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In(III)/$PhCO_2H$ Binary Acid Catalyzed Tandem [2 + 2] Cycloaddition and Nazarov Reaction between Alkynes and Acetals

Lihui Zhu, Zhi-Guo Xi, Jian Lv, and Sanzhong Luo*

Beijing National Laboratory for Molecule Sciences (BNLMS), CAS Key Laboratory for Molecular Recognition and Function, Institute of Chemistry, Chinese Academy of Sciences, Beijing 100190, People's Republic of China

luosz@iccas.ac.cn

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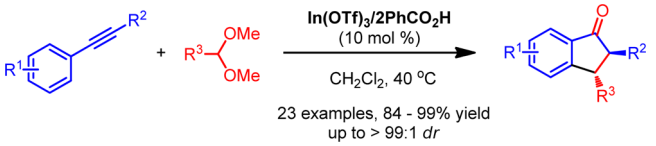
ABSTRACT



A facile tandem [2 + 2] cycloaddition and Nazarov reaction has been developed. The combination of $In(OTf)_3$ and benzoic acid was found to synergistically promote the coupling of alkynes and acetals to form 2,3-disubstituted indanones in excellent yield and diastereoselectivity.

The Nazarov reaction of aryl vinyl ketones is one of the most straightforward strategies to build indanone-containing structures with promising biological profiles that widely occur in natural products.[1−3] Accordingly, new catalysts or catalytic strategies for the cyclization of aryl vinyl ketones have been actively pursued to address the associated challenges such as insufficient reactivity, limited scope, and the lack of enantioselective control.[4,5]

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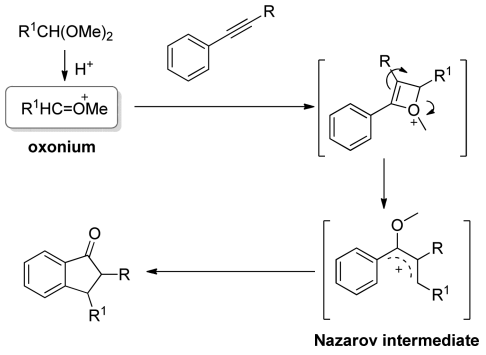
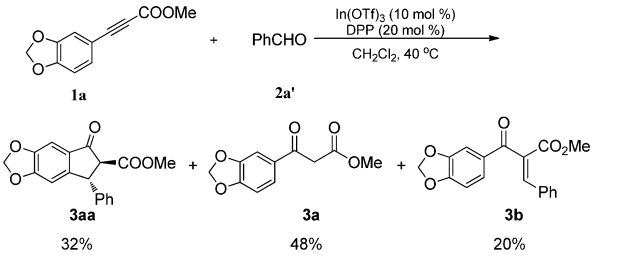
Yne-carbonyl metathesis is an atom-economic process for the synthesis of enones.[6,7] With judiciously designed substrates, this reaction has been utilized to deliver versatile structural skeletons such as cyclic enones,[8] amides,[9] oxetenes,[10] and lactones[11] in tandem transformations initialized by the [2 + 2] oxetene formation. Recently, the combination of yne-carbonyl metathesis and Nazarov cyclization have been reported, providing facile access to the Nazarov adducts with readily available starting materials.[12] Unfortunately, those processes still suffer from the use of overstoichiometric amounts of acid catalysts, harsh conditions, or limited scope. Herein, we present a new variant of tandem [2 + 2] and Nazarov cyclization involving aryl alkynes and acetals (Scheme 1). The reactions, which are enabled by the simple binary acid $In(OTf)_3$/benzoic acid,[13,14] exhibit unprecedentedly broad scope for the synthesis of 1-indanones under rather mild conditions.

