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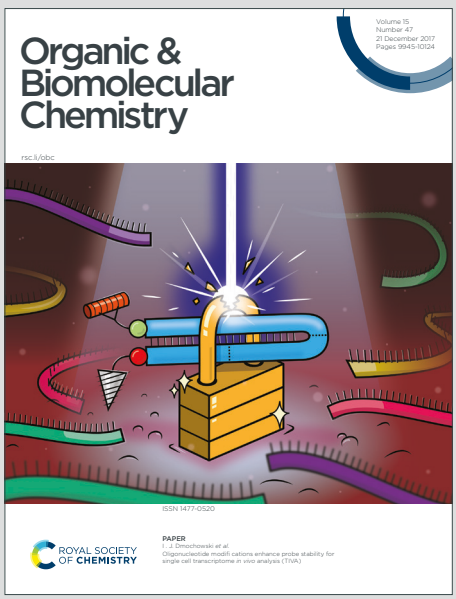

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COMMUNICATION

Sequential Conia-Ene-Type Cyclization and Negishi Coupling by Cooperative Functions of $B(C_6F_5)_3$, ZnI_2, $Pd(PPh_3)_4$ and an Amine

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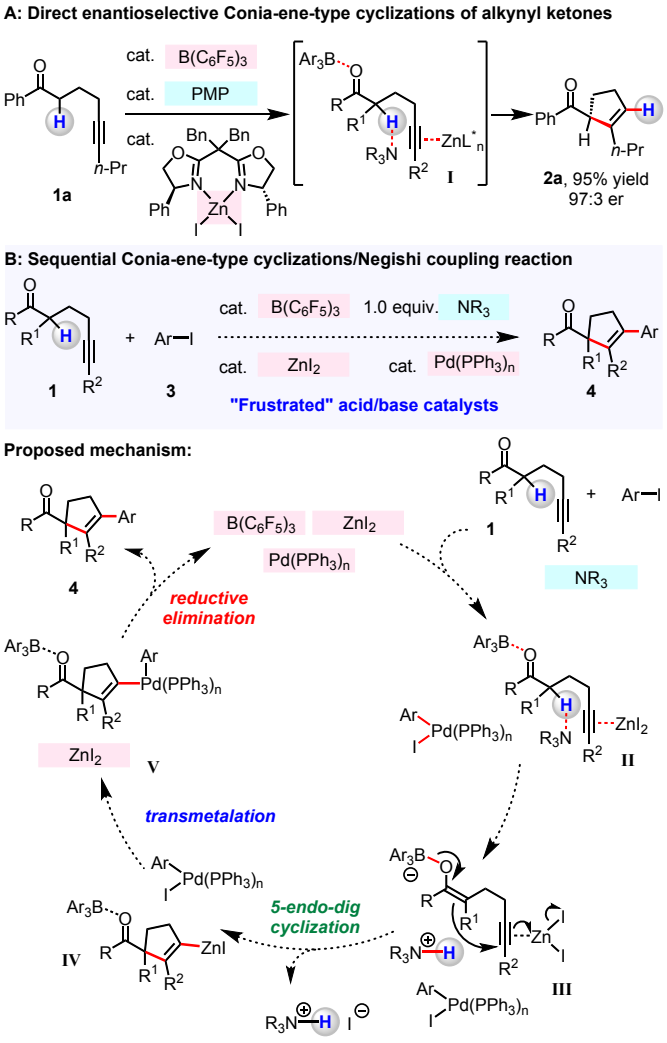
We disclose a method for sequential Conia-ene-type cyclization/Negishi coupling for the union of alkynyl ketones and aryl iodides. This process is promoted through cooperative actions of Lewis acidic $B(C_6F_5)_3$, ZnI_2, Pd-based complex, and a Brønsted basic amine. The three Lewis acid catalysts with potential overlapping functions play their independent roles as activators of carbonyl group, alkyne moiety, and alkenyl zinc intermediate, respectively. A variety of 1,2,3-substituted cyclopentenes can be synthesized with high efficiency.

Cooperative Lewis acid/Lewis base catalysts can promote the union of nucleophilic and electrophilic intermediates that are generated in situ from substrates that would not react efficiently using a single acid or base catalyst.[1-2] This mode of substrate activation has been widely applied to the synthesis of essential intermediates for bioactive compounds and natural product synthesis.[1-2] However, a fundamental problem remains unaddressed. Specifically, undesirable catalyst deactivation often occurs in a reaction mixture which contains Lewis acid and base catalysts, together with other acid- and/or base-sensitive substrates, intermediates, and products. Consequently, these processes typically possess limited substrate scopes, poor efficiency, and modest functional group tolerance.[1-2] Such acid–base complexation becomes more problematic when three or more independent catalysts that can form stable acid/base adducts are involved.

