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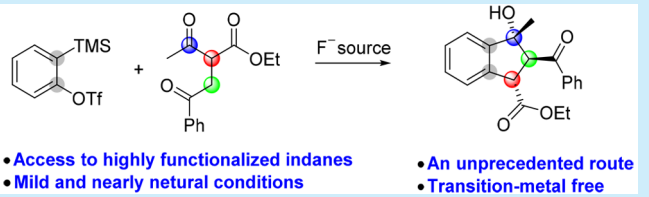
Access to Highly Functionalized Indanes from Arynes and α,γ-Diketo Esters

Wanyao Hu,[†,§] Cong Zhang,[†,§] Jie Huang,[*,‡] Yingying Guo,[†] Zhenqian Fu,[*,†] and Wei Huang[*,†]

[†]Key Laboratory of Flexible Electronics & Institute of Advanced Materials and [‡]Institute of Advanced Synthesis, School of Chemistry and Molecular Engineering, Jiangsu National Synergetic Innovation Center for Advanced Materials, Nanjing Tech University, 30 South Puzhu Road, Nanjing, 211816, China

Supporting Information

ABSTRACT: An unprecedented method for the synthesis of highly functionalized indanes from arynes and α,γ-diketo esters is described. Importantly, mild and nearly pH-neutral conditions ensure excellent functional group tolerance. Theoretical studies indicated that the reaction proceeds through a benzocyclobutane intermediate.



Indanes (benzocyclopentanes) are often presented as the core structural scaffolds in numerous natural products and pharmaceuticals with a wide range of promising biological properties (Figure 1).[1] Specifically, Indinavir,[2] one of World Health Organization's List of Essential Medicines, is used for treating HIV/AIDS. Fredericamycin A[3] displays potent antitumor activity against a variety of in vivo tumor models, involving P388 leukemia, B16 melanoma, and CD8F mammary. SB 209670[4] exhibits a highly potent antagonist selective for the endothelin receptors. Moreover, indanes are also found as the core motifs for organocatalysts[5] and ligands.[6] Consequently, considerable effort has been devoted to this field. Many elegant approaches have been successfully developed,[7] mainly including intramolecular cyclization,[8] intermolecular [4 + 1],[9] and [3 + 2][10] annulation (Scheme 1). Notably, the above-mentioned methods often require the use of acids, bases, or transition-metal catalysts, hindering tolerance of functional groups. The development of a conceptually new synthetic methodology for highly functionalized indanes still remains a considerable challenge and is in high demand.

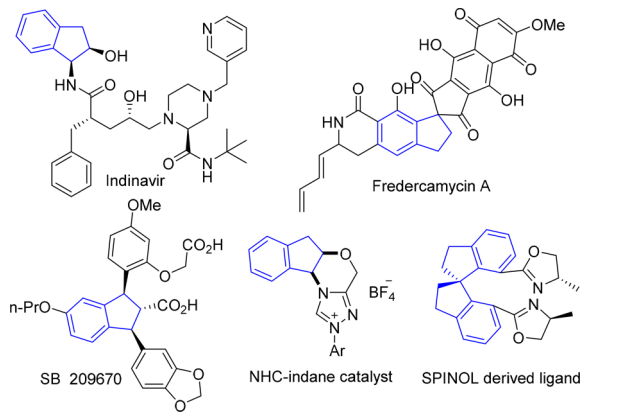
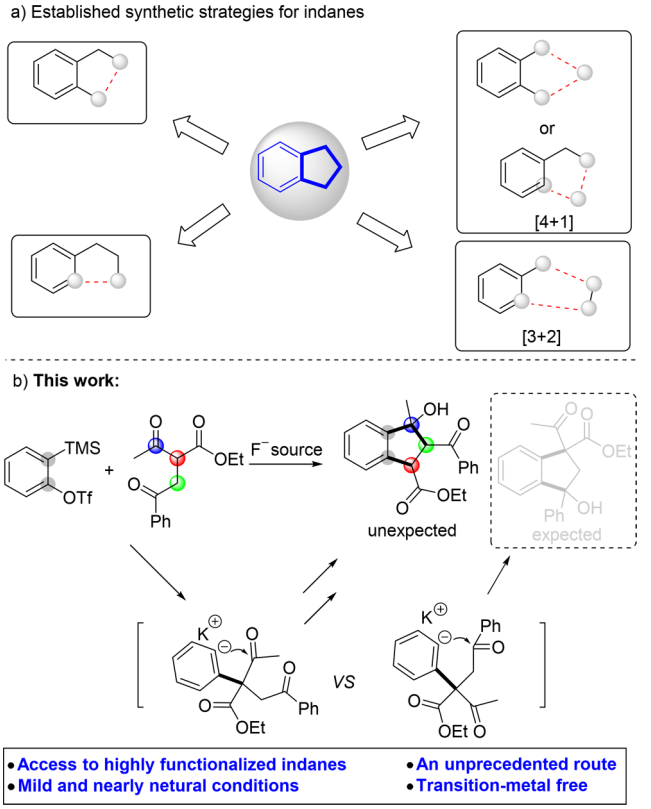