Scheme 1. [2 + 2] and Nazarov Cyclization between Aryl Alkynes and Acetals



Previously, we reported a binary acid strategy for the Nazarov reaction of aryl vinyl ketones.[15] However, the nontrivial synthetic efforts to access the required vinyl ketones have seriously limited the substrate scope, which prompted us to seek a more convenient protocol. In this regard, a [2 + 2] coupling between methyl piperonylpropionate (**1a**) and benzaldehyde (**2a′**) was attempted in the presence of the previously identified optimal catalyst $In(OTf)_3$/diphenylphosphoric acid (DPP). Unfortunately, the reaction afforded only minor desired product along with various major byproducts such as the hydration product **3a** and enone **3b** (Scheme 2). Extensive optimization by changing the Lewis acid, Brønsted acid, or solvent did not lead to any improvements. In all cases, hydration of the arylpropiolates were generally formed as the major products, indicating that [2 + 2] cycloaddition is not favored under these conditions. At this point, we sought to employ oxonium ions,[16] more electrophilic species generated in situ from acetals, for the coupling. An intramolecular version of enyne-acetals coupling[7f,g] has recently been reported to furnish Nazarov-type adducts.[8c] To the best of our knowledge, intermolecular coupling of alkynes and acetals in the context of Nazarov chemistry has not been reported.

Scheme 2. Tandem [2 + 2] Cycloaddition using Aldehyde



To our delight, the desired Nazarov product was obtained in a decent 46% yield when benzaldehyde dimethylacetal (**2a**) was employed in the presence of $In(OTf)_3$/DPP (Table 1, entry 1). The reaction can be readily improved by screening different Lewis acids, Brønsted acids, and their combinations. $In(OTf)_3$/benzoic acid was found to be the optimal binary acid catalyst to furnish the desired Nazarov product in quantitative yield (Table 1, entry 2). Other screened binary acids gave inferior results (Table 1, entries 3−9). In control reactions, the use of only a Lewis acid or a Brønsted acid showed virtually no activity, highlighting the synergistic feature of the combinations of two acids (Table 1, entries 10 and 11). The ratio of the two acids has also been examined, and a 1/2 $In(OTf)_3$/benzoic acid ratio was found to deliver the best result (Table 1, entry 2 vs entries 12 and 13).

After identifying $In(OTf)_3$/benzoic acid as the optimal catalyst, we turned our attention to explore the substrate scope (Figure 1). The reactions are quite broad with respect to internal alkynes. As usually observed in Nazarov chemistry, electron-rich aryl moieties on aryl

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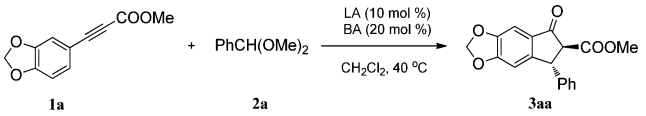
Table 1. Screening of Catalyst and Reaction Conditions for the Tandem [2 + 2] Cycloaddition and Nazarov Reaction[a]



1a 2a 3aa

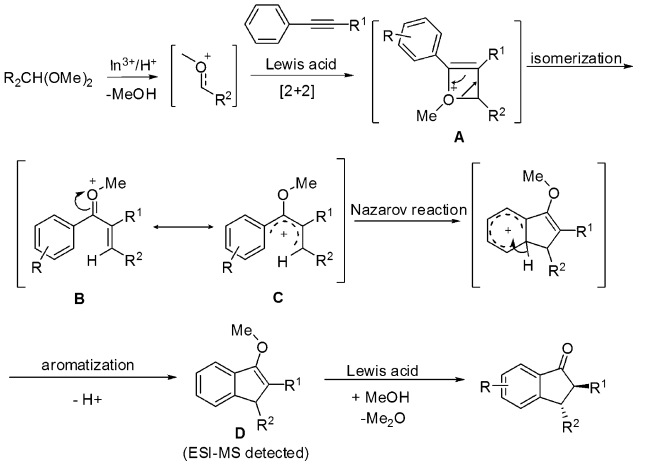
entry	Lewis acid	Brønsted acid	time (h)	yield (%)[b]
1	$In(OTf)_3$	DPP[c]	24	46
2	$In(OTf)_3$	PhCOOH	24	99
3	$In(OTf)_3$	TFA	24	30
4	$In(OTf)_3$	AcOH	24	<5
5	$In(OTf)_3$	TfOH	24	92
6	$Bi(OTf)_3$	PhCOOH	24	71
7	$Ni(OTf)_2$	PhCOOH	24	<5
8	$Cu(OTf)_2$	PhCOOH	24	<5
9	$Sc(OTf)_3$	PhCOOH	24	89
10	none	PhCOOH	>72	<5
11	$In(OTf)_3$	none	>72	10
12[d]	$In(OTf)_3$	PhCOOH	48	72
13[e]	$In(OTf)_3$	PhCOOH	36	89

