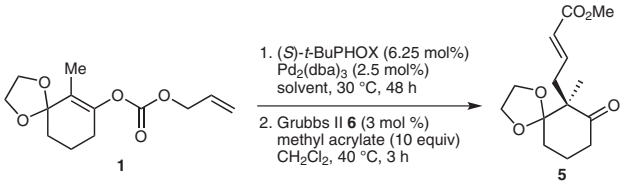
In order to obtain ketone **4** with high levels of enantioselectivity, we conducted high-throughput, parallel screening to determine the required catalyst and reaction conditions. Experiments were conducted in 1 mL vials within 96-well microtiter plates using a Symyx™ Technologies (Santa Clara, CA) 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 hours 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**,[20] 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 (entries 7 and 8). The best enantioselectivities were observed with the use of nonpolar 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 palladium catalyst precipitated from the reaction mixture. We believe that the use of a nonpolar 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]

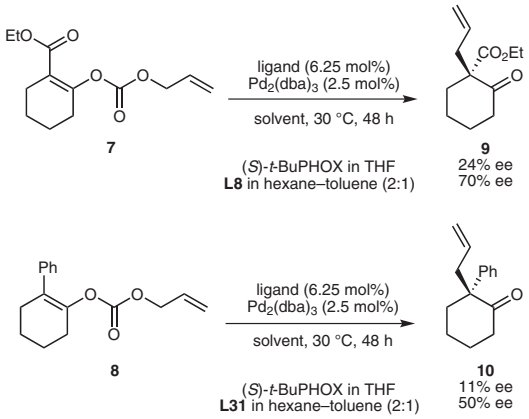
Table 1 Evaluation of Reaction Solvent



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

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

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**–**8**) 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, heteroatomic chelating group (**L10**–**12**) resulted in low yields and very low ee (< 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%.[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 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 nonpolar 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]



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

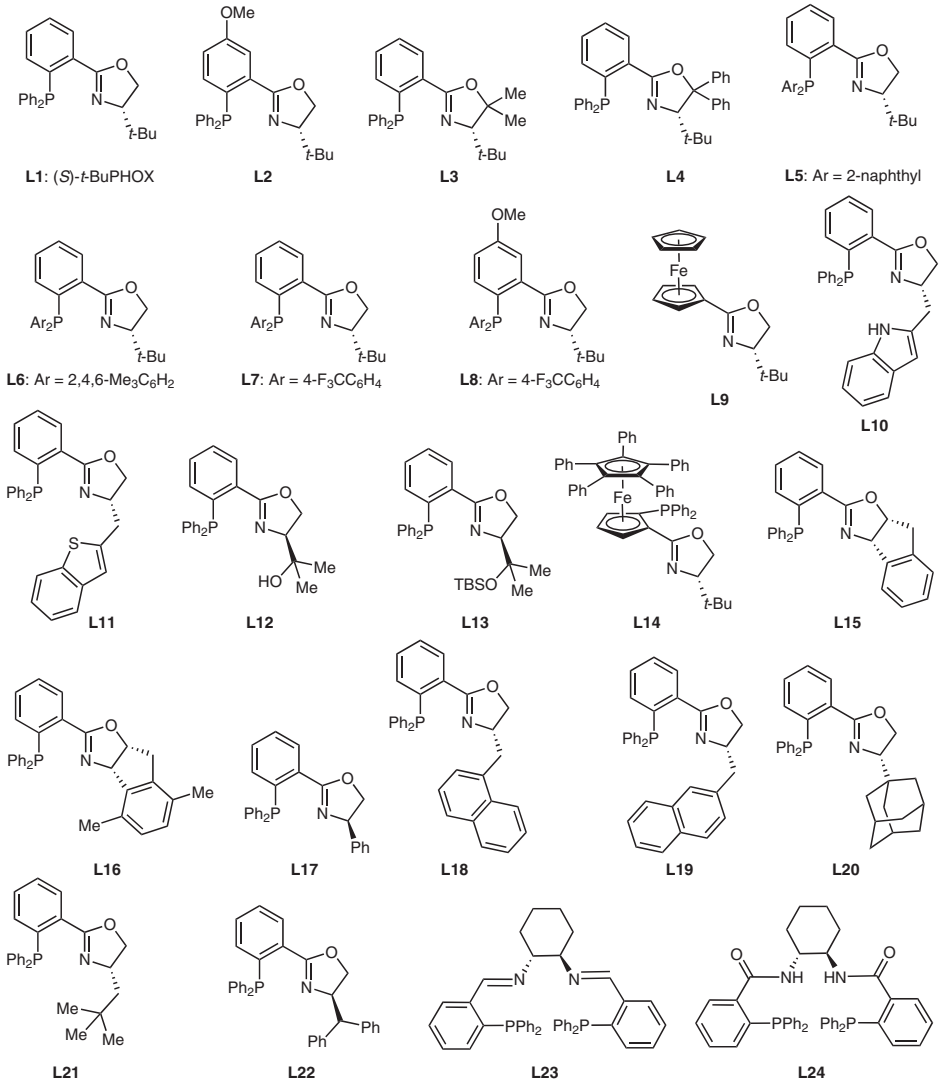


Figure 1 Ligands screened in the Pd-catalyzed decarboxylative alkylation reaction of **1**

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 nonpolar 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 nonpolar 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 nonpolar solvent mixture (hexanes–toluene, 2:1) and electron-deficient *t*-BuPHOX derivatives.

