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[3+2] regioselective annulation reaction of 2-arylidene-1,3-indandiones towards synthesis of spirocyclopentenes: understanding the mechanism of γ-attack *vs.* α-attack using DFT studies†

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A regioselective [3+2] cyclisation reaction between 2-arylidene-1,3-indanedione and ethyl 2,3-butadienoate catalysed by triphenylphosphine has been demonstrated to synthesize functionalised spirocyclic cyclopentenes. The reaction tolerated various electron-rich and electron-deficient aryl substituted 2-arylidene-1,3-indanediones with high to excellent chemical yields (up to 99%) and moderate to good regioselectivity (up to 5 : 1). DFT studies have also been carried out to understand the regioselective nature of this reaction. The results of Frontier molecular orbital calculations and the activation energy (E_a) favour the formation of compound **3a** *via* γ-attack compared to that of **4a** *via* α-attack.

Introduction

Nucleophilic phosphine-catalysed annulation of allenes has emerged as a powerful tool for the construction of diverse carbocycles and heterocycles.[1] Various electrophiles such as activated alkenes,[2] enones,[3] ketones,[4] imines,[5] oxo-dienes,[6] cyclic ketimines,[7] chromenones,[8] azomethine imines,[9] salicyl *N*-thiophosphinyl imines,[10] alkylidene malononitriles,[11] exocyclic enones,[12] aldehydes,[13] *N*-acyldiazenes,[14] naphthaquinones,[15] *p*-quinine methide,[16] amino esters,[17] and diones[18] have been used for the annulation reaction. The first [3+2] asymmetric process was reported by Zhang *et al.*[19] Later on several chiral annulation reactions were investigated.[20]

1,3-Indandione is an important constituent of numerous natural products and bioactive skeletons (Fig. 1)[21] and has been used as a reaction substrate extensively.[22] Some of these natural products display activity due to spirocyclic moieties[23] of various sizes. In recent years, a readily accessible material *i.e.* 2-arylidene-1,3-indandiones[24] has started gaining importance in the field of phosphine catalysed annulations.[25] A regioselective [4+2][26] cyclisation between 2-arylidene-1,3-indandiones and γ-substituted allenoates was carried out explicitly by Huang and co-workers towards synthesis of spiro[4.5]dec-6-ene skeletons as δ-adduct (eqn (a), Scheme 1).[27] Very recently, Zheng and Er-Qing carried out a phosphine catalysed [3+2] cyclisation with γ-methyl allenoates for the synthesis of spirocyclopentene as α-adduct (eqn (b), Scheme 1).[28] In continuation with our interest towards the synthesis of spiro carbocycles,[29] we herein report a regioselective [3+2] cyclisation of 2-arylidene-1,3-indandiones and 2,3-butadienoate catalysed by triphenylphosphine (eqn (c), Scheme 1). To the best of our knowledge, this is the first report

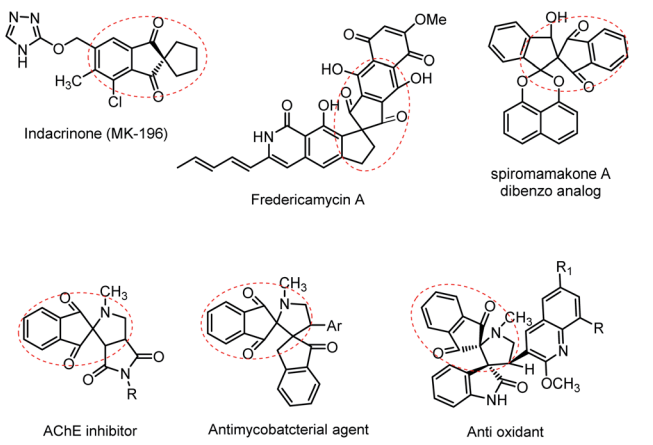

Fig. 1 Natural and bioactive molecules containing Indanedione based spirocarbocycles and spiroheterocycles.

