Highly regio- and stereoselective intermolecular tandem reaction to synthesize chloro-substituted 1,3-butadienes[†]

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A palladium catalyzed highly regio- and stereoselective intermolecular tandem reaction of alkynes, $CuCl_2$ and alkenes by a sequence of chloropalladation/Heck reaction to produce chloro-substituted 1,3-dienes is achieved.

Diene-containing natural products which have been investigated comprehensively recently due to their remarkable biological activities are likely to play an important role in biological processes.¹ Especially, members of the leptomcyin family have attracted a great deal of attention because of their potent cell-cycle-regulating properties and apoptotic, antifungal, and antiviral activities.² Given that most diene-containing natural products can be prepared from an array of 1,3-diene fragments,^{1a,b,3} the effective and stereoselective synthesis of multi-substituted 1,3-dienes appears to be a logical first choice. In addition, tandem reaction has been proven to be a very attractive method to construct polyfunctionalized molecules in a convergent way. In connection with our interest in chloropalladation chemistry on triple bonds,⁴ we herein disclose a regio- and stereoselective intermolecular tandem reaction of cupric chloride, alkynes and alkenes catalyzed by palladium to produce chloro-substituted 1.3-dienes.⁵

The reaction of methyl non-2-ynoate and methyl acrylate was initially investigated in the presence of 10% PdCl₂ and 3 equiv. CuCl₂ in various solvents (entries 1-5, Table 1). Obviously, this palladium catalyzed transformation showed great dependence on the solvent used. Only trace amounts of the desired dienes were detected in toluene and 1,4-dioxane (entries 1 and 3, Table 1). The use of ethyl acetate led to a low yield (25%), but with a high regio- and stereoselectivity at 93:7 (3a:4a, entry 2, Table 1).⁶ The reactions were carried out in aqueous media resulting in low yields (entries 4 and 5, Table 1). When the reaction was performed in 2 mL methyl acrylate in the absence of any other solvent, the yield of the desired adduct was increased sharply to 72% with good selectivity at 96:4 (entry 6, Table 1). Optimization of the amount of cupric chloride showed that 6 equiv. cupric chloride was optimal, with a small increase of yield to 76% at the same isomeric ratio at 96:4 (entry 7, Table 1). In addition, no reaction occurred in the absence of PdCl₂ (entry 10, Table 1). $Pd(OAc)_2$ and $Pd(PPh_3)_2Cl_2$ gave unsatisfactory results (entries 11 and 12, Table 1). Adding LiCl resulted in lower

Table 1 Optimization of the reaction conditions for the three-
component coupling reaction a

n-C ₆ H ₁₃ -	COOMe	$\begin{array}{c c} Pd] catalyst & CI \\ \underline{MCI_{n}(x eq)} & & \\ solvent & n-C_{6}H_{13} \\ \underline{S0^{1}C} & \end{array}$	COOMe COOMe n 3a		COOMe _/ DOMe
Entry	[Pd]	[Cl ⁻]	Solvent	Yield ^b / %	3a : 4 a ^c
1	10% PdCl ₂	3 equiv. CuCl ₂	Toluene	Trace	_
2	10% PdCl ₂	3 equiv. CuCl ₂	Ethyl acetate	25	93:7
3	$10\% \text{ PdCl}_2$	$3 equiv. CuCl_2$	1,4-dioxane	Trace	
4	10% PdCl ₂	$3 \text{ equiv. } \text{CuCl}_2$	$THF-H_2O =$	32	67:33
			1:1		
5	$10\% PdCl_2$	3 equiv. CuCl ₂	$2\mathbf{a}: \mathbf{H}_2\mathbf{O} = 3 \cdot 1^d$	35	87:13
6	10% PdCl ₂	3 equiv. CuCl ₂	2a	72	96:4
7	10% PdCl ₂	6 equiv. CuCl ₂	2a	76	96:4
8	10% PdCl ₂	9 equiv. CuCl ₂	2a	72	94:6
9	$10\% \text{ PdCl}_2$	1 equiv. CuCl ₂	2a	57	96:4
10		6 equiv. CuCl ₂	2a	0	_
11	10%	6 equiv. CuCl ₂	2a	28	95:5
	$Pd(OAc)_2$				
12	10%	6 equiv. CuCl ₂	2a	Trace	
	Pd(PPh ₃) ₂ Cl ₂	· -			
13	10% PdCl ₂	1 equiv. CuCl ₂	2a	62	43:57
		4 equiv. LiCl			