One approach to overcome the mutual quenching problem has been to utilize a pair of Lewis acid and base catalysts that have limited affinity to form stable adducts due to their steric hindrance and electronic disparity.[3] Using these "frustrated" Lewis pair catalysts,[4] we developed enantioselective Conia-ene-type cyclization[5] of alkynyl ketones **1a** (Scheme 1A). We proposed that Brønsted basic 1,2,2,6,6-pentamethylpiperidine (PMP) deprotonates $B(C_6F_5)_3$-activated carbonyl unit of **1a** to afford a boron–enolate and $[H–PMP]^+$ (**I**). Enantioselective 5-*endo-dig* carbocyclization involving the boron–enolate and chiral Box–Zn-activated alkyne units, followed by protonation of the resulting alkenyl ZnL_n intermediate by $[H–PMP]^+$ provides the desired cyclopentene derivative **2a** in up to 97:3 er. No C–C bond formation was observed in the absence of each one of the three catalysts. However, the roles of L_nZn–Box complex, which could activate either carbonyl and/or alkyne units of **1a**, remained undetermined.[6]



Scheme 1. Transformations involving 5-*endo-dig* cycloaddition

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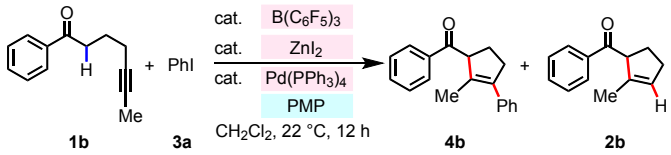
Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

To shed light on the mechanism of the Conia-ene-type reaction, we investigated if the proposed alkenyl ZnI intermediate **IV** derived from **1** by 5-*endo*-*dig* carbocyclization (via **1** → **II** → **III** → **IV**; Scheme 1B) can undergo transmetallation with an appropriate Pd(II)-based complex (**IV** → **V**). The latter species may be formed in situ through oxidative addition of $Pd(PPh_3)_4$ and an aryl iodide **3**. The resulting $[(Ar)(I)Pd^{II}(PPh_3)_n]$ **V** can undergo C–Ar bond forming reductive elimination to afford 1,2,3-substituted cyclopentene derivative **4**. The sequential Conia-ene-type carbocyclization/Negishi coupling reactions could provide evidence supporting the mechanistic hypothesis that the π-philic Zn-based catalyst is responsible for activation of alkyne unit in **1**, thereby generating **IV**.[7-8] Here, we describe a process promoted by $B(C_6F_5)_3$, *N*-alkylamine, ZnI_2, and $Pd(PPh_3)_4$ that play their independent catalytic roles while overcoming the undesirable acid–base complexation to afford 1,2,3-substituted cyclopentenes in high efficiency.

To begin, we probed the ability of $B(C_6F_5)_3$, PMP, ZnI_2, and $Pd(PPh_3)_4$ to catalyze the cyclization of 1-phenylnon-5-yn-1-one **1b** to give the alkenyl ZnI complex **IV**, followed by Negishi coupling of **IV** with iodobenzene **3a** (CH_2Cl_2, 12 h, 22 °C) to generate **4b** (Table 1). The combination of 10 mol% $B(C_6F_5)_3$, 1.0 equivalent of PMP, 50 mol% ZnI_2, and 2.0 mol% $Pd(PPh_3)_4$, produced **4b** in >95% yield (entry 1). In addition, cyclopentene derivative **2b** formed by protonation of cyclopentene–ZnI intermediate was obtained in <5% yield. In the absence of $Pd(PPh_3)_4$, only **2b** was generated in >95% yield (entry 2). When ZnI_2 or PMP was not added, neither **4b** nor **2b** were produced (entries 3–4). However, PMP, ZnI_2, and $Pd(PPh_3)_4$ were found to promote the formation of **4b** in the absence of $B(C_6F_5)_3$, although only 20% yield of **4b** was obtained (entry 5). This observation suggests that deprotonation of alkynyl ketone **1b** can be promoted by cooperative functions of the Pd-based complex and PMP.[9] This process was found to require a stoichiometric amount of PMP because the formation of $[PMP–H]^+[I]^-$ in the 5-*endo*-*dig* carbocyclization step (**III** → **IV**; Scheme 1B) may inhibit the regeneration of PMP; when the loading of PMP was lowered to 50 mol%, **4b** was obtained in 52% (entry 6). When the loading of ZnI_2 was lowered to 20 mol%, the yield of **4b** declined to 41% (entry 7).[10] This sequential cycloaddition/cross-coupling reaction could proceed with a minimal amount of $Pd(PPh_3)_4$ (1.0 mol%), as **4b** could be obtained in >95% yield (entry 8). Under none of the reaction conditions tested, PdL_n-catalyzed α-arylation of **1b**-derived enolate was observed.[11]

