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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

Min Cao^a, Ahmet Yesilcimen^a, Soumil Prasad^a, Jason Genova^a, Tanner Myers^a, Masayuki Wasa^a

^aDepartment of Chemistry, Merkert Chemistry Center, Boston College, Chestnut Hill, Massachusetts 02467, United States.

Abstract

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 cyclopentenones can be synthesized with high efficiency.

Graphical Abstract

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

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

Correspondence to: Masayuki Wasa.

Conflicts of interest

There are no conflicts to declare.

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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 cyclization⁵ of alkynyl ketones **1a** (Scheme 1A). We proposed that Brønsted basic 1,2,2,6,6-pentamethylpiperidine (PMP) deprotonates B(C₆F₅)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

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 transmetalation with an appropriate Pd(II)-based complex (**IV** → **V**). The latter species may be formed in situ through oxidative addition of Pd(PPh₃)₄ and an aryl iodide **3**. The resulting [(Ar)(I)Pd^{II}(PPh₃)_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(C₆F₅)₃, *N*-alkylamine, ZnI₂, and Pd(PPh₃)₄ that play their independent catalytic roles while overcoming the undesirable acid–base complexation to afford 1,2,3-substituted cyclopentenones in high efficiency.

To begin, we probed the ability of B(C₆F₅)₃, PMP, ZnI₂, and Pd(PPh₃)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** (CH₂Cl₂, 12 h, 22 °C) to generate **4b** (Table 1). The combination of 10 mol% B(C₆F₅)₃, 1.0 equivalent of PMP, 50 mol% ZnI₂, and 2.0 mol % Pd(PPh₃)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(PPh₃)₄, only **2b** was generated in >95% yield (entry 2). When ZnI₂ or PMP was not added, neither **4b** nor **2b** were produced (entries 3–4). However, PMP, ZnI₂, and Pd(PPh₃)₄ were found to promote the formation of **4b** in the absence of B(C₆F₅)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 ZnI₂ 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 $\text{Pd}(\text{PPh}_3)_4$ (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 alkynes was found to be necessary; with 1-phenylhex-5-yn-1-one, containing a terminal alkyne moiety ($\text{R}^2 = \text{H}$), 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-dimethyliodobenzene and 1-iodo-2-methoxynaphthalene 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 $\text{Ar}-\text{Cl}$ 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 $\text{Pd}(\text{II})$ complexes through transmetalation (**IV** $\rightarrow$ **V**; Scheme 1B), the use of aryl iodides that undergo facile oxidative addition with $\text{Pd}(\text{PPh}_3)_4$ to afford reactive $[(\text{Ar})(\text{I})\text{Pd}^{\text{II}}(\text{PPh}_3)_n]$ intermediates is necessary.

Conclusions

In brief, we have developed a cooperative catalyst system which constitutes of $\text{B}(\text{C}_6\text{F}_5)_3$, an amine, ZnI_2 , and $\text{Pd}(\text{PPh}_3)_4$ to promote sequential Conia-ene-type cycloaddition/Negishi coupling reactions. This process affords 1,2,3-substituted cyclopentenones 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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

Table 1.

Evaluation of Reaction Parameters^{a,b}

entry	B(C ₆ F 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

^aConditions: 1-phenylnon-5-yn-1-one (**1a**, 0.10 mmol), iodobenzene (**3a**, 0.12 mmol) B(C₆F₅)₃, 1,2,2,6,6-pentamethylpiperidine, ZnI₂, Pd(PPh₃)₄, CH₂Cl₂ (0.5 mL), under N₂, 22 °C, 12 h.

^bYield 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), $\text{B}(\text{C}_6\text{F}_5)_3$ (10 mol%), 1,2,2,6,6-pentamethylpiperidine (100 mol%), ZnI_2 (50 mol%), $\text{Pd}(\text{PPh}_3)_4$ (1.0 mol%), CH_2Cl_2 (0.5 mL), under N_2 , 22 °C, 12 h.

^b Yield of isolated and purified product.