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Synthesis of Functionalized Alkylidene Indanes and Indanones through Tandem Phosphine–Palladium Catalysis

Yi Chiao Fan and Ohyun Kwon

Department of Chemistry and Biochemistry, University of California, Los Angeles, California 90095-1569, United States

Ohyun Kwon: astohyun@chem.ucla.edu

Abstract

Densely functionalized alkylidene indanes and indanones can be prepared efficiently in one pot, in high yields with good stereoselectivities (in some cases exclusively the *Z*-isomer), through a route involving phosphine-catalyzed Michael addition followed by palladium-catalyzed Heck cyclization. These transformations tolerate substrates bearing various substituents around the indane/indanone motif. Employing this technology, a concise formal synthesis of sulindac, a nonsteroidal anti-inflammatory drug, has been established.

First discovered in the mid-1800s, organocatalysis has maintained great importance in the synthetic organic chemistry community.¹ Most organocatalysts offer several attractive features, including minimal environmental impact, stability to moisture and air, and ready accessibility at low cost. Of the many established organocatalysts, phosphines are among the most efficient and versatile, catalyzing many reactions.² For many years, however, tertiary phosphines were designed and used mainly as ligands for transition metal catalysis. It was not until recently, in the past two decades, that the field of phosphine catalysis boomed.³ Despite rapid growth in phosphine catalysis in recent years, examples of tandem catalysis using both phosphines and transition metals have remained scarce.

Recently, we reported an efficient route for the synthesis of functionalized alkylidene phthalans using tandem Michael–Heck cyclization.⁴ The idea of harnessing the dual reactivities of the phosphine, as an organocatalyst and as a ligand for palladium, emerged as a powerful tool for access to phthalan heterocycles. To further explore the utility of such tandem phosphine–palladium catalysis, we embarked on the development of a simple and efficient method to prepare functionalized alkylidene indane and indanone carbocycles.

Correspondence to: Ohyun Kwon, astohyun@chem.ucla.edu.

Supporting Information: Procedure details and NMR spectra. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Indanes and indanones are important structural motifs in molecules of great pharmaceutical significance, displaying, for example, anti-inflammatory,⁵ anticancer,⁶ and antiviral properties.⁷ These multifarious bioactivities render both indanes and indanones as valuable candidates for biological screenings. To the best of our knowledge, however, there are no examples of simple transformations for accessing functionalized indanes and indanones. Conventional methods involving multistep alkylations,⁸ Michael additions,⁹ or Knoevenagel¹⁰ condensations from indanones are not always efficient and offer limited degrees of functionalization. Other methods, such as intramolecular cyclizations, require elaborated disubstituted alkyne intermediates that may be difficult to access.^{11–13}

As part of a program aimed at advancing nucleophilic phosphine catalysis, we were prompted to design a simple and efficient annulation strategy to grant access to these important indane and indanone compounds. In this Letter, we disclose an efficient method for synthesizing functionalized indanes and indanones from 2-iodobenzylmalonates and 2-iodobenzoyl-acetates.

To test the viability of Michael–Heck annulation in forming carbocycles, 2-iodobenzylmalonate (**1a**) was employed to examine the stepwise Michael addition and Heck cyclization process (Scheme 1). Using triphenylphosphine as the catalyst, the malonate **1a** underwent smooth conjugate addition onto methyl propiolate (**2a**), producing the desired Michael adduct **3** in excellent yield. The alkylidene indane **4a** was then obtained in good yield after subjecting the enoate **3** to the conditions of a Heck reaction.^{14,15}

With the success of both these Michael and Heck reactions, the idea of tandem Michael–Heck annulation was tested (Scheme 2). Upon completion of the Michael reaction, palladium was introduced, triggering the subsequent cyclization to form the indane **4a**. Although the one-pot transformation led to the desired carbocycle, the reaction yield was only modest.¹⁶

Revisiting the stepwise transformations (Scheme 1), the intramolecular Heck annulation appeared to be the yield-limiting step. To address this issue and improve the efficiency of the one-pot process, reaction optimization was performed by closely examining the Heck cyclization conditions (Table 1). The use of different palladium catalysts led to similar reaction efficiencies (entries 1–5). Testing both electron-deficient and -rich phosphines led to only minor decreases in yield (entries 6–9). Employing bidentate phosphines, namely 1,2-bis-(diphenylphosphino) ethane (DPPE) and 1,3-bis(diphenylphosphino) propane (DPPP), did not improve the yield substantially (entries 10 and 11).¹⁷ Changing the salt additive did, however, have a significant effect on the yield (entries 12–18). To our delight, an excellent yield was achieved when using tetra-*n*-butylammonium acetate as the additive (entry 19).

