

An Improved Scalable Process for the Synthesis of (*S,S*)-DACH-Ph Trost Ligand

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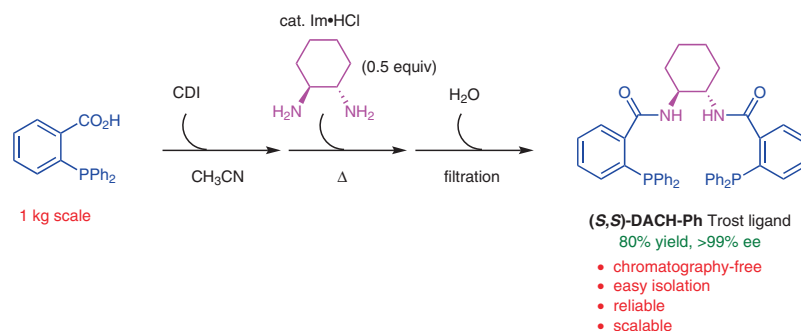
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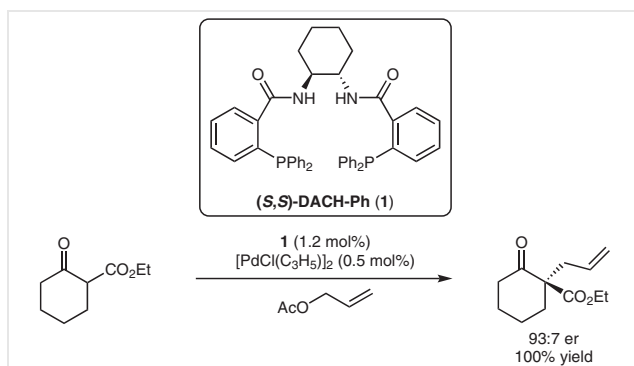
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Abstract An improved chemical process has been developed for the synthesis of (*S,S*)-DACH-Ph Trost ligand. The amidation of 2-diphenylphosphinylbenzoic acid and (*S,S*)-diaminocyclohexane is promoted by stoichiometric CDI and catalytic imidazole hydrochloride. The resulting product, (*S,S*)-DACH-Ph Trost ligand, is isolated as a white solid in 80% yield with >99% ee by simple filtration without column chromatography. The current facile process is also demonstrated on kilogram scale.

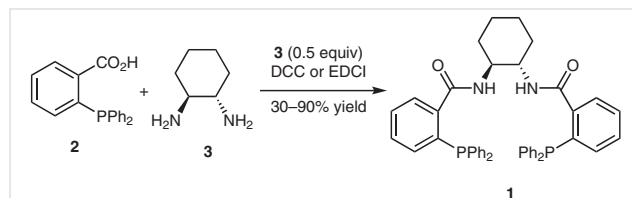
Key words Trost ligand, DACH-Ph, coupling, 2-diphenylphosphinylbenzoic acid, chiral diaminocyclohexane, CDI, imidazole hydrochloride, kilogram

Since the pioneering work from the Trost group at Stanford University, (*S,S*)-DACH-Ph Trost ligand **1** has been identified as an exceptionally powerful ligand for Pd-catalyzed asymmetric allylic alkylation (AAA), allowing for the rapid synthesis of a diverse range of chiral products with high yields and excellent levels of enantioselectivity (Scheme 1).¹



Scheme 1 Structure of (*S,S*)-DACH-Ph Trost ligand **1** and an example of its application in asymmetric allylic alkylation¹

Despite the well-known applications of **1** in a variety of important asymmetric transformations, its synthesis has not been extensively investigated. Typically, **1** is prepared by an amide coupling reaction between 2-diphenylphosphinylbenzoic acid (**2**) and (*S,S*)-diaminocyclohexane (DACH) (**3**) with dicyclohexylcarbodiimide (DCC) or 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide (EDCI) as the coupling reagent and dichloromethane as the solvent (Scheme 2).²



Scheme 2 The synthesis of (*S,S*)-DACH-Ph Trost ligand **1** reported in the literature

A survey of the literature indicated that highly variable yields of ligand **1** ranging from 30–90% have been reported. Notably, a purification by column chromatography on silica gel is generally required. Berl and co-workers obtained a moderate isolated yield (64%) when EDCI was added to the mixture of the acid and DMAP before the addition of the amine. Their resulting product **1** was isolated by recrystallization from acetonitrile without chromatography.³ Recently, we required a large quantity of **1** to support the scale-up of our chemical process involving asymmetric allylic alkylation. However, limited supply of the ligand was available in the market for bulk quantities with a short lead time at a desirable cost.⁴ Therefore, we determined that a more efficient and reliable process toward **1** would be highly desirable to the synthetic community to reduce its cost in the

scale-up of AAA. Herein, we report our efforts toward the development of a scalable process for facile synthesis of ligand **1** in good yield.

