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A Scalable, One-Pot Synthesis of 1,2,3,4,5-Pentacarbomethoxycyclopentadiene

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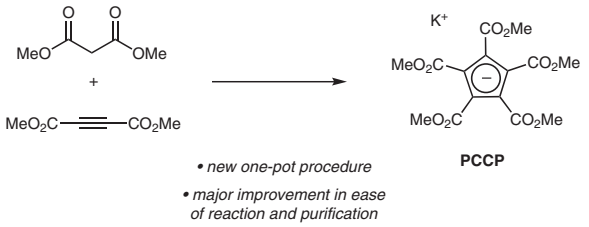

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Abstract 1,2,3,4,5-Pentacarbomethoxycyclopentadiene (PCCP) is a strong organic acid and a precursor to useful organocatalysts, including chiral Brønsted acids and silicon-based Lewis acids. The synthetic route to PCCP, first reported in 1942, is inconvenient for a number of reasons. The two-step synthesis requires the purification of intermediates from intractable side-products, high reaction temperatures, and extensive labor (3 days). We have developed an improved procedure that delivers PCCP efficiently in 24 hours in one pot at ambient temperature and without isolation.

Key words Brønsted acid, PCCP, cyclopentadiene, dimethyl malonate, dimethyl acetylenedicarboxylate

Cyclopentadiene and its derivatives comprise a family of exceptionally important organic molecules. Due to the stabilizing aromaticity of the cyclopentadienyl anion, the cyclopentadienes are markedly more acidic compared to analogous hydrocarbons. The acidity of the cyclopentadiene can be further increased through introduction of stabilizing groups, such as cyano or carbonyl substituents.[1] Notably, the highly electron-deficient 1,2,3,4,5-pentacarbomethoxycyclopentadiene (PCCP; **1**), first reported by Otto Diels in 1942,[2] is approximately as acidic as HCl[1] (Figure 1A).

We recently reported that the PCCP scaffold offers a viable platform for organocatalysis.[3] One of the major attractive features of this scaffold is the fact that the carboxymethyl substituents of **1** are readily derivatized, allowing facile access to a range of PCCP analogues (Figure 1B).[4] Using this strategy, we have developed chiral PCCP derivatives that act as Brønsted acid catalysts for enantioselective Mukaiyama–Mannich and oxocarbenium aldol reactions[3a] and for the inverse-demand Diels–Alder cycloaddition of

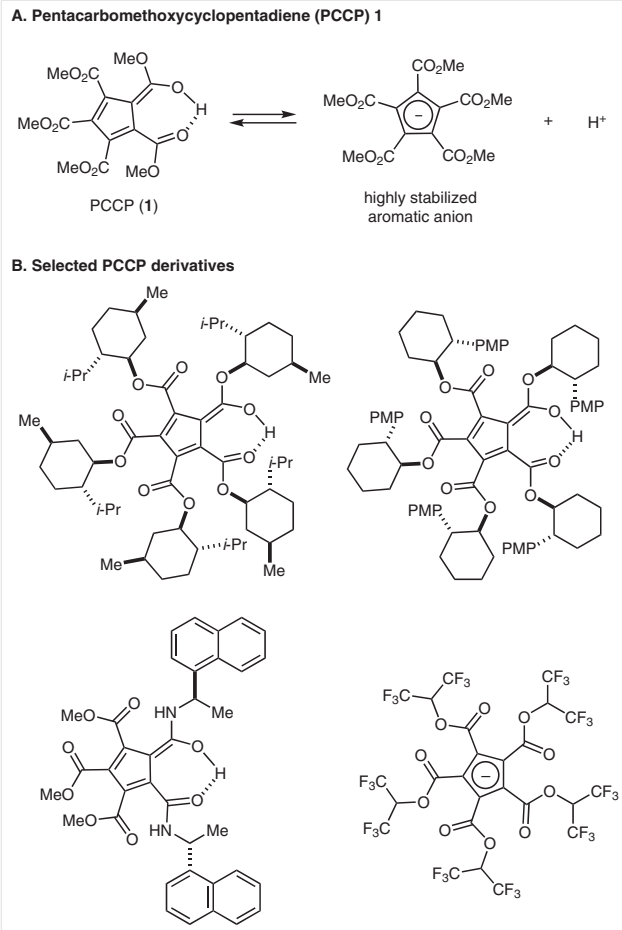


Figure 1 PCCP (**1**) and selected derivatives

salicylaldehyde acetals.[3b] In addition, we have demonstrated that silylated PCCP derivatives can serve as effective silicon Lewis acid catalysts to promote C–C bond-forming reactions.[3c] We are currently exploring the use of metal–PCCP complexes[5] as catalysts for a range of transformations.