With optimized conditions in hand, various pronucleophiles were subjected to the tandem Michael–Heck reaction (Scheme 3). Although other nucleophiles, including the 1,3-dione **4b**, the β -ketoester **4c**, and the malononitrile **4d**, were suitable for the reaction, dimethyl malonate derived pronucleophiles prevailed, giving excellent yields of the indanes **4a** and **4e–k**. High efficiencies were observed when electron-donating substituents [e.g., methoxy (**4e**) and methyl (**4f** and **4g**) groups] were present. The reaction could also tolerate various

other substituents on the benzene ring system. Trifluoromethyl (**4h**) and fluoro (**4i**) groups gave high product yields. Interestingly, the indanes **4e** and **4f** were isolated solely as single *Z*-stereoisomers. The exclusive *Z*-selectivity presumably originated from a nonstereospecific Heck cyclization caused by the steric bulk of the substituent at the 7-position of the indane. Such an effect was evident also in the stepwise reactions (Scheme 1). Additional types of functionalization, using sterically more demanding benzyl (**4j**) and *tert*-butyl propiolate (**4k**), also resulted in reactions having good efficiencies.

In addition to the formation of alkylidene indanes, this methodology can also generate an array of functionalized indanones when using 2-iodobenzoylacetates as pronucleophiles (Scheme 4). Various types of substitution on the benzene ring of the indanone were well tolerated. Substrates bearing electron-donating functionalities [e.g., methoxy (**6b**), benzyloxy (**6c** and **6d**), dimethoxy (**6e**), and methyl (**6f** and **6g**) groups] afforded their products in good to excellent yields. Those bearing electron-withdrawing moieties [e.g., fluoro (**6h**), chloro (**6i**), and trifluoromethyl (**6j**) groups] also provided good to high yields of their indanones. In addition to the α -methyl-substituted 2-iodobenzoylacetates, the α -butyl-substituted substrate (**5k**) also underwent smooth annulation with high efficiency. Similar to the situation when forming the indanes, substituents ortho to the iodide group exerted excellent stereochemical control, leading exclusively to *Z*-indanones (**6b** and **6f**).

Next, various activated alkynes were investigated for their use in the tandem Michael–Heck reaction (Table 2). Like the reaction of methyl propiolate (**2a**), that of the sterically more congested benzyl propiolate (**2b**) also afforded its desired indanone **7a** in excellent yield (entry 1). Although strongly activated alkynones could be employed in this transformation, the resulting indanones were obtained in only moderate yields (entries 2–4). Less-activated propiolamides also participated with high reaction efficiency (entry 5).

To demonstrate the broad utility of the tandem Michael–Heck reaction, a concise formal synthesis of sulindac, a nonsteroidal anti-inflammatory drug, was undertaken (Scheme 5).¹⁸ Starting from the β -ketoester **8** and benzyl propiolate (**2b**), the target indanone **9** was produced in good yield. The formal synthetic target **10** was obtained in high yield through a hydrogenolysis–decarboxylation–hydrogenation cascade under the influence of H₂ gas and 10% platinum on charcoal.

In conclusion, we have developed a simple and rapid method that grants access to various functionalized indanes and indanones from readily accessible 2-iodobenzylmalonates and 2-iodobenzoylacetates and electron-poor alkynes. Furthermore, this tandem Michael–Heck technology enabled the concise formal synthesis of sulindac in one step from the indanone **9**. The strategy reported herein may serve as a model for the design of other tandem phosphine/palladium-catalyzed reactions and may provide new avenues for the efficient synthesis of compounds of pharmaceutical significance.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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15. The *E*- and *Z*-geometries of the isomeric compounds **4**, **6**, and **7** were assigned based on the NOESY analysis. NOESY spectra of compounds **E-4a**, **Z-4a**, **E-4b**, **Z-4b**, **Z-4d**, **Z-4e**, **Z-4f**, **Z-6b**, and **Z-6f** are provided in the Supporting Information. The geometries of the other indanes and indanones were determined based on analogy to the above-mentioned compounds. The most characteristic peak is the signal in the ¹H NMR spectrum for the proton at the 7-position of the indane/indanone. For the *Z*-isomers, this signal appears in the regular aromatic region; for the *E*-

isomers, it appears in the range δ 8.5–9.5 ppm. In TLC analyses, the *Z*-isomers were, consistently, more polar than their *E*-counterparts.

