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Indium-catalyzed, novel route to β,β-disubstituted indanones *via* tandem Nakamura addition–hydroarylation–decarboxylation sequence†

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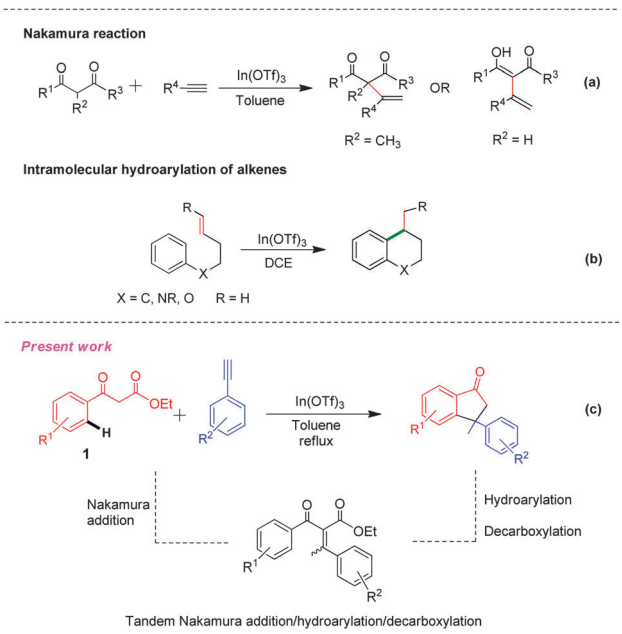
A novel method for the construction of β,β-disubstituted indanones has been developed *via* tandem Nakamura addition–hydroarylation–decarboxylation process. Indium(III) triflate was demonstrated as a versatile multitasking catalyst, which catalyzes three different chemical transformations under one-pot conditions.

In recent years, the design and development of one-pot, multi-tasking catalysis[1] has gained much attention because of its potential to conjugate multiple reactive centres *via* various fundamentally different chemical transformations in a tandem manner under one-pot reaction conditions. The evaluation of such catalytic systems for the generation of complex and valuable molecules from simple starting materials is highly desirable. Indanone is a valuable molecule that serves as a synthetic intermediate[2] and exists in numerous natural products and pharmaceuticals.[3] Intramolecular Friedel–Crafts acylation of 3-arylpropionic acid derivatives[4] is the basic approach that has been studied extensively for the construction of indanone derivatives. Though this method effectively accesses the target indanones, it suffers some limitations, like the requirement of strong acids, elevated temperatures and pre-requisite synthesis of starting 3-arylproponic acid derivatives. In this regard, the development of alternative novel approaches is the ongoing challenging task, which has been addressed with few fruitful results.[5] In 2005, Iwasawa[5a] and Hayashi[5b] successfully reported a novel, rhodium-catalyzed isomerization of α-arylpropargyl alcohols to β-monosubstituted indanones. Another rhodium-catalyzed, useful method for the synthesis of β,β-disubstituted indanones was demonstrated by Hayashi's group *via* addition of arylzinc reagents to aryl alkynyl ketones.[5c] Recently, enantio-selective synthesis of substituted indanones[5d,e] was also achieved. These novel methods have encouraged us to explore new strategies, mainly from readily available starting materials, to avoid multi-step substrate synthesis in the absence of any additives.

The addition of 1,3-dicarbonyl compounds to unactivated alkynes is a versatile tool for the construction of C–C bonds. Nakamura's group[6] has contributed enormously to this subject by employing indium salts as an effective catalytic system. Nakamura reaction involves the addition of indium enolates to unactivated alkynes to generate a vinylic double bond at the α-position of the carbonyl compound (Scheme 1, path a). Further elaboration of Nakamura products[6g] is highly attractive due to the presence of potential alkene functionality. The intramolecular hydroarylation of alkenes[7] is a powerful, atom-economic method for the construction of aromatic ring-fused cyclic systems. Various metal-catalyzed protocols were developed to activate the intramolecular hydroarylation process, including



Scheme 1 Indium-catalyzed tandem strategy.