[a] The general reaction was conducted with **1a** (0.1 mmol) and **2a** (0.11 mol) in CH_2Cl_2 (0.5 mL) at 40 °C. [b] Isolated yield. [c] DPP = diphenylphosphoric acid. [d] $In(OTf)_3$ (5 mol %). [e] PhCOOH (10 mol %).

alkynes (e.g., methoxylbenzenes) are generally preferred to facilitate the electrophilic cyclization. In our studies, an unsubstituted phenyl ring can also participate in the [2 + 2]-Nazarov tandem sequence (e.g., **3ba, 3ca** and **3cb**). On the other hand, the other terminal position of aryl alkynes can tolerate a number of different substituents including carboxylic esters, as well as alkyl and aromatic groups. In particular, 1,2-diphenylethynes reacts regioselectively to form the desired 1-indanones as single isomers (Figure 1, **3ea-3ef, 3fa** and **3ga**), with the cyclization occurring dominantly onto the electron-rich phenyl ring. 1,2-Diphenylethynes bearing two electron-rich aromatic rings gave rather complicated reaction mixtures, indicating that an electronic bias is intrinsically preferred for smooth and clean reactions.

As to the acetals, both aromatic and aliphatic aldehydes (e.g., **3dh**−**3dj**) can be accommodated. It is noted that the reactions worked with aromatic aldehydes bearing either an electron-withdrawing or electron-rich group (e.g., **3dg**), with the former reacting much more quickly. In the latter case, increasing the loading of benzoic acid to 50 mol % was necessary to achieve a higher production. This observation stands in contrast to the typical Nazarov cyclization of preformed aryl vinyl ketones, wherein an electron-rich phenyl ring on the vinyl moiety is preferred.[15] Taken together, the preference of electron-deficient aromatic aldehydes is consistent with a rate-limiting [2 + 2] cycloaddition step in this tandem [2 + 2]-Nazarov sequence, since it is known that electron-deficient aldehydes are favored in the yne-carbonyl metathesis.[17,18]

Scheme 3. Proposed Mechanism



On the basis of the experimental results as well as the known mechanistic features of [2 + 2] cycloaddition[18] and the Nazarov reaction,[19] a plausible mechanism is proposed (Scheme 3). In this scheme, the highly active oxetene cationic intermediate **A**, generated from the coupling of alkyne with hemiacetal cation, would undergo spontaneous isomerization to form the 4π-Nazarov intermediate **B/C**, followed by facile cyclization and proton transfer to afford the Nazarov adduct. The collapse of intermediate **B/C** to vinyl ketone, the typical yne-carbonyl metathesis product, has not been observed under the present conditions, suggesting that this pathway, if it exists, is slower than the desired cyclization step. The observation of fast-reacting electron-deficient acetals is also consistent with this scenario, since the preformed vinyl ketones derived from the same acetals are rather sluggish substrates in Nazarov chemistry. In addition, we have been able to detect enol methyl ether **D** from the reaction mixture by ESI-MS, adding further support to the proposed mechanism.

In conclusion, we have developed a novel type of tandem [2 + 2] cycloaddition and Nazarov reaction using cheap and readily available starting materials as well as an environmentally benign catalyst. Simply combining $In(OTf)_3$ and benzoic acid as a dual catalyst provides excellent performance in widespread substrates with the best activity so far for this type of substrate in Nazarov chemistry. Further synthetic applications and the