As shown in Scheme 1, the established synthesis of PCCP **1** consists of two sequential reactions. In the first step, dimethyl malonate (DMM) combines with three equivalents of dimethyl acetylenedicarboxylate (DMAD) to generate an isomeric mixture of octacarbomethoxycyclohepta-

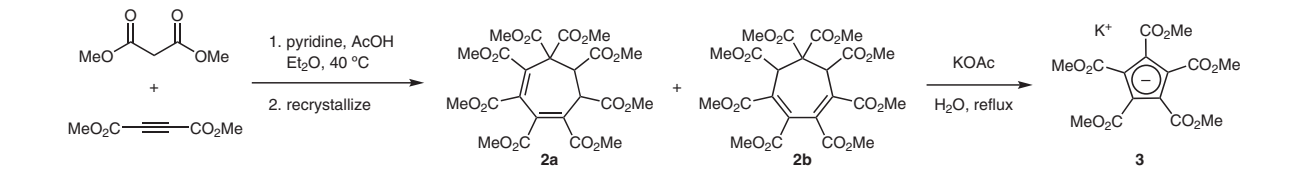
Biographical Sketches

M. Alex Radtke studied at the University of British Columbia (Canada), where he received his B.Sc. with honours in 2013 after performing research with Prof. David Perrin. He joined the Lambert group at Columbia University (USA) to work on the synthesis and derivatization of functionalized cyclopentadienes, obtaining his Ph.D. in 2018. He is currently working on natural product synthesis as a post-doctoral fellow in the lab of Prof. Amos B. Smith, III, at the University of Pennsylvania (USA).

Caroline Dudley was born and raised in Buffalo, NY (USA). In 2016, she began a B.A. in chemistry at Cornell University (USA). Since early 2018, she has conducted research in the laboratory of Tristan Lambert. Her research has focused on the development of chiral Brønsted acids for applications in asymmetric catalysis.

Jacob O'Leary was born and raised in Huntsville, AL (USA). He received his B.S. in chemistry from Birmingham-Southern College in 2016 and his M.A. in chemistry from Columbia University in 2018. He is currently a third-year doctoral student at Cornell University under the supervision of Tristan Lambert. His research has focused on Brønsted acid catalysis as well as copper-catalyzed nitrene transfer reactions.

Tristan Lambert was born in Madison, WI (USA), in 1976 and grew up in the small town of Black Earth. He graduated from the University of Wisconsin at Platteville (USA) in 1998 with a B.S. in chemistry. The same year he began graduate studies at UC-Berkeley (USA) as one of Dave MacMillan's first students. In 2000, Tristan moved with the MacMillan group to Caltech (USA) where he earned his Ph.D. for the development and application of novel Claisen rearrangements. In 2004, he began postdoctoral studies with Sam Danishefsky at the Memorial Sloan-Kettering Cancer Center in New York (USA). At Sloan-Kettering he completed a total synthesis of UCS1025A, a putative telomerase inhibitor. In 2006, Tristan accepted a faculty position in the Department of Chemistry at Columbia University (USA). In 2011, he was promoted to Associate Professor and in 2016 to Full Professor. In January 2018, he moved to the Department of Chemistry and Chemical Biology at Cornell University (USA). His research group focuses on the study of intriguing chemical building blocks such as aromatic ions and their application to problems in the areas of catalysis, reaction design, and polymers.



Scheme 1 Synthesis of PCCP potassium salt **3** from dimethyl malonate and dimethyl acetylenedicarboxylate as reported by Diels

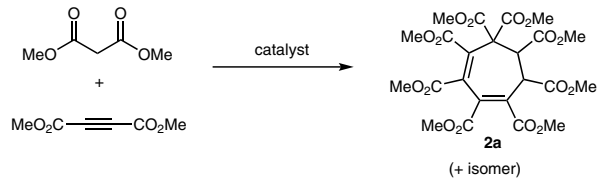
dienes **2a** and **2b**.[6] In the second step, **2a** and **2b** undergo a base-mediated ring contraction to generate the potassium salt of PCCP, **3**.[7] Upon protonation, PCCP (**1**) precipitates and can be collected by filtration.

