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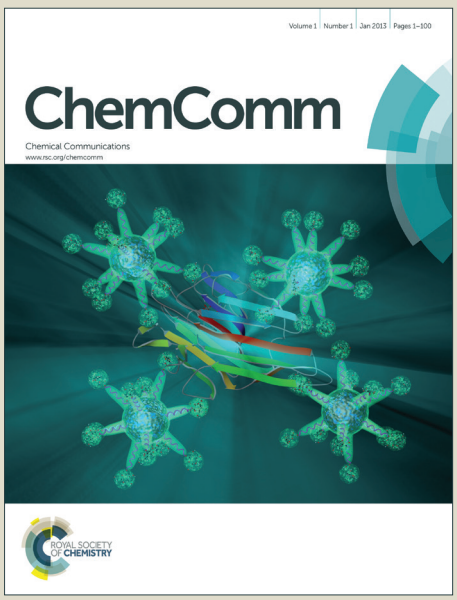

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ARTICLE TYPE

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

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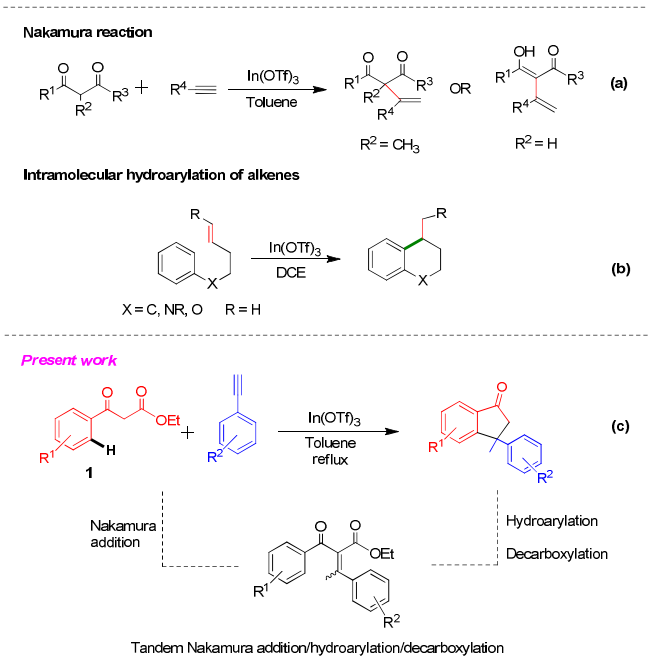
A novel method for the construction of *β,β*-disubstituted indanones has been developed *via* tandem Nakamura addition-hydroarylation-decarboxylation process. Indium (III)triflate has been demonstrtated as a versatile multitasking catalyst, which catalyzes three different chemical transformations under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

In recent years, design and development of one-pot multitasking catalysis[1] has gained much attention because of their potential to conjugate multiple reactive centres *via* various fundamentally different chemical transformations in tandem manner under one-pot reaction conditions. In particular, evaluation of such catalytic systems for generation of complex and valuable molecules from simple starting materials is highly desirable. Indanone is one of the valuable molecules which serves as synthetic intermediate[2] and exists in numerous natural products and pharmaceuticals.[3] Intramolecular Friedal-Craft acylation of 3-arylpropionic acid derivatives[4] is the basic approach which has been studied extensively for construction of indanone derivatives. Though this method effectively accesses the target indanones, suffer some limitations like requirement of strong acids, elevated temperatures and pre-requisite synthesis of starting 3-arylproponic acid derivatives. In this regard, development of alternative novel approaches is the ongoing challenging task, which was addressed by 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, enantioselective synthesis of substituted indanones[5d,5e] 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.

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 vinylic double bond at α-position of carbonyl compound (Scheme 1: path a). Further elaboration of Nakamura product[6g] is highly attractive due to the presence of potential alkene functionality. The intramolecular hydroarylation of alkenes,[7] a powerful atom-economic method for the construction of aromatic ring fused cyclic systems. Various metal catalyzed protocols were developed to activate intramolecular hydroarylation process including indium salts to generate potential scaffolds (Scheme 1: path b). In our continuous efforts on indium catalysis,[8] we engaged to monitor the potential of indium salts in one-pot Nakamura reaction and intramolcular hydroarylation of alkenes by providing 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 underwent hydroarylation step with the available double bond functionality under one-pot indium catalyzed conditions to generate *β,β*-disubstituted indanones. With this idea, we initiate 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).