Figure 1. Selected indane-containing bioactive compounds, catalysts, and ligands.

Scheme 1. Synthetic Strategies for Indanes



Direct difunctionalization of arenes can directly and efficiently increase the complexity of arenes. Representative methods

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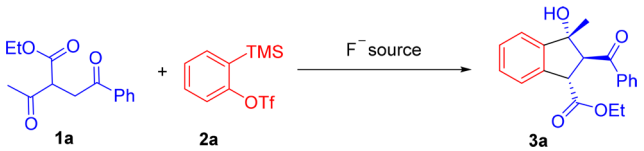
include transition metal-catalyzed direct difunctionalization of aryl halides[11] and transition metal-free direct difunctionalization of arynes.[12,13] Owing to arynes possessing several advantages, such as ease of availability, high reactivity, transition metal-free, and mild reaction conditions, the use of arynes for the direct difunctionalization of arenes has received considerable attention. As part of our ongoing interest in the synthesis of carbo- and heterocycles,[14] we envisaged that a new strategy for the synthesis of highly functionalized indanes might be achieved from the reaction of arynes and α,γ-diketo esters under mild conditions. Actually, there are two possible reaction pathways when α,γ-diketo esters were employed in aryne chemistry. One involves a formal [3 + 2] annulation of arynes with α,γ-diketo esters to give indanes **3′**. The other involves the formation of benzocyclobutane[15] followed by ring-opening and intramolecular cyclization, finally to generate indanes **3**. We presumed that five-membered ring formation would be dominant over four-membered ring formation due to the ring stain. Consequently, indanes **3′** should be the expected products. Surprisingly, the unexpected products **3** were indeed obtained. Herein, we describe an unprecedented approach for the direct synthesis of highly functionalized indanes from arynes and α,γ-diketo esters under mild and nearly pH-neutral conditions. Notably, in contrast with phenyl moieties as three-, four-, or five-carbon synthons in previous work, aryne precursors were used as two-carbon synthons for the construction of indanes via an unprecedented domino process. Importantly, mild and nearly pH-neutral conditions ensure excellent tolerance of functional groups.