While this synthetic route makes use of relatively inexpensive reagents, a number of issues make it highly inconvenient to run, particularly on a large scale. First, formation of the octacarbomethoxycycloheptadienes **2a** and **2b** must be closely monitored due to the highly exothermic nature of this reaction and the rapid precipitation of the products. Although the reaction requires heating to achieve full conversion, the flask should nevertheless be cooled with an ice bath until it ceases to reflux on its own. This precaution is very important: if the reaction is not cooled and stirred efficiently, the mixture can erupt violently. Second, even when highly pure starting materials are used, significant by-products are formed at this stage, necessitating a recrystallization step prior to proceeding to step two. This recrystallization results in a significant reduction in the yield of **2a** and **2b** and greatly extends the time of the overall procedure. When **2a** and **2b** are carried on to the next step without recrystallization, the second reaction yields a nearly intractable mixture of the PCCP salt and undefined, dark, insoluble matter, which significantly diminishes the yield of the product. When purified **2a** and **2b** are used, the second reaction generally proceeds smoothly, but high temperatures are required due to the insolubility of **2a** and **2b**. Hot filtration is required to remove reaction by-products, and only after a slow, overnight precipitation is the PCCP potassium salt obtained.

Given these significant drawbacks, we sought to develop an improved route to PCCP (**1**) that would address the undesirable elements of this procedure and reduce the number of steps and the time required to complete the synthesis. Herein, we report a simple, one-pot procedure that delivers the PCCP potassium salt **3**, and thus to **1** via protonation, in a single day.

We began by evaluating the conditions under which the two octacarbomethoxycycloheptadiene isomers **2a** and **2b** can be formed. We aimed to determine whether **2a** and **2b** could be generated in solution in a synthetically useful yield. As shown in Table 1, no alternative to the pyridine and acetic acid mixture employed by Diels (Table 1, entry 1) was productive for the promotion of this reaction (entries 2–5). However, when diethyl ether solvent was replaced with dichloromethane (entry 6), in which **2a** and **2b** are freely soluble, the reaction proceeded smoothly within three hours without heating. Even on a large (~50 g) scale, where exothermic events are cause for significant concern, a room temperature water bath was sufficient to keep the reaction under control.

Table 1 Investigation of Conditions under which **2a** and **2b** Form



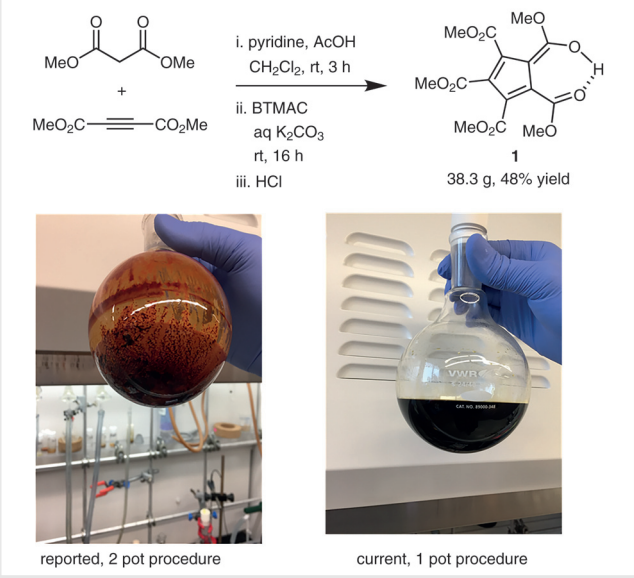
Entry	Catalyst	Solvent	Yield (%)[a]
1	pyridine/AcOH	Et_2O	74
2	DABCO/AcOH	Et_2O	0
3	pyridine/HBr	Et_2O	0
4	pyridine/TsOH	Et_2O	0
5	2,6-lutidine/AcOH	Et_2O	0
6	pyridine/AcOH	CH_2Cl_2	61

[a] Yields determined by ^{1}H NMR spectroscopy.