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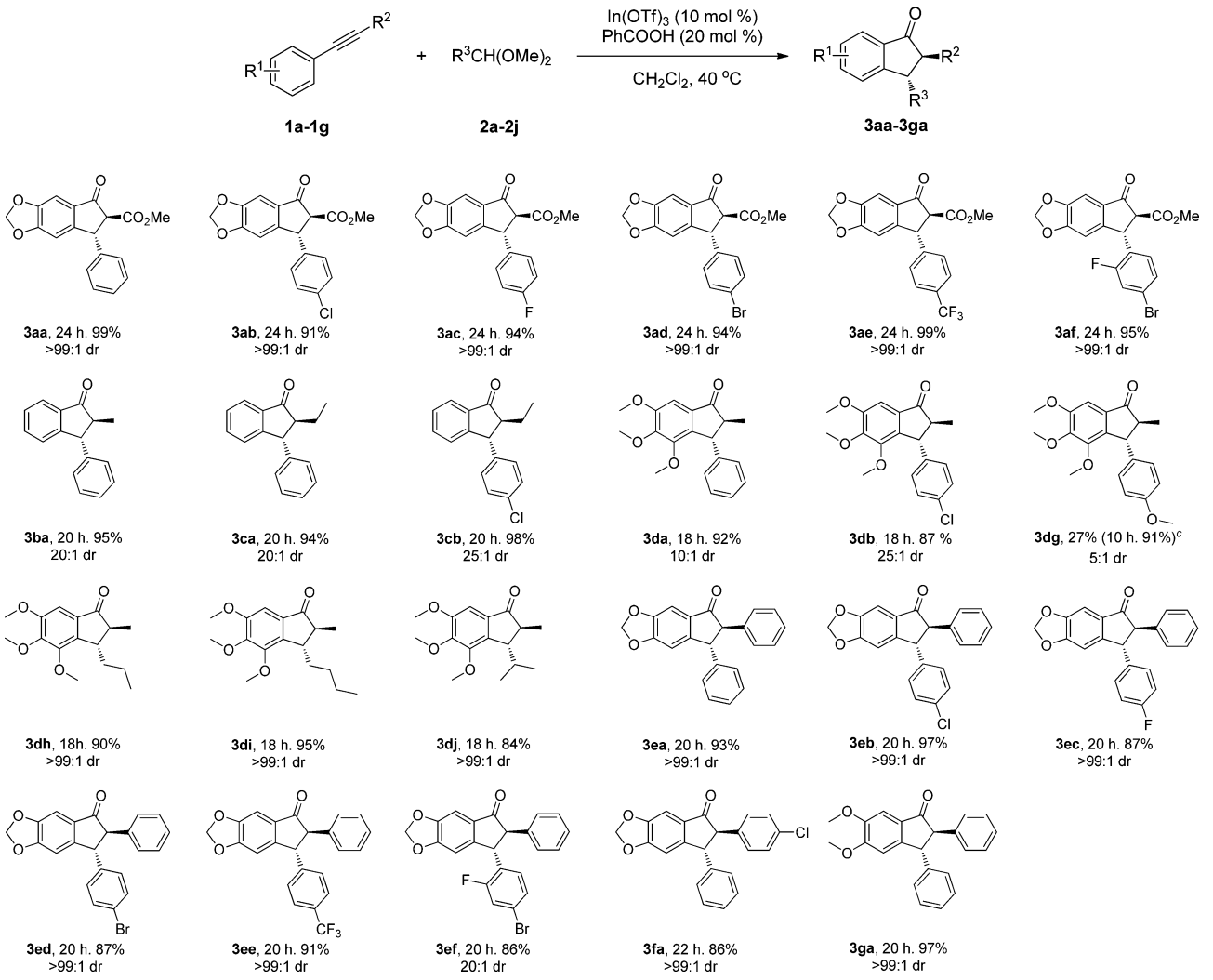

Figure 1. Scope of the tandem [2 + 2] cycloaddition and Nazarov reaction between alkynes and acetals: (*a*) the reaction was carried out with **1a** (0.1 mmol) and **2a** (0.11 mmol) in CH_2Cl_2 (0.5 mL) at 40 °C; (*b*) isolated yields are given; (*c*) 50 mol % benzoic acid was used.

development of asymmetric versions are underway and will be reported in due course.

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Supporting Information Available. Text and figures giving experiment procedures and ^1H and ^{13}C NMR spectral data for compounds **1d**, **1f**, and **3**. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.