One-Pot Synthesis of Highly Substituted Allenylidene Derivatives *via* Palladium- or Nickel-Catalyzed Tandem Michael Addition– Cyclization Reaction

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Abstract: A simple and tandem synthetic approach, which offers an efficient, direct route to highly substituted indenes, has been developed by palladiumor nickel-catalyzed cyclization of propargylic compounds and nitrogen nucleophiles. The reaction takes place under mild conditions, and a possible mechansim is proposed.

Keywords: allenes; cyclization; nickel; palladium; propargylic compounds

Tandem reactions involving a transition metal-promoted step have emerged as a powerful tool to construct cyclic and polycyclic structures.^[1] Strategies used in the design and synthesis of complex biologically active compounds and natural products have received considerable attention in organic synthesis.^[2] During the past decades, the Michael addition has remained one of the most popular methods for the construction of carbon-carbon and carbon-heteroatom bonds. The synthesis of highly substituted annular compounds through a one-pot or tandem Michael addition-cyclization process has attracted increasing attention, due to its efficient and atom-economic methodology.^[3] Balme reported a Cu-mediated annulation reaction of stabilized carbon with unactivated alkynes, leading to highly substituted methylenecyclopentanes [Scheme 1, Eq (1)].^[4] However, few reports are known concerning a one-pot cyclization strategy of the stabilized carbon nucleophiles to propargylic compounds. Such reactions were particularly challenging because the regio- and chemoselectivity of the organometallic activation must be well controlled to avoid the formation of intractable mixtures.

The interesting reactivity of allenes originates mainly from their unique strained structure, and thus continuous efforts have been made to construct 1,2-



Scheme 1.

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dienic moieties.^[5] We have reported a novel palladium-catalyzed intermolecular reaction for the synthesis of indene compounds including an allene functional group with high regioselectivity and excellent yields.^[6] Recently, Wu reported a effective cyclization process of indole with 2-[2-(alkynyl)benzylidene]malonate mediated by *t*-BuOK [Scheme 1, Eq. (2)].^[7] In connection with our research on carboannulation reactions for the preparation of indene derivatives by transition metal catalysis,^[8] we conceived that a tandem annulation, in which both carbon-carbon and carbon-heteroatom bond were constructed, could possibly occur with suitable nucleophiles initiating an intermolecular Michael addition.

Fortunately, we discovered that diethyl 2-{2-[3-(ethoxycarbonyloxy)prop-1-ynyl]benzylidene} malonate **1a** undergoes a tandem reaction with aniline as nucleophile under Pd-tuned conditions, thus offering an efficient, direct route for the synthesis of allenylindene derivative 3a. The starting materials could be easily obtained from propargyl aldehyde.^[9] In this process, intermolecular nucleophilic attack happened prior to the following intramolecular reaction. The experiments were carried out by using 1.0 equiv. of benzylidenemalonate 1a and 2.0 equiv. of aniline with 5 mol% of $Pd(PPh_3)_4$ under argon at room temperature. In initial investigations, no reaction was observed without base or when t-BuOK, NaOEt, NaH or Et₃N as the base was employed (Table 1, entries 1–5). The desired product 3a was obtained in 36% yield in the presence of K_2CO_3 (entry 6). *t*-BuOK furnished a moderate isolated yield (entry 7). Remarkably, switching the base to Cs₂CO₃ led to the formation of target product in 76% yield and a shorter reaction