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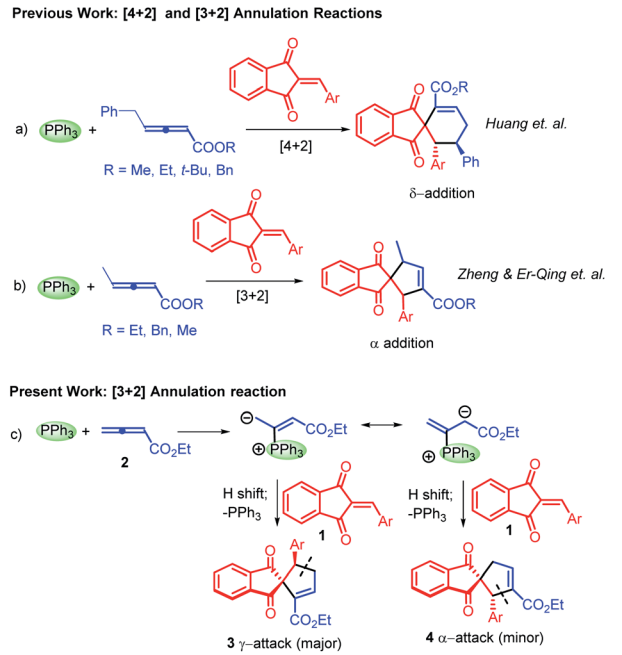


Scheme 1 PPh_3 driven annulation reaction of 2-arylidene-1,3-indanedione using allenoates.

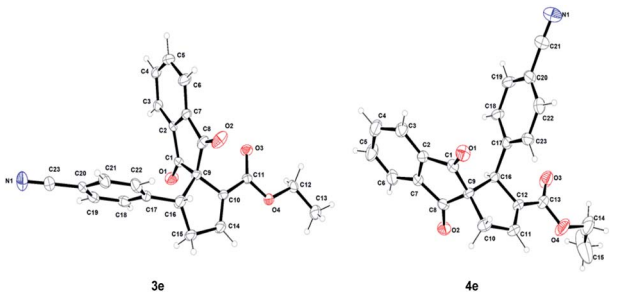


Fig. 2 Crystal structures of **3e** (CCDC 921839) and **4e** (CCDC 921702).

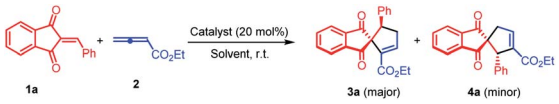
for the synthesis of functionalised spirocyclopentenes as γ-addition as well as α-addition adduct.

Interestingly, spirocyclopentene **3** was obtained predominantly *via* γ-attack along with **4** as a minor product through α-attack of ethyl-2,3-butadienoate **2** on benzylidene-1,3-indanedione **1** using PPh_3 (eqn (c), Scheme 1). The structures of both the products were further confirmed by single X-ray crystallography (Fig. 2).

Results and discussion

We initially carried out the reaction of 2-(benzylidene)-1,3-indanedione **1a** with allenoate **2** using Ph_3P (Table 1). The reaction was carried out in CH_3CN at ambient temperature to give separable products **3a** and **4a** with a total chemical yield of 22% (Table 1, entry 1). The isolated yield of the reaction was improved to 41% when THF was used (Table 1, entry 2). A relatively electron-rich catalyst such as Bu_3P showed the same reactivity with a marginal increase in yield using toluene as solvent (Table 1, entry 3). Improvement in the yield of the reaction was observed using Ph_3P in toluene that resulted in good regioselectivity of 5 : 1 (Table 1, entries 4 and 5). Drastic improvement in the chemical yield of the reaction was observed when the reaction was performed under dilute conditions (Table 1, entries 6 and 7). A culminating point was observed in the yield of the reaction on a further increase in the volume of the reaction (Table 1, entry 8).