We first repeated the coupling of **2** and **3** with water-soluble EDCI as the coupling reagent and a catalytic amount of 4-(dimethylamino)pyridine (DMAP) in CH_2Cl_2 . We observed two main side products. By carefully analyzing the reaction mixture by mass spectrometry, we determined that both side products have the same mass [$\text{MS} = 462 (\text{M} + \text{H})^+$] and are likely derived from rearrangement of the key intermediate *O*-acylisourea to the stable *N*-acylurea.⁵ This might be related to slow coupling in the formation of the second amide due to steric hindrance. By taking advantage of the amine functional group from EDCI, both *N*-acylurea side products were easily washed off via MTBE extraction under acidic conditions. The product **1** was isolated in 50–55% yield from CH_3CN by crystallization without column chromatography. Considering the moderate yields of the amidation as a consequence of significant mass loss from the formation of the undesired side products, the coupling efficiency needed to be improved.

To that end, we selected 1,1'-carbonyldiimidazole (CDI) as the coupling reagent for the optimization of amidation as it is easy to handle and readily available on large scale. Instead of toxic CH_2Cl_2 , environmentally safe CH_3CN was chosen as the solvent, which would also allow crystallization of the product **1** directly after amidation. The acylimidazole formation proceeded smoothly and greater than 97% conversion was observed when **2** and CDI were mixed in CH_3CN at 23 °C. No amidation was observed at 23 °C after the addition of (*S,S*)-DACH. But when the mixture was heated to 60 °C, the formation of **1** was observed. However, the reaction was sluggish and gave a 68% yield after 8 hours at 82 °C (Table 1, entry 1). Moreover, we observed a thick paste, which made stirring the reaction mixture difficult at the beginning after the mixture was heated to 80 °C. In order to improve the yield, we added 10 mol% of 2-hydroxy-5-nitropyridine.⁶ In this case the reaction yield was improved to 73% after 8 hours (Table 1, entry 2). A further increase of the amount of 2-hydroxy-5-nitropyridine did not improve the conversion and reaction rate. Besides 2-hydroxy-5-nitropyridine, we also utilized DBU (0.5 equivalents) to facilitate the amidation (Table 1, entry 3).⁷ After 7 hours, the product **1** was isolated in 68% yield. When imidazole hydrochloride (Im·HCl) (1.5 equivalents) was employed as reported,⁸ a thick paste was observed that was difficult to agitate before the mixture was heated to 82 °C. After 8 h, the reaction gave a cleaner HPLC profile compared to the that with 2-hydroxy-5-nitropyridine. The product **1** was isolated in 80% yield as a white solid (Table 1, entry 4). Interestingly, when the amount of imidazole hydrochloride was decreased to 0.5 equivalents, no thick paste was observed and thus the process scalability was improved (Table 1, entry 5). Additionally, the quantity of imidazole hydrochloride could be reduced even further to 10 mol% to provide a similar

yield of 79% (Table 1, entry 6). To secure the quality of the product and process robustness, 0.5 equivalents of imidazole hydrochloride was applied on large scale.

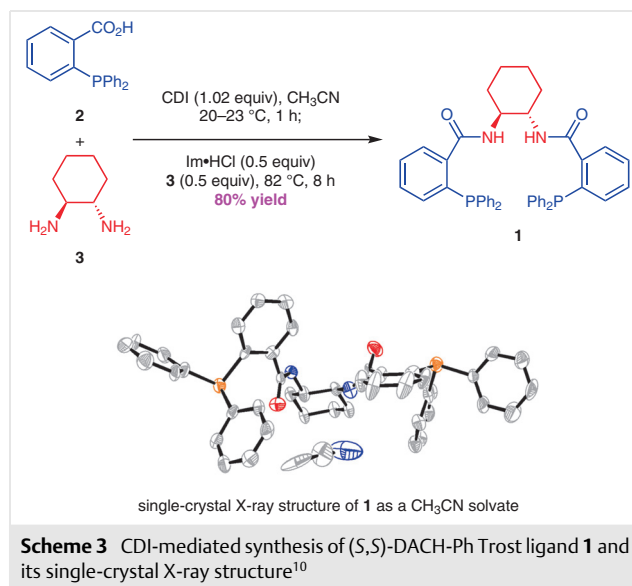
Table 1 Optimization of the Amidation for the Synthesis of (*S,S*)-DACH-Ph Trost Ligand **1**^a

Entry	Additive (amount)	Yield ^b	Color of product 1
1	none	68%	beige
2	2-HO-5-NO ₂ -pyridine (0.1 equiv)	73%	beige
3	DBU (0.5 equiv)	68%	white
4	Im·HCl (1.5 equiv)	80%	white
5	Im·HCl (0.5 equiv)	80%	white
6	Im·HCl (0.1 equiv)	79%	beige

^a Reaction conditions: **2** (5.00 g, 16.3 mmol), CDI (2.79 g, 16.63 mmol), CH_3CN (10 mL), 23 °C, 1 h; then **3** (2.70 g, 8.16 mmol), additive, CH_3CN (3 mL), 82 °C, 8 h.