A variety of alkynyl ketones with different carbonyl and alkyne substituents proved to be suitable substrates for the sequential Conia-ene-type carbocyclization/Negishi coupling with iodobenzene **3a** (**4b–4g**; Table 2). Phenyl, naphthalen-2-yl, 2-methoxyphenyl, and furan-2-yl-substituted ketones gave the corresponding products (**4b–4f**) in 65 to 98% yield. An alkyl substituted ketone was also found to be a suitable substrate as **4g** was obtained in 91% yield. However, the use of internal

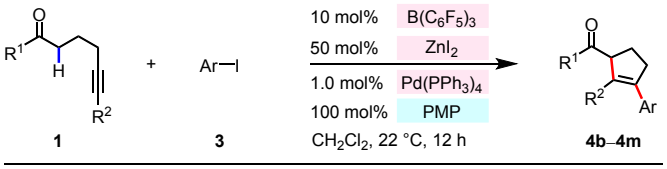
Table 1. Evaluation of Reaction Parameters [a,b]

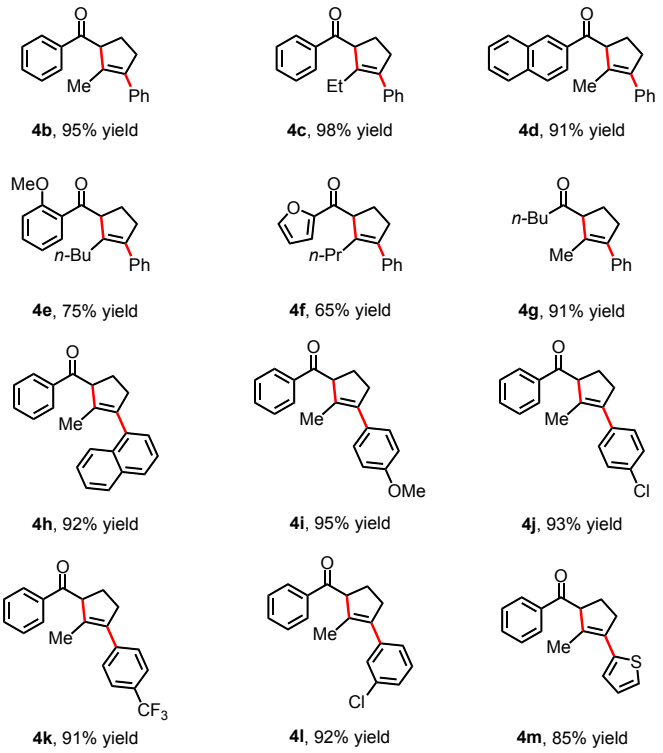


entry	$B(C_6F_5)_3$ (mol%)	PMP (mol%)	ZnI_2 (mol%)	$Pd(PPh_3)_4$ (mol%)	yield(%) 4b	2b
1	10	100	50	2	>95	<5
2	10	100	50	none	0	>95
3	10	100	none	2	0	0
4	10	none	50	2	0	0
5	none	100	50	2	20	0
6	10	50	50	2	52	<5
7	10	100	20	2	41	<5
8	10	100	50	1	>95	<5

[a] Conditions: 1-phenylnon-5-yn-1-one (**1a**, 0.10 mmol), iodobenzene (**3a**, 0.12 mmol) $B(C_6F_5)_3$, 1,2,2,6,6-pentamethylpiperidine, ZnI_2, $Pd(PPh_3)_4$, CH_2Cl_2 (0.5 mL), under N_2, 22 °C, 12 h. [b] Yield was determined by ^1H NMR analysis of unpurified reaction mixtures with mesitylene as the internal standard.