Scheme 1: Indium catalyzed tandem strategy

To test our hypothesis, we initiated our study by choosing ethyl benzoylacetate **1a** and phenyl acetylene **2a** as the model

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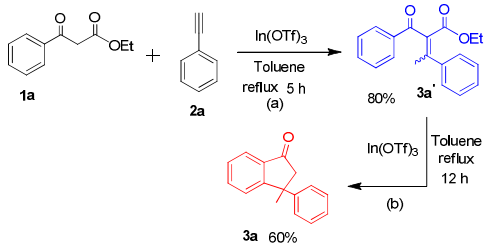
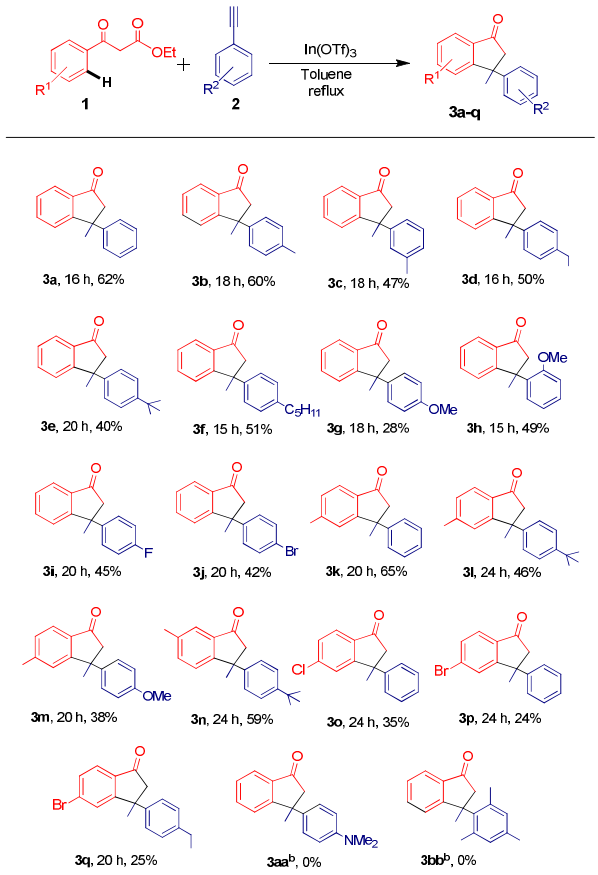
substrates. In the preliminary experiment, a model reaction between **1a** and **2a** was carried out by employing 10 mol% indium(III)triflate as a catalyst in toluene at 100 °C for 24 h. To our delight, the formation of *β,β*-disubstituted indanones in 51% yield was observed. It was quite exciting to note that, in addition to our expected Nakamura addition/hydroarylation sequence, decarboxylation also took place in 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 catalysed conditions. With this promising unexpected result, we dedicated our attention to study 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 tandem manner, we predict that the isolation of intermediate (may be the product of any one chemical transformation) would provide clear note about the reaction pathway. In agreement with Zhang 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 it would isomerizes to Knoevenagel type product.[6h] In next turn, a sequential reaction was tried by employing isomerised Nakamura product under current indium catalyzed conditions. Gratifyingly, the formation of *β,β*-disubstituted indanone **3a** was observed in 60% yield (Scheme 2: Step b).



Scheme 2: Sequential study

In order to figure out the standard reaction conditions, we further carried out the optimisation studies with different metal catalysts and solvents (See Supporting information: 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 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 preformed isomerised addition product 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 groups like halogen was present on the aromatic ring of terminal alkynes; fluoro and bromo substituted phenyl acetylene produces **3i** and **3j** with 45% and 42% yield respectively. Sterically hindered terminal alkynes, for example 1-ethnyl-2,4,6-trimethyl benzene was ineffective in the present study, even addition product was also not observed (Table 1: entry 3bb). Dimethylamino substituted terminal alkyne was inhibited entirely, may be because of the coordination of the amino group to the indium(III) atom (Table 1: entry 3aa). In the next turn, variation in other substrates i.e. ethyl benzoylacetate were tried (Table 1: entries **3k-3q**). These studies revealed that electron-rich ethyl benzoylacetates (4-Me and 3-Me) undergoes the tandem sequence smoothly with various terminal alkynes to afford the desired products in 65-38% yield (Table 1: entries **3k-3n**). Halogen substituted ethyl benzoylacetates had significantly reduced the conversion and shifted the yield towards lesser side (Table 1: entries **3o-3q**).