The reaction of readily available ethyl 2-acetyl-4-oxo-4-phenylbutanoate **1a** and Kobayashi benzyne precursor[16] **2a** was selected as a model reaction for optimizing the conditions. The key results are summarized in Table 1. When CsF was used as the F^- source in CH_3CN at room temperature, the expected indane **3a′** was not observed. Instead, the unexpected indane **3a** was obtained in 70% yield with 2.4:1 dr (entry 1). Their structures were confirmed by X-ray diffraction analysis.[17] Other common solvents screening, such as THF, DCM, 1,4-dioxane, and the solvent mixture of CH_3CN and THF, did not further improve the product yield and diastereoselectivity. Switching F^- source to TBAF with CH_3CN as solvent, the indane **3a** was obtained in 63% yield with 3.9:1 dr. Similarly, other common solvents investigation did not give satisfactory outcomes. Subsequently, we moved to using KF as a F^- source and 18-crown-6 as an additive in THF at room temperature, the product **3a** was obtained in up to 74% yield with 5.1:1 dr. To our delight, decreasing reaction temperature (0 °C) can further improve the product yield to 78% with up to 6.0:1 dr. Notably, other diastereomers of **3a** were not detected, perhaps due to this transformation through a sequential domino process.

Table 1. Screening Reaction Conditions[a]



entry	F^- source	additive	solvent	yield (%)[b]	dr[c]
1	CsF		CH_3CN	70	2.4:1
2	CsF		THF	61	1.9:1
3	CsF		DCM	68	1.8:1
4	CsF		dioxane	52	1.5:1
5	CsF		CH_3CN/THF = 1:1	68	2.1:1
6	TBAF		CH_3CN	63	3.9:1
7	TBAF		THF	59	3.5:1
8	TBAF		DCM	60	2.0:1
9	TBAF		dioxane	62	2.5:1
10	KF	18-crown-6	THF	74	5.1:1
11	KF	18-crown-6	CH_3CN	50	3.0:1
12[d]	KF	18-crown-6	THF	78	6.0:1

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (1.2 equiv), F^- source (3.0 equiv), 18-crown-6 (3.0 equiv) in solvent (2.0 mL) at room temperature. [b]Isolated yields after column chromatography. [c]Diastereomeric ratio of **3a**, determined via ^1H NMR analysis of unpurified reaction mixtures. [d]At 0 °C.

With acceptable optimized conditions in hand (Table 1, entry 12), we then evaluated the scope of α,γ-diketo esters substrates by using Kobayashi benzyne precursor **2a** as a model substrate (Scheme 2). Changing the R^1 group from ethoxy group to methoxy group, benzoxy, and even methyl group, the reactions proceeded smoothly to give the corresponding products **3b**−**3d**, respectively. For R^2, the methyl group can be replaced with an ethyl or phenyl group, with the corresponding products **3d** and **3e** obtained with moderate yields and dr. The substrates with R^3 bearing several substituted groups (Me, OMe, F, Cl, Br) on the aromatic rings were used under standard conditions, affording the corresponding products **3f**−**3l** in acceptable yields and dr. When R^3 is the 2-naphthyl group, the indane **3m** was obtained in 69% yield with 2.2:1 dr. Only ring-opening product **3n** was found probably due to unsuccessful deprotonation of ester groups under reaction conditions. When α,δ-diketo ester **1o** was used, expected benzocyclohexane was not detected. Instead, ring-opening product **3o** was formed, albeit with a lower yield. Notably, a 1-g reaction of **2a** worked very well, affording **3a** in 61% yield and 2.1:1 dr. Replacement of R_2CO with methyl or phenyl did not give the desired product.

Then, we investigated the generality of aryne precursors **2**, and the results are summarized in Scheme 3. Arynes bearing electron-donating groups, such as 4-methyl, 4,5-dimethoxy, and 3-methoxy groups on the aromatic rings, the reactions proceeded smoothly to furnish the indanes **3p** and **3r** in 53−69% yields with 2.2:1−5.7:1 dr. Both symmetric and unsymmetric naphthyl aryne precursors were suitable substrates for this transformation to give the products **3s** and **3t**, respectively. To our delight, aryne precursor with a 4,5-difluoro group was also a suitable substrate, leading to the formation of product **3u** in 42% yield with 3.9:1 dr.