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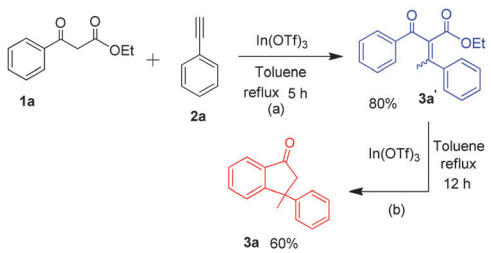
indium salts to generate potential scaffolds (Scheme 1, path b). In our continuous efforts on indium catalysis,[8] we engaged in monitoring the potential of indium salts in one-pot Nakamura reaction and the intramolecular hydroarylation of alkenes by providing the necessary environment to starting substrates. We envisioned that the aromatic β-keto esters, like ethyl benzoylacetate, would participate in Nakamura reaction with terminal alkynes, which further undergo a hydroarylation step with the available double bond functionality under one-pot, indium-catalyzed conditions to generate β,β-disubstituted indanones. With this idea, we initiated our work and disclose here a novel, indium-catalyzed tandem route to β,β-disubstituted indanones *via* Nakamura reaction–hydroarylation–decarboxylation sequence (Scheme 1, path c).

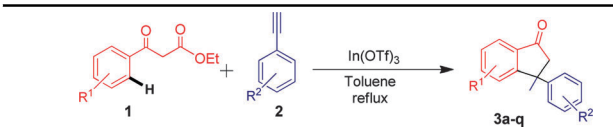
To test our hypothesis, we initiated our study by choosing ethyl benzoylacetate **1a** and phenyl acetylene **2a** as the model substrates. In the preliminary experiment, a model reaction between **1a** and **2a** was carried out by employing 10 mol% indium(III) triflate as a catalyst in toluene at 100 °C for 24 h. To our delight, the formation of β,β-disubstituted indanones in 51% yield was observed. It was quite exciting to note that, in addition to our expected Nakamura addition–hydroarylation sequence, decarboxylation also took place in the one-pot condition to generate β,β-disubstituted indanones. It is well known that decarboxylation of β-keto esters[9] can be achieved under metal-catalyzed conditions. With this promising unexpected result, we dedicated our attention to studying this novel tandem reaction in detail. Increase in yield (62%) was observed when we carried out the model reaction in refluxing toluene for 16 h. As the reaction is believed to progress in a tandem manner, we predict that the isolation of an intermediate (which may be the product of any one chemical transformation) would provide a clear note about the reaction pathway. In agreement with Zhang's report,[10] the formation of isomerised Nakamura product **3a′** was observed within 5 h in 80% yield (Scheme 2, step a) as *E*:*Z* isomeric mixture. In case of unsubstituted β-keto esters, after the formation of Nakamura product, they would isomerize to a Knoevenagel-type product.[6h] Next, a sequential reaction was tried by employing isomerised Nakamura products under current indium-catalyzed conditions. Gratifyingly, the formation of β,β-disubstituted indanone **3a** was observed in 60% yield (Scheme 2, step b).

