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

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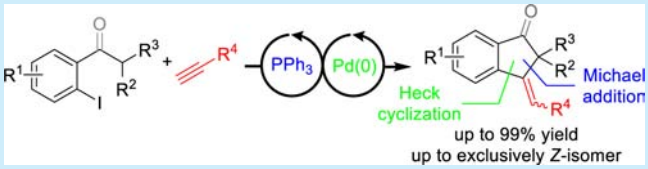
Supporting Information

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.

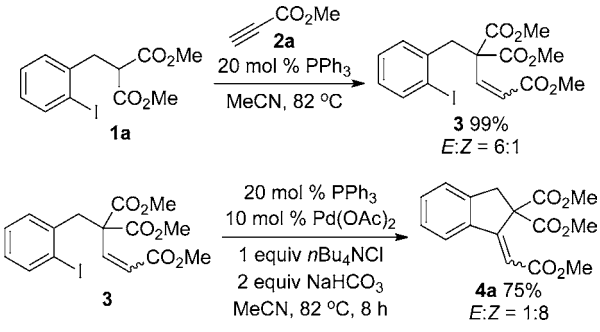
Recently, we reported an efficient route for the synthesis of functionalized alkylidene phthalans using tandem Michael–Heck cyclization.[4] The idea of harnessing the dual reactivities of the phosphine, as an organocatalyst and as a ligand for palladium, emerged as a powerful tool for access to phthalan 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.

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 Knoevenagel[10] 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-iodobenzoylacetates.

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,

Scheme 1. Stepwise Michael Addition and Heck Cyclization of 2-Iodobenzylmalonate



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

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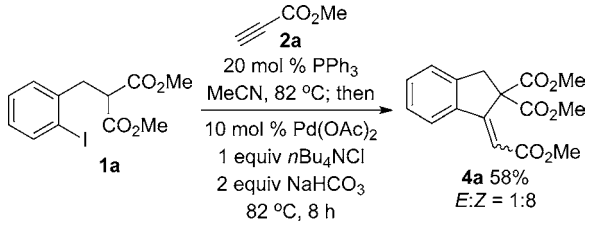
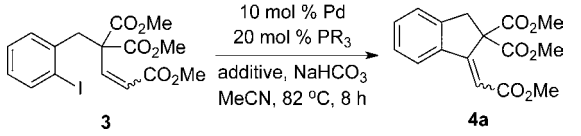
Scheme 2. Tandem Michael–Heck Annulation of 2-Iodobenzylmalonate with Methyl Propiolate



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).

Table 1. Reaction Optimizations for the Intramolecular Heck Cyclization of Compound 3[a]



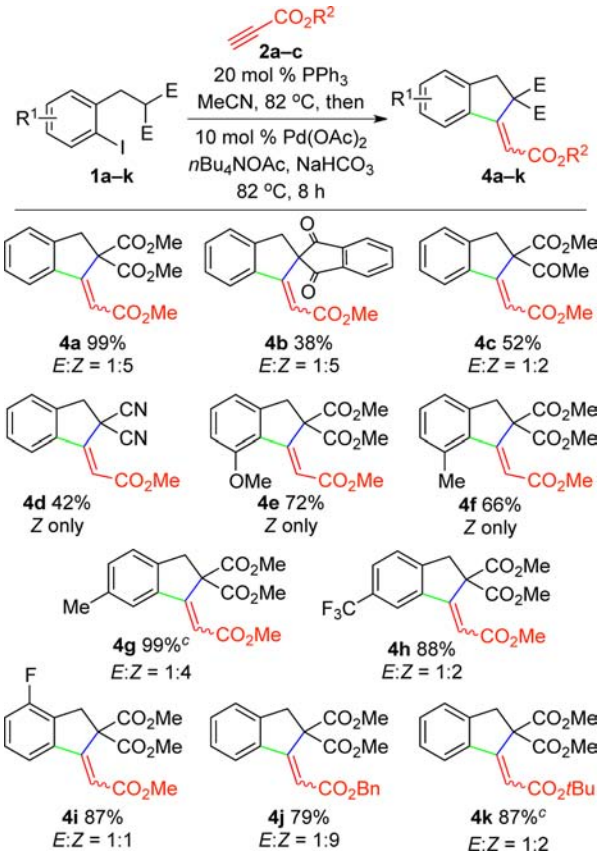
entry	Pd	PR_3	additive	yield[b] (%)
1	$Pd(OAc)_2$	PPh_3	nBu_4NCl	72
2	$Pd(PPh_3)_2Cl_2$	PPh_3	nBu_4NCl	71
3	$PdCl_2$	PPh_3	nBu_4NCl	69
4	$Pd_2(dba)_3CHCl_3$	PPh_3	nBu_4NCl	68
5	$Pd_2(dba)_3$	PPh_3	nBu_4NCl	67
6	$Pd(OAc)_2$	$P(p\text{-}FC_6H_4)_3$	nBu_4NCl	64
7	$Pd(OAc)_2$	$P(p\text{-tolyl})_3$	nBu_4NCl	62
8	$Pd(OAc)_2$	$P(o\text{-furyl})_3$	nBu_4NCl	63
9	$Pd(OAc)_2$	PBu_3	nBu_4NCl	62
10	$Pd(OAc)_2$	DPPE	nBu_4NCl	69
11	$Pd(OAc)_2$	DPPP	nBu_4NCl	73
12	$Pd(OAc)_2$	PPh_3	LiBr	41
13	$Pd(OAc)_2$	PPh_3	NH_4Cl	40
14	$Pd(OAc)_2$	PPh_3	NH_4CO_3	43
15	$Pd(OAc)_2$	PPh_3	nEt_4NBr	25
16	$Pd(OAc)_2$	PPh_3	nBu_4NI	38
17	$Pd(OAc)_2$	PPh_3	$BnBu_3NCl$	79
18	$Pd(OAc)_2$	PPh_3	nBu_4NBr	93
19	$Pd(OAc)_2$	PPh_3	nBu_4NOAc	98

[a]A solution of the iodide **3** (0.1 mmol), $Pd(OAc)_2$, triphenylphosphine, nBu_4NOAc (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.