^{*a*} Reactions were carried out using [Pd] catalyst (10 mol%), MCl_n (*x* equiv.), 2 mL solution, under N₂ in a capped tube, heating at 60 °C for 24 h. ^{*b*} Isolated yield. ^{*c*} Determined by ¹H NMR analysis of the crude reaction mixture before column separation. ^{*d*} 1.5 mL methyl acrylate and 0.5 mL H₂O.

yield and very low selectivity (entry 13, Table 1). Hence, the best conditions are shown in entry 7, Table $1.^{7}$

To examine the scope of this methodology, a variety of alkynes and alkenes were investigated to generate the diene derivatives under the optimum conditions. Representative results are shown in Table 2. The electron-deficient alkynes gave good yields of chloro-substituted 1,3-dienes in excellent stereoselectivities with trans-chloropalladation providing the major products. The stereochemistry of 3c and 3d was further confirmed by NOE studies.8 The regiochemistry was controlled by the electron-withdrawing properties of the substituents on the triple bond (entries 1–6 and 8–9, Table 2).^{4,9} For a non-activated triple bond, the desired 1,3-diene (entry 10, Table 2) can be obtained in good yield, but with low stereoselectivity. It is noteworthy that when acrylonitrile is applied as olefin source, CN substituted 1,3-diene can be obtained. It is the structural motif found in a variety of complex bioactive natural products, such as Araceae, which offers protection against herbivory and biforines.10

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 Table 2
 Highly regio- and stereoselective intermolecular tandem reaction to synthesize chloro-substituted 1,3-butadienes^a

CI

 R^2

50

	$R^{1} \xrightarrow{R^{2}} + R^{3} \xrightarrow{PdCl_{2}, CuCl_{2}} R^{1} \xrightarrow{R^{3}} R^{1} \xrightarrow{Cl} R^{2}$ $R^{2} \xrightarrow{R^{3}} R^{1} \xrightarrow{R^{2}} R^{2}$					
Entry	Alkyne	Alkene	Major product	Yield ^e /%	3:4 ^f	
1	n-C ₀ H ₁₃ ————COOMe 1a	COOMe 2a		76	96:4	
2	n-C ₆ H ₁₃ ─────COOMe 1a	COOEt 2b	$r_{n-C_6H_{13}}$	78	97:3	
3	PhCOOMe 1b	COOMe 2a	CI Ph COOMe COOMe	73	96:4	
4	H ₃ CCOOEt 1c	COOMe 2a		53	99:1	
5		COOMe 2a		41 ^{<i>b</i>}	98:2	
6		COOMe 2a		63 ^b	98:2	
7	EtOOCCOOEt 1f	CN 2c		74 ^c	96:4	
8	n-C ₈ H ₁₃ COOMe 1a	√ N 2d	$r - C_6H_{13}$	82 ^d	87:13	
9	PhCOOMe 1b	 N_ 2d	3h Cl Ph N 3i	62 ^{<i>d</i>}	83:17	
10	ng ng	↓ N 2d		78 ^{<i>d</i>}	52:48	

^{*a*} PdCl₂ (9 mg, 10 mmol%), CuCl₂ (6 equiv., 400 mg) and 2 mL of methyl acrylate, alkynes (0.5 mmol), under N₂ in a capped tube, heating at 60 °C for 24 h. ^{*b*} At 70 °C. ^{*c*} In 2 mL of toluene. ^{*d*} In 2 mL of 1,4-dioxane. ^{*e*} Isolated yield. ^{*f*} Determined by ¹H NMR analysis of the crude reaction mixture before column separation.

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A potential mechanism for the intermolecular threecomponent reaction is depicted in Scheme 1. (*E*)-Vinylpalladium intermediate **1** was formed as a major product by *trans*chloropalladation of alkyne in the presence of excess halide ion,⁶ followed by a Heck reaction with alkene through a β -H elimination. Pd(II) was regenerated in the presence of CuCl₂ for the next cycle.