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 till the reaction is complete. [b]Reaction was carried out in toluene for 24 h.

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 were

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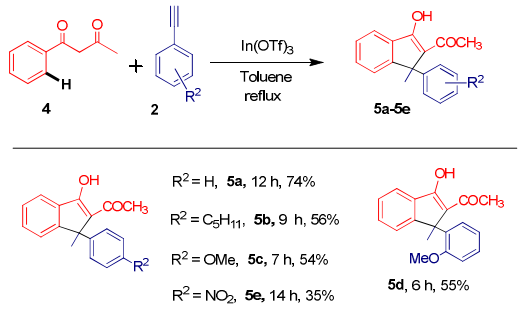
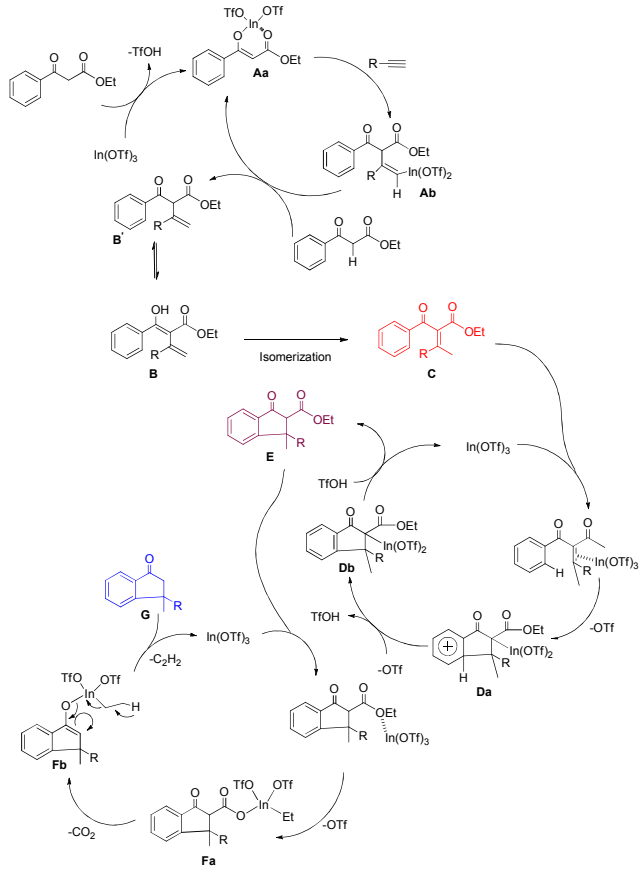
summarized in Table 2. In all cases, tandem addition/hydroarylation process took place exclusively and furnished the target products within the time period of 6-14 h in good to moderate yields (Table 2: entries **5b-5e**). However, exploration of benzoyl-1,1,1-trifluoroacetone as a 1,3-diketone partner was completely failed under the current tandem conditions.

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) till the reaction is complete.

On the basis of our sequential study, a plausible mechanism was proposed in Scheme 3.



Scheme 3: Possible mechanism

The reaction was initiated with the generation of indium enolate[6a] **Aa** from $In(OTf)_3$ and β-keto ester, which further added across the terminal alkyne to form alkenyl indium intermediate **Ab**. Protonation of alkenyl indium **Ab** by β-keto ester resulted in the formation of addition product **B** and regeneration of indium enolate for further cycle. Addition product **B'** tautomerizes to enol form **B** and underwent isomerization to afford knoevenagel type product **C**. In the next step, indium activates the double bond functionality in **C**, which further hydroarylated 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 ester group from **E** can be explained on the basis of mechanistic 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 was 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 underwent elimination process to furnish the final product **G** along with the removal of ethylene and regeneration of catalyst for 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 absence of any additives or co-catalysts to generate indanones derivatives in low to good yields. Exploration of 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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