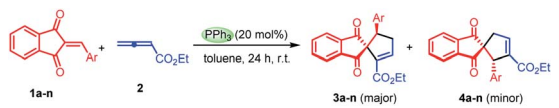
Table 1 Optimization of reaction conditions[a]



Entry	Catalyst (mol%)	Solvent	Time (h)	(**3a** : **4a**)[b]	Yield[c]
1	PPh_3	CH_3CN	24	n.d.	22
2	PPh_3	THF	24	n.d.	41
3	PBu_3	Toluene	24	5 : 1	44
4	PPh_3	Toluene	12	5 : 1	51
5	PPh_3	Toluene	24	5 : 1	55
6[d]	PPh_3	Toluene	24	6 : 1	76
7[e]	PPh_3	Toluene	24	5 : 1	88
8[f]	PPh_3	Toluene	24	5 : 1	99

[a] Unless otherwise noted, reactions were carried out with (0.1 mmol) of **1a** with (0.2 mmol) of **2** using 20 mol% of catalyst in 400 μL solvent under N_2 atmosphere. [b] Determined by ^{1}H-NMR analysis of crude reaction mixture. [c] Total isolated yield of products **3a** and **4a**. [d] Reaction was carried out at 0.1 M conditions (2.0 mL solvent). [e] Reaction was carried out at 0.05 M conditions (4.0 mL solvent). [f] Reaction was carried out at 0.03 M conditions (6.0 mL solvent).

Table 2 Substrate Scope towards cascade formal [3+2] annulation[a]



Entry	Ar	Product	(**3** : **4**)[b]	Yield[c]
1	C_6H_5	**3a**/**4a**	5 : 1	99
2	4-$NO_2C_6H_4$	**3b**/**4b**	4 : 1	99
3	4-$MeCO_2C_6H_4$	**3c**/**4c**	1 : 1	84
4	4-$CF_3C_6H_4$	**3d**/**4d**	3 : 2	87
5	4-CNC_6H_4	**3e**/**4e**	5 : 1	99
6	4-FC_6H_4	**3f**/**4f**	2 : 1	96
7	4-ClC_6H_4	**3g**/**4g**	7 : 2	98
8	4-BrC_6H_4	**3h**/**4h**	3 : 2	88
9	4-$AcOC_6H_4$	**3i**/**4i**	4 : 1	89
10	4-$CH_3C_6H_4$	**3j**/**4j**	4 : 1	95
11	4-$CH_3OC_6H_4$	**3k**/**4k**	3 : 1	77
12	4-$N(CH_3)_2C_6H_4$	**3l**/**4l**	2 : 1	63
13	3-Thienyl	**3m**/**4m**	3 : 2	82
14	2-Thienyl	**3n**/**4n**	1 : 2	91

[a] Unless otherwise noted, all reactions were carried out with 0.1 mmol of **1** with 0.2 mmol of **2** using 20 mol% of PPh_3 in 6.0 mL toluene (0.03 M conditions) under N_2 atmosphere. [b] Determined by ^{1}H-NMR analysis of crude reaction mixture. [c] Total isolated yield of products **3** & **4**.

With the optimised reaction conditions realised, we carried out the generalisation of the present protocol using various substituted 2-arylidene-1,3-indanediones **1b–n**. It was observed that both electron-donating and electron-withdrawing groups were tolerable in the *para*-position of the phenyl ring in **1** (Table 2). The use of electron-withdrawing groups did not alter the reactivity of the reaction and the regioselectivity with quantitative yields was maintained (Table 2, entries 1 and 2). The chemical structures of γ- and α-substituted products were initially assigned by ^{1}H, ^{13}C-NMR, and HRMS analysis and were unambiguously assigned by single crystal X-ray diffraction for products **3e** and **4e** (Fig. 2).[30]

The methyl ester group on the phenyl ring decreased the regioselectivity of the reaction presumably due to a decrease in electrophilicity of Michael acceptor **1c** (Table 2, entry 3). The use of the –CN group demonstrated better regioselectivity and reactivity when compared to that of the $-CF_3$ group (Table 2, entries 4–5). The presence of halogen-substituents in *para*-position of the phenyl ring was well tolerated with moderate regioselectivity and high chemical yields (Table 2, entries 6–8). The use of an acetoxy group was also compatible under the present reaction conditions (Table 2, entry 9). The use of electron-donating groups such as methyl, methoxy, and *N*,*N*-dimethyl on phenyl ring decreased the yield and regioselectivity for the formation of products **3j**/**4j** to **3l**/**4l** presumably due to the creation of electron density at the electrophilic carbon atom (Table 2, entries 10–12). Excellent chemical yields albeit with moderate regioselectivity when heteroaromatic substrates were used (Table 2, entries 13 and 14).