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

Scheme 3. Synthesis of Functionalized Alkylidene Indanes[a,b]



[a]The acetylene **2** (0.25 mmol) in MeCN (1.0 mL) was added dropwise to a refluxing solution of the nucleophile **1** (0.1 mmol) and triphenylphosphine in MeCN (1.0 mL). Upon complete consumption of **1**, $Pd(OAc)_2$, nBu_4NOAc (0.1 mmol), and $NaHCO_3$ (0.2 mmol) were added and the reaction was heated under reflux. The same conditions were used in the reactions presented in Table 2 and Schemes 4 and 5. [b]Isolated yields and *E*:*Z* ratios are given. [c]The *E*-isomer was contaminated with a byproduct. See the Supporting Information (SI) for details.

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

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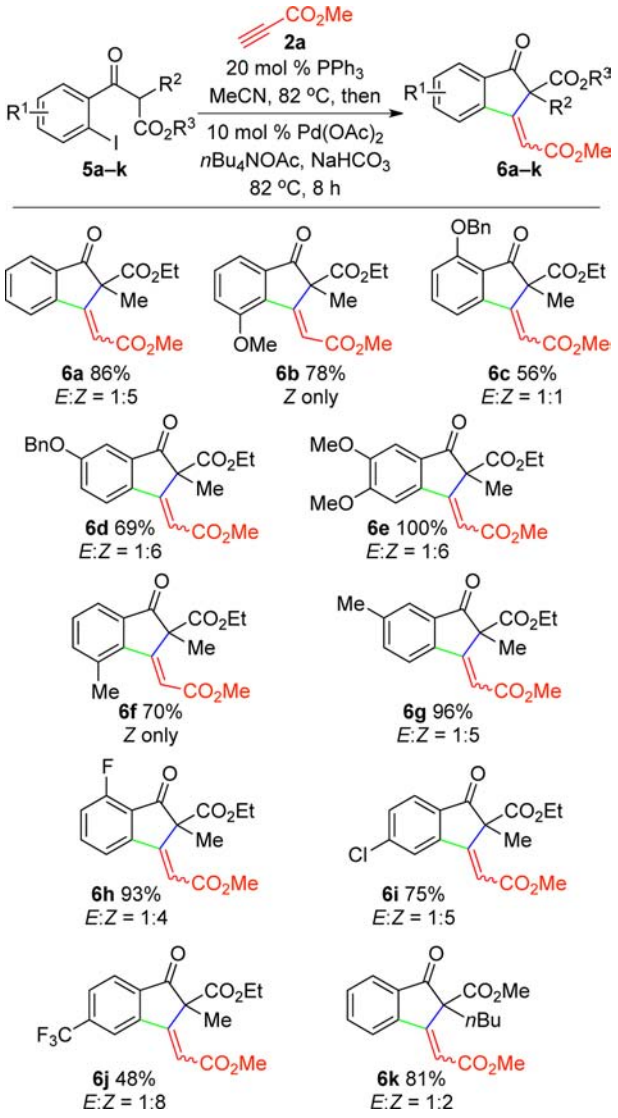
indanones when using 2-iodobenzoylacetates as pronucleophiles (Scheme 4). Various types of substitution on the

Scheme 4. Synthesis of Functionalized Alkylidene Indanones[a]



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

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

Table 2. Synthesis of Alkylidene Indanones Using Activated Alkynes[a]

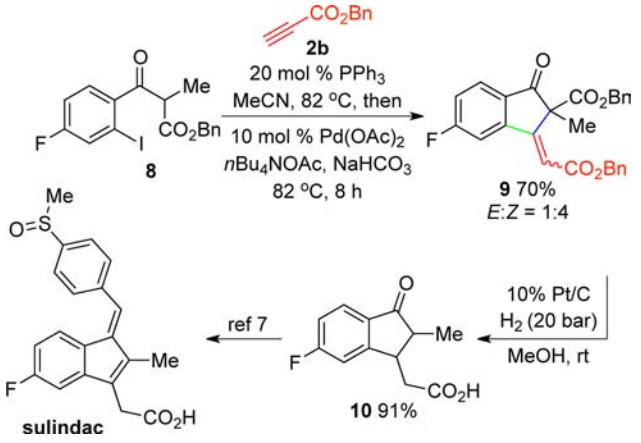
entry	R	*E*:*Z*	yield (%)
1	OBn	1:3	**7a**, 97
2	Ph	1:1	**7b**, 51
3	thienyl	1:2	**7c**, 53
4	4-NCC$_6$H$_4$	1:6	**7d**, 55
5	N(OMe)(Me)	1:3	**7e**, 88

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

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

Scheme 5. Synthetic Application of Tandem Michael–Heck Reaction



(**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 H_2 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.

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■ ASSOCIATED CONTENT

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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Notes

The authors declare no competing financial interest.

■ 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 ^{1}H 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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