In conclusion, a palladium catalyzed intermolecular threecomponent coupling of alkyne, $CuCl_2$ and alkene to synthesize 1,3-butadienes has been successfully achieved by a simple manipulation. This method is attractive due to its high atom efficiency, good regio- and stereoselectivity and tolerance for a range of functional groups. Hence, it is a good alternative for the synthesis of 1,3-butadienes. An investigation to increase the scope of this methodology is underway in our group.

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Scheme 1 The possible reaction mechanism.

Notes and references

- 1 (a) D. Amans, V. Bellosta and J. Cossy, Chem.-Eur. J., 2009, 15 3457; (b) G. Ramamoorthy, C. M. Acevedo, E. Alvira and M. A. Lipton, Tetrahedron: Asymmetry, 2008, 19, 2546; (c) A. M. Boldi, Curr. Opin. Chem. Biol., 2004, 8, 281; (d) Y. Liao, Y. Hu, J. Wu, Q. Zhu, M. Donovan, R. Fathi and Z. Yang, Curr. Med. Chem., 2003, 10, 2285; (e) J. Kutney, K. Han, F. Kuri-Brena, R. Milanova and M. Roberts, Heterocycles, 1997, 44, 95; (f) Y. Takaishi, K. Shishido, N. Wariishi, M. Shibuya, K. Goto, M. Kido, M. Takai and Y. Ono, Tetrahedron Lett., 1992, 33 7177
- 2 M. Kalesse and M. Christmann, Synthesis, 2002, 981.
- 3 (a) L. J. Perez, H. L. Shimp and G. C. Micalizio, J. Org. Chem., 2009, 74, 7211; (b) P. J. Parsons, H. Gold, G. Semple and T. Montagnon, Synlett, 2008, 8, 1184; (c) P. Kommana, S. W. Chung and W. A. Donaldson, Tetrahedron Lett., 2008, 49, 6209; (d) R. M. Patel and N. P. Argade, J. Org. Chem., 2007, 72, 4900; (e) P. G. Williams, E. D. Miller, R. N. Asolkar, P. R. Jensen and W. Fenical, J. Org. Chem., 2007, 72, 5025; (f) A. Deagostino, C. Prandi, C. Zavattaro and P. Venturello, Eur. J. Org. Chem., 2006, 2463 and references cited therein; (g) K. C. Nicolaou, S. A. Snyder, T. Montagnon and G. Vassilikongiannakis, Angew. Chem., Int. Ed., 2002, 41, 1668 and references cited therein.
- 4 J. Huang, L. Zhou and H. Jiang, Angew. Chem., Int. Ed., 2006, 45, 1945
- 5 During the course of preparing this manuscript, an intramolecular process to produce 3-chloro-1-methyleneindenes was reported. See: S. Ye, K. Gao, H. Zhou, X. Yang and J. Wu, Chem. Commun., 2009 5406
- 6 Trans-chloropalladation of alkyne occurred predominantly in the presence of excess halide ion, see: (a) Q. Zhang, W. Xu and X. Lu, J. Org. Chem., 2005, 70, 1505; (b) J. E. Bäckvall, Y. I. M. Nilsson and R. G. P. Gatti, Organometallics, 1995, 14, 4242.

- 7 General procedure for the tandem reaction to afford 3a: A mixture of PdCl₂ (8.9 mg, 10 mmol%), CuCl₂ (6 equiv., 3 mmol) and 2 mL methyl acrylate was stirred for 5 min in a capped tube (10 mL) at room temperature, then methyl 2-nonynoate (87 µl, 0.5 mmol) was added. The mixture was stirred under N2 at 60 °C for 24 h. The reaction mixture was extracted with diethyl ether (2×15 mL). The combined organic layer was washed with water (15 mL), brine (10 mL) and then dried over anhydrous magnesium sulfate. The organic solvent was removed on a rotary evaporator under vacuum. The residue was purified by column chromatography on silica gel (petroleum ether-ethyl acetate 10:1) and 3a was obtained as a yellow oil (110 mg, 76%).
- Configuration of products 3c, 3d (2E,4Z) was further confirmed by ¹H NMR and NOE studies. NOE studies for 3c:



irradiation at CH₃ signal

irradiation at OCH₃ signal



- 9 K. Kaneda, T. Uchiyama, Y. Fujiwara, T. Imanaka and S. Teranishi, J. Org. Chem., 1979, 44, 55.
- 10 G. G. Coté, Am. J. Bot., 2009, 96, 1245.