

Ru-Catalyzed Decarbonylative Addition of Aliphatic Aldehydes to Terminal Alkynes

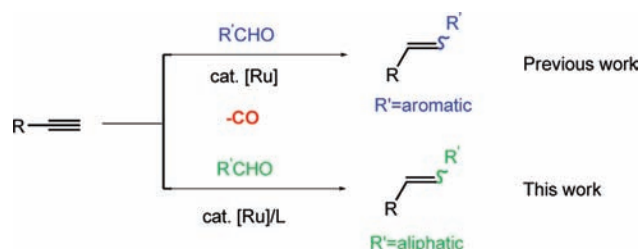
Xiangyu Guo, Jun Wang, and Chao-Jun Li*

Department of Chemistry, McGill University, 801 Sherbrooke St. West, Montreal, Quebec H3A 2K6, Canada

cj.li@mcgill.ca

Received May 13, 2010

ABSTRACT



A novel method for the formation of isolated C=C bonds was developed via a ruthenium-catalyzed decarbonylative addition of aliphatic aldehydes and alkynes. An unprecedented complete switch of chemoselectivity from aromatic aldehydes to aliphatic aldehydes was observed simply by using tri(2,4,6-trimethoxyphenyl)phosphine as ligand. A synthesis by this method of an insect sex pheromone was demonstrated.

Carbon–carbon double bond forming reactions are vital to the synthesis of various fine chemicals, pharmaceuticals, and natural products.¹ Many synthetic methodologies have been developed throughout the history of organic chemistry for an effective olefination¹ such as the Wittig-type reactions,² the Heck-type reactions,³ and olefin metathesis.⁴ Alternatively, the Negishi-type addition of various organometallic reagents to alkynes provided a versatile strategy for alkene

synthesis.⁵ On the other hand, the cleavage of the C–H bond in aldehydes promoted by transition metal leads to acyl hydrido metal intermediates, which could undergo decarbonylation reactions or further reactions to generate carbonyl compounds.⁶ Recently, we reported an olefination strategy via a ruthenium-catalyzed decarbonylative addition reaction of aldehydes to alkynes, suggesting a new method for C=C bond formation.⁷ However, the first generation catalyst was limited to only aromatic aldehydes (Scheme 1, reaction a). On the other hand, isolated alkenes are the structural feature

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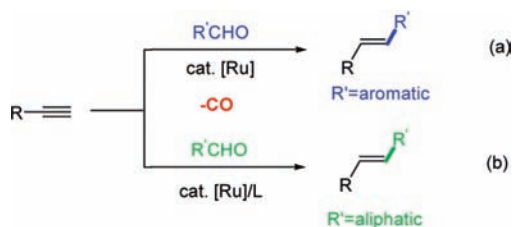
(4) For some examples, see: (a) Schrock, R. R.; Meakin, P. *J. Am. Chem. Soc.* **1974**, *96*, 5288. (b) Nguyen, S. T.; Johnson, L. K.; Grubbs, R. H. *J. Am. Chem. Soc.* **1992**, *114*, 3975. (c) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18. (d) Vehlou, K.; Wang, D.; Buchmeiser, M. R.; Blechert, S. *Angew. Chem., Int. Ed.* **2008**, *47*, 2615. (e) Alcaide, B.; Almendros, P.; Luna, A. *Chem. Rev.* **2009**, *109*, 3817.

(5) (a) Negishi, E.; Van Horn, D. E.; Yoshida, T.; Rand, C. L. *Organometallics* **1983**, *2*, 563. (b) Studemann, T.; Ibrahim-Ouali, M.; Knochel, P. *Tetrahedron* **1998**, *54*, 1299. (c) Xie, M.; Gu, X.; Wang, J.; Zhang, J.; Lin, G.; Wang, S. *Appl. Organomet. Chem.* **2009**, *23*, 258.

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(7) Guo, X.; Wang, J.; Li, C.-J. *J. Am. Chem. Soc.* **2009**, *131*, 15092. Varela et al. also reported an alternative ruthenium catalyzed formation of cyclic alkene from aldehyde and alkyne via the cleavage of C≡C bond; see: Varela, J. A.; Gonzalez-Rodriguez, C.; Rubin, S. G.; Castedo, L.; Saa, C. *J. Am. Chem. Soc.* **2006**, *128*, 9576. Krische and co-workers reported a direct vinylation of aldehyde and alcohol with alkynes to give allyl alcohols recently; see: Patman, R. L.; Chaulagin, M. R.; Williams, V. W.; Krische, M. J. *J. Am. Chem. Soc.* **2009**, *131*, 2066.