Table 2. Sequential Conia-Ene-Type Carbocyclization/Negishi Coupling Reactions with Different Ketones [a,b]





[a] Conditions: Alkynyl ketone (**1**, 0.10 mmol), aryl iodide (**3**, 0.12 mmol), $B(C_6F_5)_3$ (10 mol%), 1,2,2,6,6-pentamethylpiperidine (100 mol%), ZnI_2 (50 mol%), $Pd(PPh_3)_4$ (1.0 mol%), CH_2Cl_2 (0.5 mL), under N_2, 22 °C, 12 h. [b] Yield of isolated and purified product.

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alkynes was found to be necessary; with 1-phenylhex-5-yn-1-one, containing a terminal alkyne moiety (R^2 = H), the transformation was inefficient (<5% yield, see the Supporting Information for details).

An array of aryl- and heteroaryl-iodides reacted efficiently with **1b** to afford **4h–4m**. Cyclopentene derivatives with 1-naphthyl group (**4h**) as well as those containing arenes with electron-donating (**4i**) and electron-withdrawing (**4j–4l**) groups were obtained in 91 to 95% yield. Thiophen-2-yl-substituted **4m** could also be produced in 85% yield. The reaction of **1b** with more sterically hindered 2,6-dimethyliodebenzene and 1-iode-2-methoxynaphthalele only gave the Conia-ene-type product **2b** (see the Supporting Information for details). This sequential Conia-ene-type cycloaddition/Negishi coupling reaction was found to proceed only with iodoarenes; bromoarenes gave no desired product (Conia-ene-type product **2b** was obtained using bromobenzene: see the Supporting Information for details). Furthermore, for the reaction of **1b** and 1-chloro-3-iodobenzene to afford **4l**, no byproduct formed through oxidative addition into Ar–Cl bond was detected. The treatment of **1b** with allyl iodide under the standard catalytic conditions lead to the formation of **2b** (see the Supporting Information for details). These results suggest, in order to effectively trap the alkenyl ZnI species by Pd(II) complexes through transmetallation (**IV** → **V**; Scheme 1B), the use of aryl iodides that undergo facile oxidative addition with $Pd(PPh_3)_4$ to afford reactive $[(Ar)(I)Pd^{II}(PPh_3)_n]$ intermediates is necessary.

Conclusions

In brief, we have developed a cooperative catalyst system which constitutes of $B(C_6F_5)_3$, an amine, ZnI_2, and $Pd(PPh_3)_4$ to promote sequential Conia-ene-type cycloaddition/Negishi coupling reactions. This process affords 1,2,3-substituted cyclopentenes with various carbonyl, alkyl, and aryl substitutes from readily available alkynyl ketones and aryl iodides. Furthermore, the results obtained provide a mechanistic insight into how the Lewis acidic catalysts with potential overlapping functions serve as activators of carbonyl, alkyne, and alkenyl–ZnI intermediate. The principles outlined here demonstrate that a combination of four different catalyst units with different functions can be used to promote the union of in situ generated reactive intermediates from poorly acid- and base-sensitive starting materials. This discovery provides a rational framework for further development of cooperative multi-catalyst systems that facilitate transformations that cannot be realized by single or dual-catalyst systems. Studies aimed at achieving these objectives are currently underway.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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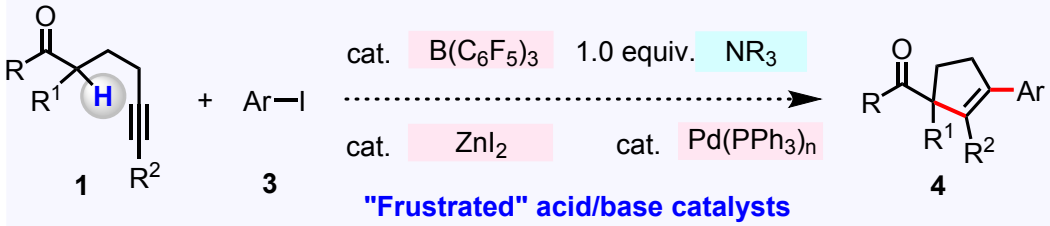
Sequential Conia-ene-type cyclizations/Negishi coupling reaction



A hybrid catalyst system for sequential Conia-ene-type cyclization/Negishi coupling for union of alkynyl ketones and aryl iodides has been developed.