^b Isolated yield.

Under our optimized conditions, the product (*S,S*)-DACH-Ph Trost ligand **1** was consistently obtained in 80% yield with >99% ee by simple filtration after the addition of water to reach a 2:1 ratio of CH_3CN /water followed by a rinse with 2:1 CH_3CN /water (Scheme 3). The current process was demonstrated on kilogram scale without any issue.^{9,10}



Scheme 3 CDI-mediated synthesis of (*S,S*)-DACH-Ph Trost ligand **1** and its single-crystal X-ray structure¹⁰

In conclusion, we have developed a simple and scalable process for the facile preparation of (*S,S*)-DACH-Ph Trost ligand **1** promoted by stoichiometric CDI and catalytic imidazole hydrochloride. The current protocol features a simple operation and high yield, along with the use of CDI as an inexpensive and abundant coupling reagent and CH_3CN as an environmentally benign solvent. Considering the impor-

tance of the (*S,S*)-DACH-Ph Trost ligand in asymmetric transformations, we believe that the convenient synthesis reported herein will further promote its application on large scale.

Conflict of Interest

The authors declare no conflict of interest.

Acknowledgment

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Supporting Information

Supporting information for this article is available online at <https://doi.org/10.1055/s-0041-1738371>.

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- (9) (a) (***S,S***)-DACH-Ph Trost Ligand (**1**)
Under nitrogen, 2-diphenylphosphinylbenzoic acid (**2**) (1.0 kg, 3.26 mol) and CDI (557.2 g, 3.33 mol) were charged into a clean and dry Reactor. After CH₃CN (2 L) had been added to give a slurry, the resulting mixture was agitated for 1 h at 20–25 °C to afford a clear and homogenous solution. The solution was transferred to a Reactor containing (*S,S*)-diaminocyclohexane (**3**) (186.4 g, 1.63 mol) and imidazole hydrochloride (170.6 g, 1.63 mol), rinsed with CH₃CN (0.60 L). The resulting mixture was then heated at 80–82 °C for 8 h. After the solution was cooled to 60 °C, a slurry was obtained. Water (1.3 L) was added over 0.5 h at 55–60 °C. After 0.5 h, the obtained slurry was cooled to 23 °C over 0.5 h. After 0.5 h, the solid was collected by filtration and then washed with CH₃CN/H₂O (2:1, 3 L) and H₂O (2 L) successively. After being dried under vacuum at 55 °C, the (*S,S*)-DACH-Ph Trost ligand (**1**) was obtained as a white solid (902.1 g, 80%) in sufficient quality for asymmetric allylic alkylation. The NMR spectroscopic data are in accordance with the literature.³ Mp 141.9–143.9 °C. ¹H NMR (600 MHz, DMSO-*d*₆): δ = 8.22 (s, 1 H), 8.20 (s, 1 H), 7.54–7.52 (m, 2 H), 7.32–7.29 (m, 14 H), 7.27 (t, *J* = 7.44 Hz, 2 H), 7.14–7.09 (m, 8 H), 6.83–6.81 (m, 2 H), 3.74 (br s, 2 H), 1.70 (d, *J* = 12.6 Hz, 2 H), 1.65 (d, *J* = 7.74 Hz, 2 H), 1.33 (m, 2 H), 1.18 (m, 2 H). ¹³C NMR (151 MHz, DMSO-*d*₆): δ = 167.7, 141.6, 141.4, 138.6, 138.5, 138.5, 138.5, 136.5, 136.3, 133.6, 133.3, 133.2, 133.2, 133.1, 129.7, 128.3, 128.3, 128.3, 128.2, 128.2, 127.7, 127.7, 52.6, 31.4, 24.5. ³¹P NMR (243 MHz, DMSO-*d*₆): δ = –9.04 (b) HPLC: ChiralPak AY-H 4.6 × 250 mm, flow rate = 0.50 mL/min, column temperature = 35 °C, heptane:[MeOH/ethanol (1:1) with 0.4% Et₃N] = 75:25, detection at 220 nm; *t*_R = 7.7 min (*S,S*), *t*_R = 8.3 min (*R,R*).
- (10) CCDC 2152627 contains the supplementary crystallographic data for this paper. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/structures.