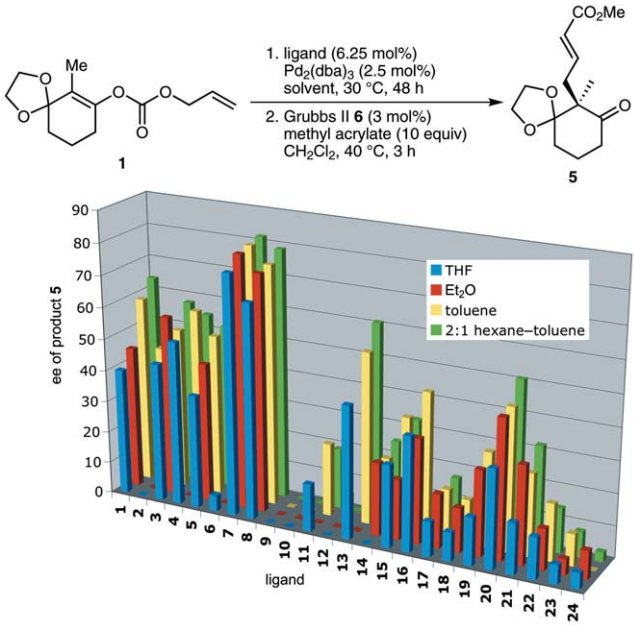


Figure 2 Dependence of enantiomeric excess of **5** on ligand structure and solvent in the decarboxylative alkylation reaction of **1**

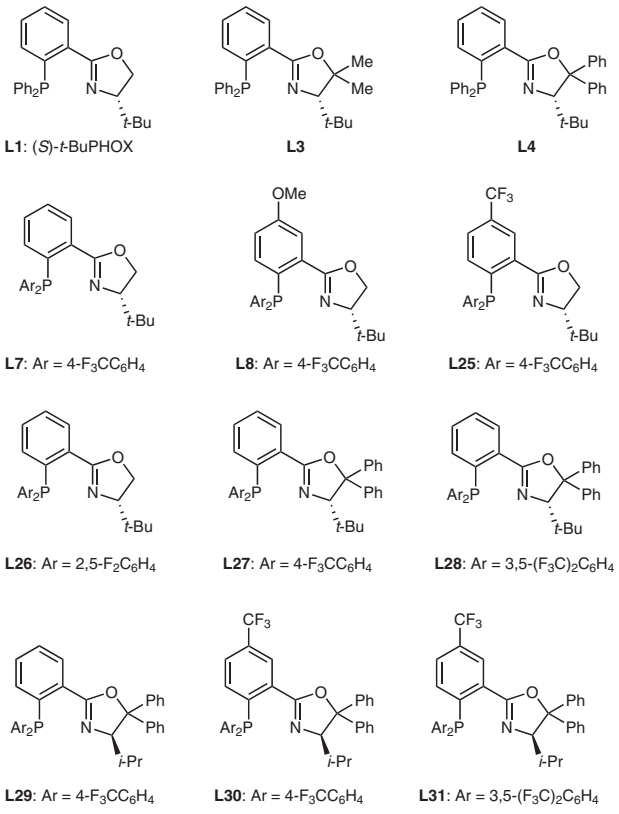


Figure 3 Ligands screened in the Pd-catalyzed decarboxylative alkylation reaction of **1**

Acknowledgment

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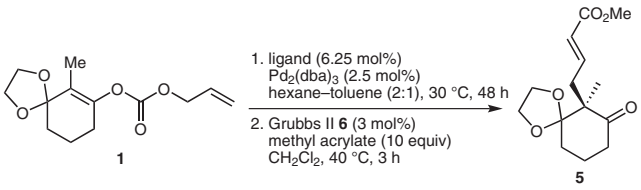
Table 2 Evaluation of Reaction Ligands



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] Enantiomeric excesses determined via chiral SFC analysis of chromatographically-purified product **5**.

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(20) **Experimental Data**

^{1}H NMR 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% MeCN–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–EtOAc = 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 second-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 40 °C for 3 h, the crude reactions were again purified via parallel silica gel chromatography, eluted with hexane–EtOAc = 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, 1 H), 5.38 (ddd, *J* = 18.6, 2.7, 1.5 Hz, 1 H), 5.29 (ddd, *J* = 10.5, 2.7, 1.5 Hz, 1 H), 4.65 (ap dt, *J* = 5.7, 1.2 Hz, 2 H), 3.97–4.03 (m, 4 H), 2.20–2.27 (m, 2 H), 1.70–1.84 (m, 4 H), 1.58 (t, *J* = 1.9 Hz, 3 H). ^{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 cm^{-1}. ESI-HRMS: *m/z* calcd 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, 1 H), 5.80 (d, *J* = 15.3 Hz, 1 H), 3.91–3.98 (m, 4 H), 3.70 (s, 3 H), 2.66 (dd, *J* = 14.7, 6.9 Hz, 1 H), 2.39–2.53 (m, 2 H), 2.36 (dd, *J* = 14.7, 6.9 Hz, 1 H), 1.89–1.94 (m, 2 H), 1.73–1.84 (m 2 H), 1.16 (s, 3 H). ^{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 cm^{-1}. ESI-HRMS: *m/z* calcd for $C_{14}H_{21}O_5$ $[M + H]^+$: 269.1384; found: 269.1382. Chiral HPLC: t_R(major) = 25.3 min; t_R(minor): 34.6 min. Chiral SFC: t_R(major) = 10.8 min; t_R(minor) = 11.8 min.