16. If all the reagents are added at the beginning of the reaction, the mixture turns black and neither the Michael nor the Heck reaction occurs.
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Scheme 1. Stepwise Michael Addition and Heck Cyclization of 2-Iodobenzylmalonate

Scheme 2. Tandem Michael–Heck Annulation of 2-Iodobenzylmalonate with Methyl Propiolate

Scheme 3. Synthesis of Functionalized Alkylidene Indanes^{a,b}

Scheme 4. Synthesis of Functionalized Alkylidene Indanones^a

Scheme 5. Synthetic Application of Tandem Michael–Heck Reaction

Table 1
Reaction Optimizations for the Intramolecular Heck Cyclization of Compound 3^a

entry	Pd	PR_3	additive	yield ^b (%)
1	$\text{Pd}(\text{OAc})_2$	PPh_3	$n\text{Bu}_4\text{NCl}$	72
2	$\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$	PPh_3	$n\text{Bu}_4\text{NCl}$	71
3	PdCl_2	PPh_3	$n\text{Bu}_4\text{NCl}$	69
4	$\text{Pd}_2(\text{dba})_3\text{CHCl}_3$	PPh_3	$n\text{Bu}_4\text{NCl}$	68
5	$\text{Pd}_2(\text{dba})_3$	PPh_3	$n\text{Bu}_4\text{NCl}$	67
6	$\text{Pd}(\text{OAc})_2$	$\text{P}(p\text{-FC}_6\text{H}_4)_3$	$n\text{Bu}_4\text{NCl}$	64
7	$\text{Pd}(\text{OAc})_2$	$\text{P}(p\text{-tolyl})_3$	$n\text{Bu}_4\text{NCl}$	62
8	$\text{Pd}(\text{OAc})_2$	$\text{P}(o\text{-furyl})_3$	$n\text{Bu}_4\text{NCl}$	63
9	$\text{Pd}(\text{OAc})_2$	PBu_3	$n\text{Bu}_4\text{NCl}$	62
10	$\text{Pd}(\text{OAc})_2$	DPPE	$n\text{Bu}_4\text{NCl}$	69
11	$\text{Pd}(\text{OAc})_2$	DPPP	$n\text{Bu}_4\text{NCl}$	73
12	$\text{Pd}(\text{OAc})_2$	PPh_3	LiBr	41
13	$\text{Pd}(\text{OAc})_2$	PPh_3	NH_4Cl	40
14	$\text{Pd}(\text{OAc})_2$	PPh_3	NH_4CO_3	43
15	$\text{Pd}(\text{OAc})_2$	PPh_3	$n\text{Et}_4\text{NBr}$	25
16	$\text{Pd}(\text{OAc})_2$	PPh_3	$n\text{Bu}_4\text{NI}$	38
17	$\text{Pd}(\text{OAc})_2$	PPh_3	BnBu_3NCl	79
18	$\text{Pd}(\text{OAc})_2$	PPh_3	$n\text{Bu}_4\text{NBr}$	93
19	$\text{Pd}(\text{OAc})_2$	PPh_3	$n\text{Bu}_4\text{NOAc}$	98

^a A solution of the iodide **3** (0.1 mmol), $\text{Pd}(\text{OAc})_2$, triphenylphosphine, $n\text{Bu}_4\text{NOAc}$ (0.1 mmol), and NaHCO_3 (0.2 mmol) in MeCN (2.0 mL) was heated under reflux.

^b The combined yield of the *E* and *Z* isomers was determined through GC analysis using diethyl fumarate as the internal standard.

Table 2
Synthesis of Alkylidene Indanones Using Activated Alkynes^a

entry	R	<i>E</i> : <i>Z</i>	yield (%)
1	OBn	1:3	7a , 97
2	Ph	1:1	7b , 51
3	thienyl	1:2	7c , 53
4	4-NCC ₆ H ₄	1:6	7d , 55
5	N(OMe)(Me)	1:3	7e , 88

^a Isolated yields and *E*:*Z* ratios are given. See SI for details.