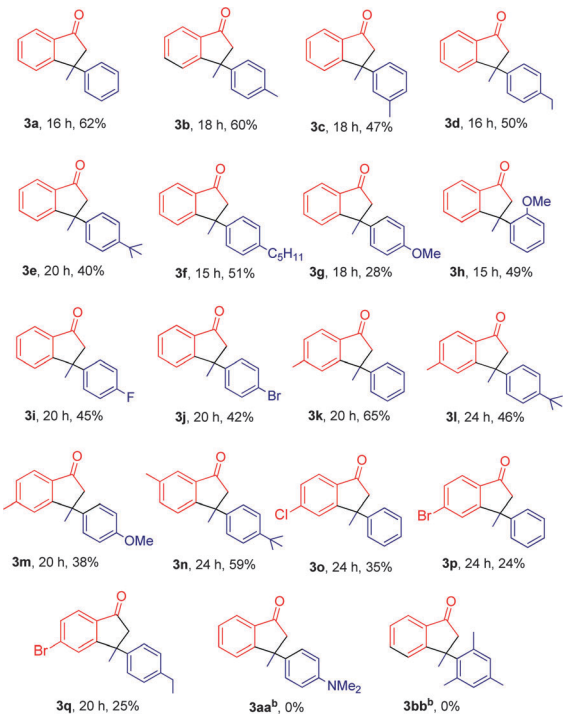
In order to figure out the standard reaction conditions, we further carried out optimisation studies with different metal catalysts and solvents (see ESI,† Table S1). These studies revealed that employing 10 mol% $In(OTf)_3$ in refluxing toluene gave the best result, and thus, it was considered as the optimised condition. With the established optimised reaction conditions, we next initiated the substrate scope study by varying a wide range of terminal alkynes. As illustrated in Table 1, several substrates bearing electron-donating and withdrawing groups on the aromatic ring of terminal alkynes were well tolerated and underwent the current tandem addition–hydroarylation–decarboxylation process to furnish the desired β,β-disubstituted indanones in low to good yields. It was quite encouraging that in all the cases, complete conversion of pre-formed isomerised addition products was observed. Electron-donating substituted terminal alkynes were well tolerated under the present indium-catalyzed conditions and afforded the target indanones in 24–62% yield (Table 1, entries **3b–3h**). Moderate yields were observed when an electron-withdrawing group like halogen was present on the aromatic ring of terminal alkynes; fluoro and bromo substituted phenyl acetylene produce **3i** and **3j** with 45% and 42% yield, respectively. Sterically hindered terminal alkynes, for example 1-ethnyl-2,4,6-trimethyl benzene, were ineffective in the present study; even addition product was also not observed (Table 1, entry **3bb**). Dimethylamino-substituted terminal alkyne was inhibited entirely, perhaps because of the coordination of the amino group to the indium(III)



Scheme 2 Sequential study.

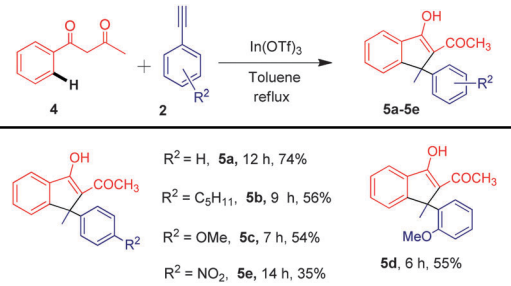
Table 1 Substrate scope for indium-catalyzed tandem sequence[a]





[a] Reaction conditions: β-ketoester (1 mmol), terminal alkyne (1.2 mmol) and 10 mol% $In(OTf)_3$ were allowed to react in toluene (6 ml) at reflux temperature until the reaction was complete. [b] Reaction was carried out in toluene for 24 h.

Table 2 Tandem Nakamura addition–hydroarylation of terminal alkynes with 1-benzoylacetone[a]

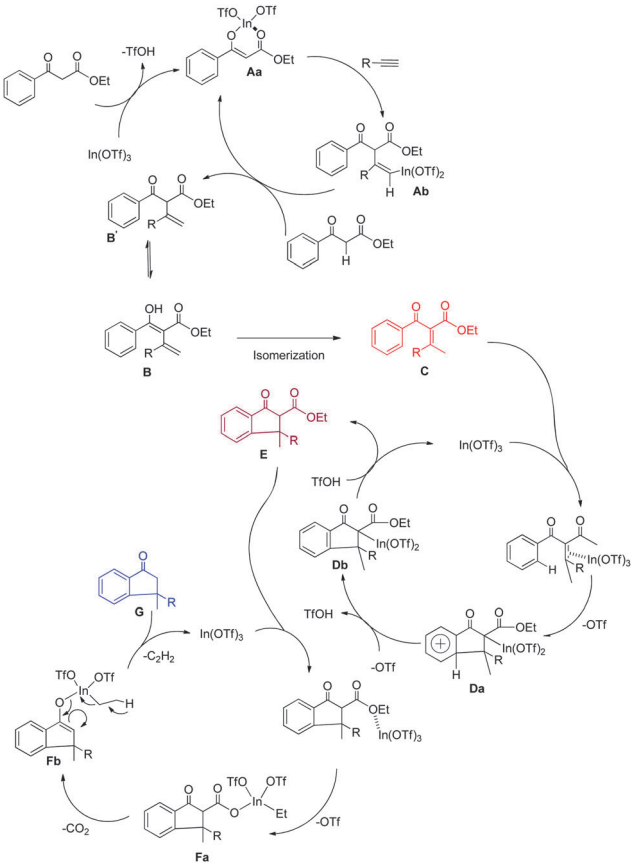


[a] Reaction conditions: 1-benzoylacetone (1 mmol), terminal alkyne (1.2 mmol) and 10 mol% $In(OTf)_3$ were refluxed in toluene (6 ml) until the reaction was complete.