Entry	Catalyst	Base	Solvent	Time [h]	Temp. [°C]	Yield [%] ^[b] of 3a	
1	_	t-BuOK	DMF	12	25	NR ^[c]	
2	$Pd(PPh_3)_4$	_	DMF	12	25	NR	
3	$Pd(PPh_3)_4$	NaOEt	DMF	12	25	NR	
4	$Pd(PPh_3)_4$	NaH	DMF	12	25	NR	
5	$Pd(PPh_3)_4$	Et ₃ N	DMF	12	25	NR	
6	$Pd(PPh_3)_4$	K_2CO_3	DMF	2	25	36	
7	$Pd(PPh_3)_4$	t-BuOK	DMF	2	25	50	
8	$Pd(PPh_3)_4$	Cs_2CO_3	DMF	1	25	76	
9	$Pd(PPh_3)_4$	Cs_2CO_3	CH ₃ CN	1	25	26	
10	$Pd(PPh_3)_4$	Cs_2CO_3	1,4-dioxane	1	25	48	
11	$Pd(PPh_3)_4$	Cs_2CO_3	toluene	1	25	40	
12	$Pd(PPh_3)_4$	Cs_2CO_3	THF	1	25	34	
13	$Pd(PPh_3)_4$	Cs_2CO_3	DMF	0.4	80	20	
14	$Pd(PPh_3)_4$	Cs_2CO_3	DMF	0.5	50	65	
15	$Pd(OAc)_2/PPh_3$	Cs_2CO_3	DMF	4	25	28	
16	$Pd_2(dba)_3/dppf$	Cs_2CO_3	DMF	4	25	13	
17	Pd/C	Cs_2CO_3	DMF	1	25	59	
18	$NiCl_2 \cdot 6H_2O^{[d]}$	Cs_2CO_3	DMF	6	45	20	
19	$Ni_3(PO_4)_2 \cdot 8H_2O^{[d]}$	Cs_2CO_3	DMF	6	45	55	
20	$Ni(acac)_2^{[d]}$	Cs_2CO_3	DMF	2	45	60	
21	Ni(PPh ₃) ₂ Cl ₂ ^[d]	Cs_2CO_3	DMF	2	45	80	
22	Ni(PPh ₃) ₂ Cl ₂ ^[d]	Cs_2CO_3	DMF	2	60	60	

^[a] Conditions: 5 mol% of catalyst in 2.0 mL solvent using 1.0 equiv. of **1a**, 2.0 equiv. of **2a** and 3.0 equiv. of base under argon.

^[b] Isolated yield.

[c] NR = no reaction.

^[d] Experiments were carried out in air.

time (entry 8). Other solvents, for example, CH₃CN, 1,4-dioxane, toluene and THF, were less effective (entries 9–12). Higher temperatures accelerated the reaction but were not beneficial to the yield (entries 13 and 14). Other catalyst systems, such as $Pd(OAc)_2$ / PPh₃ and Pd₂(dba)₃/dppf, were also screened and furnished low yields of the desired product (entries 15 and 16). A better result was obtained when the catalyst was replaced by Pd/C (entry 17). On the other hand, the inexpensive nickel catalyst could also catalyze this one-pot transformation, which was a good extension of our methodology.^[10] Screening various nickel catalysts, Ni(PPh₃)₂Cl₂ was found to be the best catalyst for this process (entry 21). However, none of other catalysts, such as NiCl₂·6H₂O, Ni₃(PO₄) ₂·8H₂O and Ni(acac)₂ gave a higher yield than Ni(PPh₃)₂Cl₂ (entries 18-20). The higher reaction temperature could not improve the yield (entry 22). Moreover, it should be noted that all reactions catalyzed by nickel could be carried out in air.

With the optimized conditions established, the scope of this reaction was then examined and the results are summarized in Table 2. The reaction went well with methyl substituent groups such that m-toluidine and p-toluidine gave excellent yields with the Pd catalyst for the corresponding products **3b** and **3c**, re-

spectively (entries 2 and 3), whereas a relatively lower yield (55%) of product 3d was observed when the methyl group was in the *ortho*-position probably due to steric hindrance (entry 4). Use of the Ni(II) catalyst also afforded the desired products in good yields. Moderate results were generated when halogenated anilines were utilized, such as chlorobenzenamine and bromobenzenamine (entries 5-8) via Pd- and Ni-catalysis. Interestingly, the electron-withdrawing nucleophile also gave rise to the product 3i smoothly (entry 9). It has been found that other amines, such as benzylamine, naphthalen-2-amine and furan-2-amine were also well tolerated under our conditions (entries 10 and 12). We have also investigated the reactions of substrates with various leaving groups, such as propargyl acetate 1b, propargyl benzoate 1c and propargyl acetate 1d afforded the desired products 3a in good yields (entries 13–15).