Based on previous work, the current results, and theoretical studies, a proposed reaction pathway for the formation of indanes is illustrated in Scheme 4. Aryne intermediate **I** was in situ generated from *o*-silyl aryl triflate **2a** mediated by the F^- source under mild and nearly pH-neutral conditions. Intermediate **II**, derived from **1a** via deprotonation, attacks aryne intermediate **I** to form intermediate **III**. Subsequently, there are two possible pathways. One is directly to form indane **3a′** (pathway 4). The other is to form benzocyclobutane intermediate **IV** followed by ring-opening to give intermediate **V**. Then, intermediate **V** undergoes proton transfer followed by intramolecular cyclization and protonation to form indane **3a**.

In order to understand the mechanism, theoretical studies were performed as shown in Figure 2a (technical details given in Supporting Information). Theoretical studies indicate that the energy barrier for the formation of the benzocyclobutane

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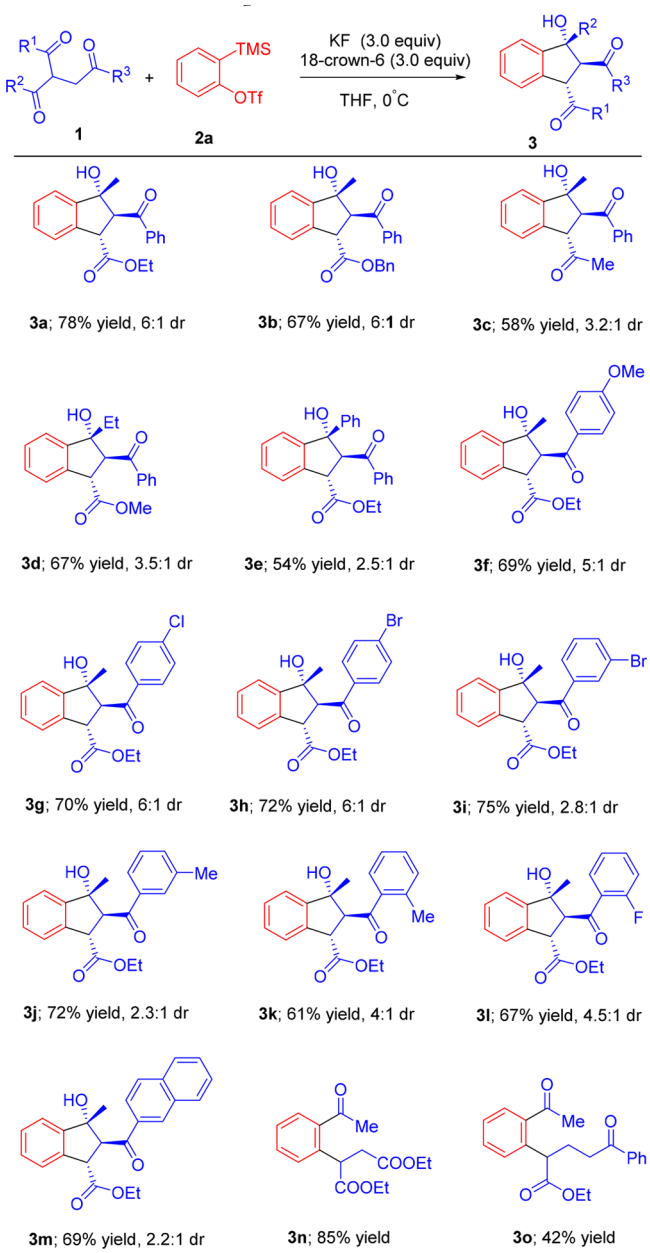
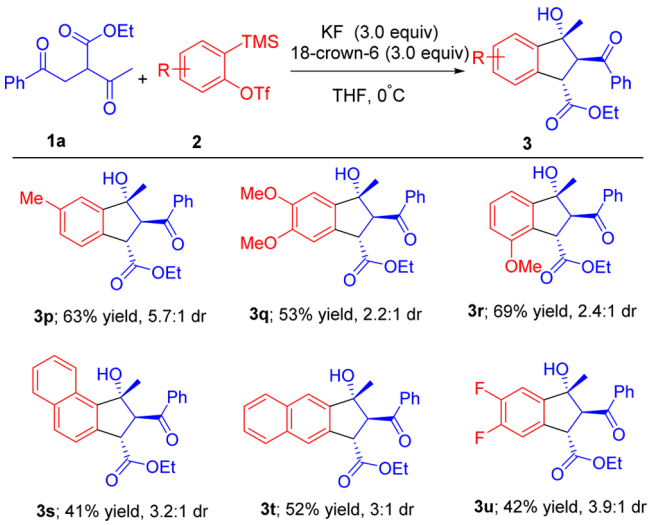
Scheme 2. Substrate Scope[a]