DFT studies

Computational methods

The computations were carried out using the Gaussian 09 suite of program.[31] All the optimisations, transition states and single point energy calculations have been carried out at B3LYP/6-31g(d)[32] level in the gas phase. The optimised conformation of reactants, intermediates and products were further confirmed that there is no imaginary frequency. Moreover, all the transition states were confirmed with a minimum of one imaginary frequency and the values are used in the discussion below.

Results and discussion. To corroborate the formation of major product spiro cyclopentene **3a** among two possible regioisomers **3a** and **4a**, Density Functional Theory (DFT) calculations were exclusively studied. The key step involved in this reaction is the formation of highly reactive zwitterions **A** and **B** (see ESI †). Zwitterion **A** and **B** were produced by the attack of PPh_3 on 2,3-butadienoate **2**. 2-Benzylidene-1,3-indanedione **1a**, zwitterions **A** and **B** were chosen as precursors for DFT calculations. Moreover, the HOMO–LUMO gap (see Fig. 3) for the zwitterions **A** and **B** was observed to be 3.17 and 2.74 eV, respectively, which confirms the lower band gap for the zwitterion **B** and its high reactivity (Fig. 3). The HOMO–LUMO gap has been calculated based on the higher oscillator strength observed for both zwitterions.

The transition states were computed for the two possible products and the results were explained in Fig. 4. As shown in Fig. 4 (potential energy surface), initially, **1a** was allowed to interact with **A** and has formed **1a**–**A** complex with the binding energy of −6.35 kcal mol^{-1}. Similarly, **1a** was allowed to interact with **B** resulting in **1a**–**B** complex with the binding energy of −7.04 kcal mol^{-1}. The binding energy difference between the two complexes was observed to be minimal *i.e.*, 0.69 kcal mol^{-1}. The results show the competitive nature of zwitterions towards the formation of products **3a** and **4a**. The attack of methylene anion of **B** on α-carbon of 2-benzylidene-1,3-indandione **1a** has produced TS1a with the vibrational frequency of −284.23 cm^{-1} and the barrier energy of 9.95 kcal mol^{-1}. Whereas, the attack of methine anion of **A** on α-carbon of 2-benzylidene-1,3-indandione **1a** has produced TS1 with the vibrational frequency of −196.10 cm^{-1} and the barrier energy of 6.72 kcal mol^{-1}. The barrier energy difference between TS1 and TS1a was observed to be 2.54 kcal mol^{-1}. This Michael addition leads to **Int 1** and **Int 1a** with enthalpies of formation (ΔH_f) −9.39 kcal mol^{-1} and −16.49 kcal mol^{-1}, respectively. It was observed that **Int 1a** is more stable than that of **Int 1** with an energy difference of 4.56 kcal mol^{-1}. The intermediates, **Int 1a** and **Int 1**, produced TS2a and TS2 with the barrier energies of 8.81 and 7.69 kcal mol^{-1}. The difference in barrier energies for both TS2 and TS2a was observed to be 1.12 kcal mol^{-1}. Intramolecular Michael addition of **Int 1a** and **Int 1** resulted in **Int 2a** and **Int 2** respectively. The enthalpy of formation (ΔH_f) of **Int 2a** and **Int 2** was observed to be 10.21 and 10.77 kcal mol^{-1}, respectively. **Int 2a** and **Int 2** undergoes 1,2-proton transfer resulting in TS3a and TS3 having the barrier energies 47.11 kcal mol^{-1} and 73.31 kcal mol^{-1}, respectively. It is clearly evident that TS3a is more stable than TS3 with a difference of 29.08 kcal mol^{-1}.

The less barrier energy observed for TS3a leads to the formation of **3a** in line with the experimental observation of higher yield than that of **4a** with the elimination of PPh_3. For products **3a** and **4a**, the enthalpy energy was observed to be 74.28 and 100.51 kcal mol^{-1}, respectively. It can be concluded that product formation **3a** shows low barrier energy (Blue line) in all the steps except TS1a. Moreover, the computational results explained the cause of the major and minor products for this reaction.