atom (Table 1, entry **3aa**). In turn, variation in other substrates, *e.g.* ethyl benzoylacetate, were tried (Table 1, entries **3k–3q**). These studies revealed that electron-rich ethyl benzoylacetates (4-Me and 3-Me) undergo the tandem sequence smoothly with various terminal alkynes to afford the desired products in 38–65% yield (Table 1, entries **3k–3n**). Halogen-substituted ethyl benzoylacetates significantly reduced the conversion and shifted the yield towards the lesser side (Table 1, entries **3o–3q**).

In order to enhance the versatility of the reaction, we next monitored the feasibility of 1,3-diketones instead of β-keto esters under the present standard conditions. Initially, a reaction between 1-benzoylacetone **4** and phenyl acetylene **2a** was tried by employing 10 mol% indium triflate as a catalyst in refluxing toluene for 12 h (Table 1, entry **5a**). As we expected, the reaction had progressed through tandem Nakamura addition–hydroarylation sequence to generate β,β-disubstituted indanone (enol form) **5a** with acetyl group at α-position in 75% yield. With this result, the scope of terminal alkynes was tested with respect to 1-benzoylacetone, and the results are summarized in Table 2. In all cases, tandem addition–hydroarylation process took place exclusively and furnished the target products within 6–14 h in good to moderate yields (Table 2, entries **5b–5e**). However, exploration of benzoyl-1,1,1-trifluoroacetone as a 1,3-diketone partner completely failed under the current tandem conditions.

On the basis of our sequential study, a plausible mechanism is proposed in Scheme 3. The reaction is initiated with the generation of indium enolate[6a] **Aa** from $In(OTf)_3$ and β-keto ester, which further adds across the terminal alkyne to form alkenyl indium intermediate **Ab**. Protonation of alkenyl indium **Ab** by β-keto ester results in the formation of addition product **B** and regeneration of indium enolate for further cycle. Addition product **B′** tautomerizes to enol form **B** and undergoes isomerization to afford Knoevenagel type product **C**. In the next step, indium activates the double bond functionality in **C**, which further hydroarylates to form alkylindium[7a] intermediate **Da**. Later on, aromatization with concomitant acid release generates the intermediate **Db**, and subsequent protonolysis of the carbon–indium bond affords the product **E**. Finally, removal of the ester group from **E** can be explained on the basis of mechanistic



Scheme 3 Possible mechanism.

aspects of decarboxylative allylation (DcA) reactions[11] and *p*-toluenesulfonic acid-promoted elimination reactions of β-keto esters.[12] We predicted that the reaction had progressed through the decarboxylative generation of indium enolate, followed by elimination process. The reaction is initiated by the oxidative addition of indium triflate with β-keto carboxylate **E** to generate indium β-keto carboxylate **Fa**, which then undergoes decarboxylation to produce indium enolate **Fb**. Finally, indium enolate undergoes the elimination process to furnish the final product **G**, along with the removal of ethylene and regeneration of catalyst for the next cycle.

In summary, we have developed a novel route for the assembly of β,β-disubstituted indanones through a tandem indium-catalyzed Nakamura addition–hydroarylation and decarboxylation sequence. Indium(III) triflate has shown remarkable ability to catalyze three fundamentally different chemical reactions under one-pot conditions in the absence of any additives or co-catalysts to generate indanone derivatives in low to good yields. Exploration of the Nakamura addition product for further synthetic elaboration was successfully demonstrated, and sequential studies were carried out with the isolated isomerized addition intermediate. Further studies are in progress to develop more novel tandem processes by utilizing indium salts as a versatile multitasking catalyst.

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