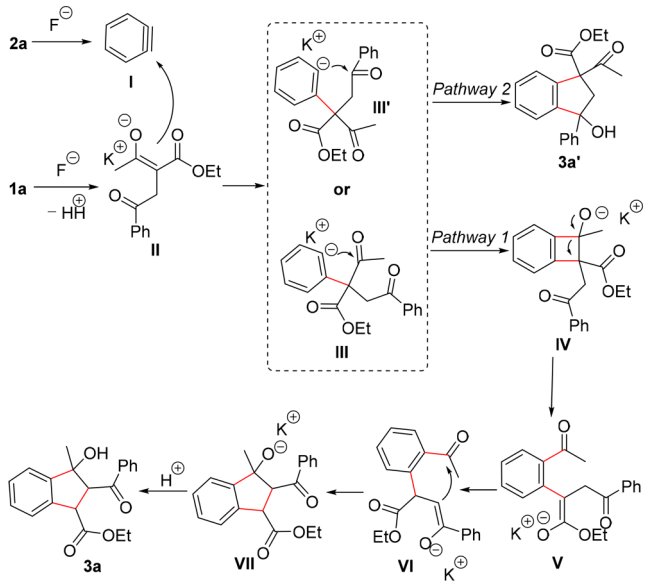
[a]Reaction conditions as in Table 1, entry 12; yields (after SiO_2 chromatography purification) were based on α,γ-diketo esters **1**. 5 mmol scale reaction.

Scheme 3. Substrate Scope[a]



[a]Reaction conditions as in Table 1, entry 12; yields (after SiO_2 chromatography purification) were based on α,γ-diketo esters **1**.

Scheme 4. Proposed Mechanism



intermediate **IV** is over 1.0 kcal/mol relative to its intermediate **III**. Meanwhile, the energy barrier for the formation of a five-membered ring is 9.5 kcal/mol for pathway 2. The energy difference suggests that pathway 1 should be more energetically favorable in kinetics. Additionally, the final product **3a** for pathway 1 is more stable than **3a′** by 7.8 kcal/mol. Therefore, pathway 1 should be more energetically preferred than pathway 2. Moreover, both of the pathways are strongly exothermic, rendering the reaction irreversible.

As shown in Figure 2b, major_int_1 and minor_int_1 were generated from the rotation of acetyl group of intermediate **VI**. Interaction between methyl group and on the same side of benzoyl group reduces their distance and also stabilizes the intermediate major_int_1. Furthermore, major isomer possesses lower energy barrier and more energy stable than minor isomers (for details, see Supporting Information). These led to the products obtained with good diastereoselectivities.

Subsequently, further synthetic transformation of the highly functionalized indanes was conducted as shown in Scheme 5. Treatment of **3c** with ammonium acetate efficiently furnished trisubstituted pyrole **4** in 65% yield via a [4 + 1] cyclization and retro-aldol process. Dehydration of indane **3c** was readily realized with P_2O_5 in toluene at reflux and led to the formation of indene **5** in 88% yield. Interestingly, DIBAL-H can selectively reduce the carbonyl group from acetyl moiety, rather than benzoyl moiety, generating **6** containing two hydroxyl groups in 89% yield with good selectivity of the hydride reduction (10:1 dr).