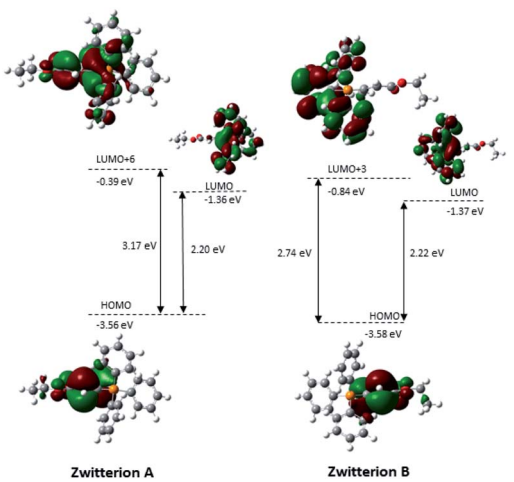


Fig. 3 Frontier molecular orbital diagram of **A** and **B** obtained at B3LYP/6-31(d) level in gas phase.

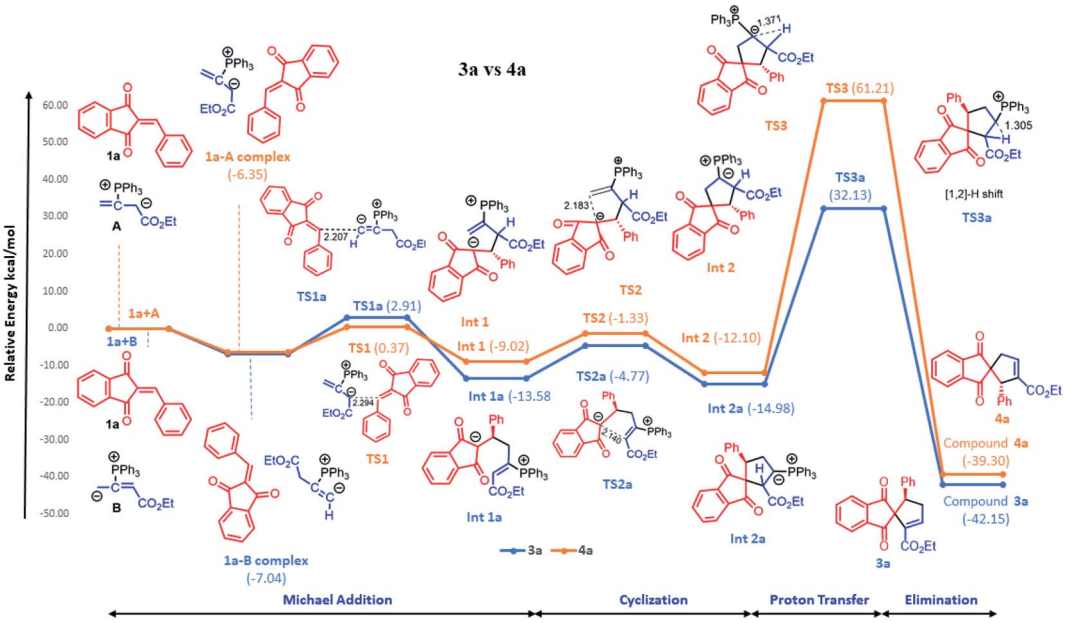
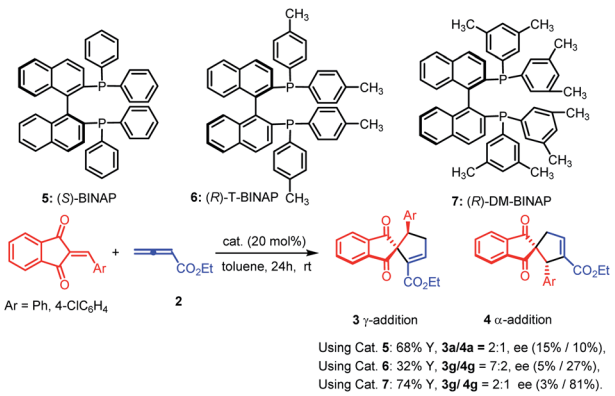


Fig. 4 Energy barrier diagram for the formation of regioisomers **3a** and **4a**.