We next sought to convert **2a** and **2b** into **3** in the same pot by the addition of organic bases to induce the ring contraction/fragmentation events. A screen of amine bases revealed that DBU promoted formation of the desired product; however, the use of stoichiometric DBU on a large scale is impractical. We next examined the possibility of using aqueous base solutions in a biphasic mixture with benzyltrimethylammonium chloride (BTMAC) as a phase-transfer catalyst. The reaction was conducted with either aqueous 1 M KOH or saturated K_2CO_3 solution. With aqueous KOH, rapid conversion of the starting materials was observed (60% in 2 h); however, significant decarboxylation of the PCCP product was detected by NMR analysis. The reaction proceeded more slowly in saturated K_2CO_3 solution, but under these conditions, significant formation of **3** was observed within 16 hours. Conveniently, the PCCP salt precipitated out of the reaction mixture without cooling. Protonation with aqueous HCl then delivered PCCP acid **1**, which was purified by recrystallization.

A key requirement of this project was to develop a synthetic route that was scalable and high-yielding compared to the previously reported synthesis. On a 38.3 gram scale, the new procedure delivered PCCP (**1**) in 48% (Scheme 2), an

improvement of 13% over an unoptimized Diels synthesis run on a similar scale. Perhaps more importantly, the extreme inconvenience of the intractable material formed in the two-pot synthesis (Scheme 2, left photo) has been eliminated in favor of a well-behaved homogeneous solution (Scheme 2, right photo).



Scheme 2 Summary of the newly reported procedure for the synthesis of PCCP including visual comparison of the reactions

In summary, PCCP (**1**) is a useful precursor to novel organic Brønsted and Lewis acid catalysts.[3,8] These organocatalysts offer a noteworthy alternative to chiral BINOL-based catalysts and have an advantage in that they are significantly more straightforward and inexpensive to access. While the PCCP methyl ester is commercially available, the high cost encourages in-house production from inexpensive precursors. Our desire to more easily access this useful scaffold led us to revisit an outdated and inconvenient synthetic methodology. We have developed a convenient and rapid one-pot route to PCCP that delivers the product in superior yield to the Diels synthesis. We anticipate that this improved synthesis will encourage future applications of this unique molecule in organic synthesis.

Dimethyl acetylenedicarboxylate was acquired from Chem-Impex. All other reagents and solvents were acquired from Sigma-Aldrich or Fisher Scientific. NMR spectra were recorded on a Bruker AV500 spectrometer. Mass spectra were collected using a Thermo Scientific Exactive DART-MS spectrometer.

1,2,3,4,5-Pentacarbomethoxycyclopentadiene (1)

To a flame-dried 3 L flask containing CH_2Cl_2 (840 mL) and a stir bar were added dimethyl acetylenedicarboxylate (82.6 mL, 95.8 g, 0.67 mol) and dimethyl malonate (76.7 mL, 88.2 g, 0.67 mol). Pyridine (2.75 mL, 2.7 g, 34 mmol) and AcOH (2.55 mL, 2.7 g, 44.8 mmol), dissolved in CH_2Cl_2 (10 mL) were added dropwise to the flask over 30 min. The reaction mixture was stirred at rt for 3 h, during which time the solution darkened to a reddish brown. After 3 h, benzyltrimethylammonium chloride (518 mg, 2.8 mmol) was added along with sat. aq K_2CO_3 (840 mL). Over the course of several hours, the biphasic mixture became viscous, and stirring was increased as necessary to ensure thorough mixing of the phases. The reaction was allowed to proceed for 16 h, during which time PCCP salt **3** precipitated. The heterogeneous mixture was filtered and the solid washed with CH_2Cl_2 (300 mL). The collected solid was dried in vacuo to furnish the PCCP salt **3**. The PCCP acid **1** was acquired by dissolving **3** in H_2O (4 mL/g) and treating this solution with concd HCl (2 mL/g). PCCP precipitated from the acidified mixture and was filtered and dried in vacuo to remove all traces of HCl. The resulting yellow powder was recrystallized from toluene/EtOAc to furnish PCCP (**1**) as large, colorless crystals; yield: 38.3 g (48%).

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 20.11 (s, 1 H), 4.06 (s, 6 H), 3.92 (s, 6 H), 3.79 (s, 3 H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 172.3, 167.7, 163.1, 133.6, 117.6, 106.4, 55.6, 52.6, 51.9.

HRMS (DART-MS): *m/z* $[M - H]^-$ calcd for $C_{15}H_{15}O_{10}$: 355.0671; found: 355.06125.

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