In summary, we have developed an unprecedented method for the synthesis of highly functionalized indanes from arynes and α,γ-diketo esters. A diverse set of indanes with highly functionalized groups was efficiently obtained in acceptable to

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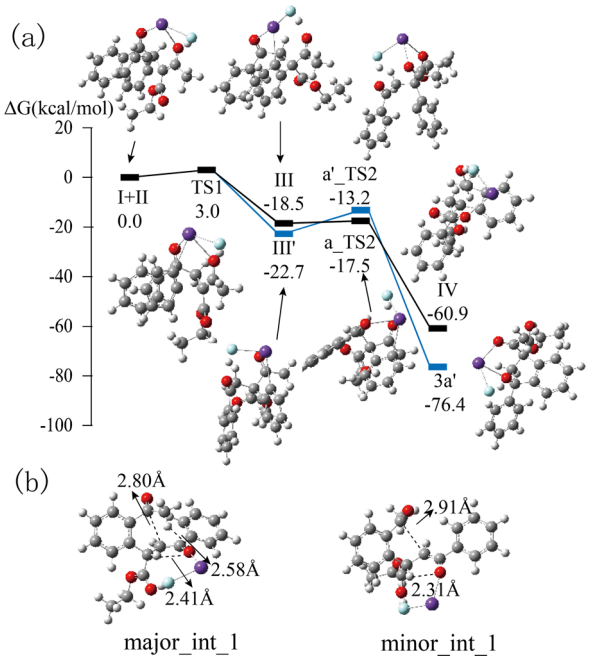
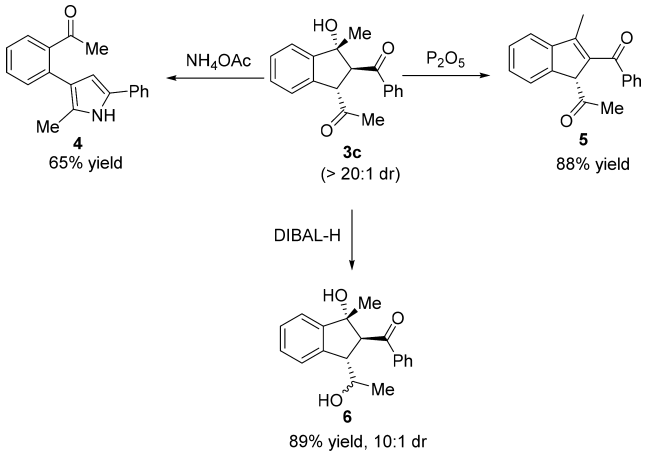


Figure 2. (a) Free energy profile for the reaction obtained at the SMD-M06-2X/6-311++G(2d,2p)//SMD-M06-2X/6-31G(d) level in THF solution. (b) Geometries of major_int_1 and minor_int_1 obtained with SMD-M06-2X/6-31G(d) method.

Scheme 5. Synthetic Transformations



good yields and diastereoselectivities. Mild and nearly pH-neutral conditions ensure excellent tolerance of functional groups. Theoretical studies indicated that the reaction proceeds through a benzocyclobutane intermediate. Synthetic transformations showed the potential application of the products. Further investigations and exploration of this process are underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b03919.

Experimental procedures and spectral data for all new compounds (PDF)

Accession Codes

CCDC 1835638, 1893205, and 1893210 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: iamjhuang@njtech.edu.cn.
*E-mail: iamzqfu@njtech.edu.cn.
*E-mail: iamwhuang@njtech.edu.cn.

ORCID

Zhenqian Fu: 0000-0002-3806-6684

Author Contributions

[§]W.H. and C.Z. contributed equally.

Notes

The authors declare no competing financial interest.

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