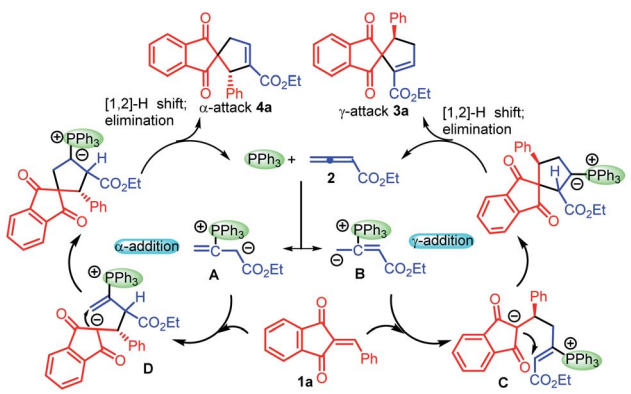


Scheme 2 Asymmetric annulation catalysed by chiral catalysts.

No other product was detected from the ^{1}H NMR analysis of the crude products, which demonstrated the efficiency of the current [3+2] cyclisation. With the standard protocol established for the synthesis of spirocyclopentenes, we next focused our attention on asymmetric variants by using various axially chiral trivalent phosphorus catalysts **5**–**7**.

The use of chiral (*S*)-BINAP **5** gave a moderate yield of 68% with low regioselectivity (*i.e.*, 2 : 1) and enantioselectivity for **3a**/**4a** (*i.e.*15 and 10% ee, respectively). The use of chiral (*R*)-T-BINAP **6** resulted in poor chemical yield for **3g**/**4g** even after 10 d of the reaction period. Finally, (*R*)-DM-BINAP **7** showed promising results with 74% yield for the formation of **3g**/**4g** with high enantioselectivity of 81% for α-attack product **4g** (Scheme 2).

A reasonable mechanism can be given for this regioselective [3+2] annulation reaction as shown in Scheme 3, catalyst Ph_3P attacks the central sp carbon of ethyl-2,3-butadienoate **2** to generate Ph_3P-allenoate zwitterionic intermediates **A** and **B**. The dipole **A** with the anion at the α-carbon position is believed to be more stable than dipole **B** with anion residing on γ-carbon position. This can be evident from the regioselectivity of products **3** and **4**. These dipole intermediates then react with the Michael acceptor **1** in a [3+2] cyclisation fashion to form **C** and **D**. Subsequent ring closure, 1,2-proton transfer and further elimination of PPh_3 gives the cyclopentenes **3** and **4** as major and minor products (Scheme 3).



Scheme 3 Possible catalytic cycle for products **3a** and **4a**.

Conclusions

In conclusion, we have demonstrated a regioselective [3+2] annulation reaction for the formation of spirocyclic cyclopentenes with high to excellent levels of chemical yield and regioselectivity. Previous work carried out using γ-substituted allenoates with 2-arylidene-1,3-indandiones in the presence of triphenylphosphine resulted in spiro[4.5]decene (*i.e.* δ-addition)[27] and spiro[4.4]non-7-ene skeletons (*i.e.* α-addition).[28] On

the other hand, the current work also involves the use of 2-arylidene-1,3-indandiones which on reaction with simple allenoate such as ethyl-2,3-butadienoate in the presence of triphenylphosphine gives γ-addition spiro[4.4]non-6-ene adduct as the major product and α-addition spiro[4.4]non-7-ene adduct as the minor product. This triphenylphosphine mediated catalysis towards the synthesis of functionalized spirocarbocyclic derivatives results in the formation of asymmetric carbon centre as well as quaternary stereocentre. The result of DFT studies of frontier molecular orbital calculation on the regioselective reaction of 2-arylidene-1,3-indanedione and ethyl 2,3-butadienoate catalysed by triphenylphosphine shows a lower HOMO–LUMO gap for zwitterion **B** compared to that of **A**. Moreover, the activation energy has also been observed to be lower for **3a** compared with that of **4a** which shows the reactivity of zwitterion **B** which favours the formation of compound **3a** as the major product.

Conflicts of interest

There are no conflicts to declare.

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