In addition, although the NMR spectroscopic data support the formation of indenes **3** (see Supporting Information), the structure was definitively secured by an X-ray crystal structure analysis of compound **3a** (Figure 1).^[11]

Phenol and diethyl malonate were found to be good nucleophiles to afford an allenylpalladium intermediate or π -propargyl palladium complex (an equi-

 Table 2. Synthesis of indenes 3 by carboannulation of propargylic compounds 1 with amines 2.^[a]



Entry		\mathbf{R}^1	\mathbb{R}^2		$Pd(PPh_3)_4$		Ni(PPh ₃) ₂ Cl ₂	
2					Time [h]	Yield [%] ^[b]	Time [h]	Yield [%] ^[b]
1	1 a	CO ₂ Et	C ₆ H ₅	3 a	1	76	2	80
2	1 a	CO_2Et	$4-CH_3C_6H_4$	3b	2	78	3	68
3	1 a	CO_2Et	$3-CH_3C_6H_4$	3c	2	81	3	70
4	1 a	CO ₂ Et	$2-CH_3C_6H_4$	3d	2	55	3	50
5	1 a	CO_2Et	$4-ClC_6H_4$	3e	1	55	2	40
6	1 a	CO ₂ Et	$3-ClC_6H_4$	3f	1	49	2	44
7	1 a	CO_2Et	$4-BrC_6H_4$	3g	1	61	2	53
8	1 a	CO ₂ Et	$3-BrC_6H_4$	3h	1	46	2	40
9	1 a	CO_2Et	$2 - NO_2C_6H_4$	3i	1	58	2	59
10	1 a	CO_2Et	benzyl	3j	1	65	3	50
11	1 a	CO_2Et	1-naphthyl	3k	4	45	5	40
12	1 a	CO_2Et	2-furyl	31	1	60	3	56
13	1b	COMe	C_6H_5	3a	1	72	2	70
14	1c	COPh	C_6H_5	3a	1	65	2	55
15	1d	CO ₂ Me	C_6H_5	3 a	1	69	2	60

[a] Pd(PPh₃)₄-catalyzed reactions were carried out under argon at 25 °C; Ni(PPh₃)₂Cl₂-catalyzed reactions were carried out in air at 45 °C.

^[b] Yields of isolated products based on the propargylic compounds.



Figure 1. X-ray structure of compound 3a.

librium process) in the previous reports.^[3,4,12] However, no intermolecular nucleophilic attack happened under the above conditions. Further raising the reaction temperature, loading the amount of catalyst and using stronger bases gave intractable mixtures (Scheme 2).

On the basis of the above observations, the following plausible reaction mechanism was proposed for this novel casade transformation (Figure 2), which



Scheme 2.

may involve the following key steps. (i) Decarboxylation of propargylic compound **1** catalyzed by Pd(0) generates an allenylpalladium complex $4^{[13]}$ or the Ni(II) species coordinates with the alkyne triple bond of **1** to afford **6**. (ii) Base mediates a Michael addition which affords intermediate **5** or **7**, respectively. (iii) **5** undergoes regioselective intramolecular stabilized carbon nucleophilic attack to afford indene **3**; on the other hand, **7** could also undergo the same attack with the activated triple bond to afford vinyl intermediate **8** and then α -heteroatom elimination (α oxygen elimination) to form indene **3**.

In summary, a simple and one-pot method for the synthesis of highly substituted indene derivatives including an allene functional group has been developed through this addition–cyclization process under mild conditions by Pd or Ni catalysis. The starting materials are easily accessible. Applications to other metal-catalyzed tandem transformations are currently



Figure 2. Proposed reaction mechanism for this cyclization.

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being studied in our research group, and will be reported in due course.

Experimental Section

Typical Experimental Procedure for Tandem Michael Addition–Cyclization Reactions (3a)

To a solution of diethyl 2-{2-[3-(ethoxycarbonyloxy)prop-1ynyl]benzylidene}malonate 1a (75.8 mg, 0.20 mmol) in DMF (2.0 mL) was added Cs₂CO₃ (197.6 mg, 0.60 mmol). After the mixture had been stirred for 10 min, Pd(PPh₃)₄ (22.5 mg, 0.01 mmol, 5 mol%) and the corresponding amine (0.40 mmol) were added under the argon at 25 °C. When the reaction was complete as monitored by TLC, the reaction mixture was quenched with a saturated aqueous solution of ammonium chloride, and the mixture was extracted with EtOAc $(3 \times 15 \text{ mL})$. The combined organic extracts were washed with water and saturated brine, dried over Na₂SO₄ and filtered. Solvents were evaporated under reduced pressure. The residue was purified by chromatography on silica gel using 80:1 hexanes/EtOAc to afford the corresponding indene **3a**. The reaction catalyzed by $Ni_3(PO_4)_2 \cdot 8H_2O$ was carried ou in the same way except that the mixture was stirred at 45°C in air.

Acknowledgements

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