Scheme 1. Decarbonylative Addition of Aldehyde to Alkynes



of a wide range of chemical products such as insect pheromones (Figure 1), which are greatly important in the agricultural industry. A simple and direct generation of isolated alkenes from readily available basic functionalities will be highly desirable in alkene synthesis. Herein, we report a new catalyst with which a highly efficient decarbonylative addition of simple aliphatic aldehydes to terminal alkynes was achieved to give isolated alkenes, enabling an astonishing complete switch of chemoselectivity from completely aromatic to completely aliphatic aldehydes (Scheme 1, reaction b).

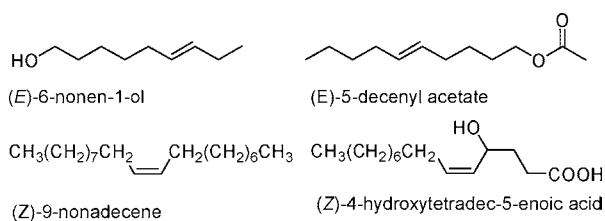
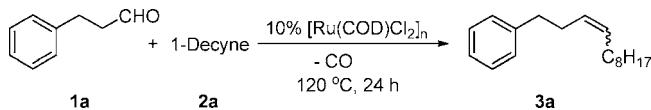


Figure 1. Examples of insect pheromones.

We chose hydrocinnamaldehyde (**1a**) and 1-decyne (**2a**) as the standard substrates for the optimization of the reaction conditions. Under our previously reported conditions for aromatic compounds, no reaction was observed (Table 1, entry 1). We postulated that a bulky ligand is necessary to form a stabilized catalyst center while still maintaining free coordination sites for the decarbonylation and additions. Thus, triisopropyl phosphite and tri(2,4,6-trimethoxyphenyl)phosphine were found to be effective in this reaction, producing the desired compound (**3a**) in 52% and 70% yield, respectively, whereas no products or low yields were obtained with other ligands (Table 1, entries 3–9). When more ligands were used, the yield dropped dramatically to 23%, possibly because of the dwindling of free-coordination sites for decarbonylation to occur. On the other hand, lesser amounts of ligands led to an unstabilized catalyst, which also reduced the yield to 38% (Table 1, entries 10 and 11). Copper chloride was also found to be essential in the reaction (Table 1, entries 12–14).

Prestirring was found to be essential for the reaction: only a trace amount of the product could be formed when all the chemicals were added at the same time and heated directly to 120 °C (Table 1, entry 16). A black residue was noticeably

Table 1. Decarbonylative Aliphatic Aldehyde–Alkyne Addition Reactions under Various Conditions^a



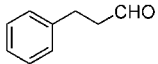
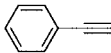
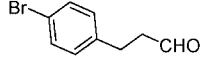
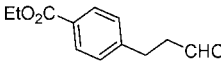
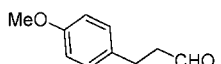
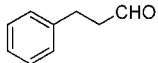
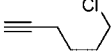
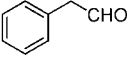
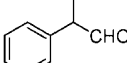
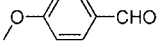
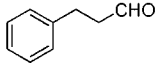
entry	additive	ligand	solvent	% yield ^b
1	30% CuCl ₂ ·2H ₂ O		toluene	0 ^c
2			toluene	0
3	30% CuCl ₂		toluene	0
4	30% CuCl ₂	20% (tBu) ₃ P	toluene	0
5	30% CuCl ₂	20% (iPrO) ₃ P	toluene	52
6	30% CuCl ₂	20% Cy ₃ P	toluene	0
7	30% CuCl ₂	20% (Me ₂ N) ₃ P	toluene	0
8	30% CuCl ₂	20% Ph ₃ P	toluene	5
9	30% CuCl ₂	20% L	toluene	70 ^d
10	30% CuCl ₂	30% L	toluene	23
11	30% CuCl ₂	10% L	toluene	38
12		20% L	toluene	0
13	20% CuCl ₂	20% L	toluene	27
14	50% CuCl ₂	20% L	toluene	44
15	30% CuCl₂	20% L	CH₂Cl₂ + toluene	95^e
16	30% CuCl ₂	20% L	CH ₂ Cl ₂ + toluene	trace ^f
17	30% CuCl ₂	20% L	dioxane	55
18	30% CuCl ₂	20% L	DCE	0
19	30% CuCl ₂	20% L	CH ₂ Cl ₂ + toluene	36 ^{g,g}
20	30% CuCl ₂	20% L	CH ₂ Cl ₂ + toluene	trace ^{e,h}

^a Conditions: the reaction was prestirred with 10% [Ru(COD)Cl₂]_n, 30% CuCl₂, 20% ligand in 0.2 mL of solvent under argon at rt for 24 h. Then, **1a** (0.2 mmol), **2a** (0.8 mmol), and solvent (0.8 mL) were added under argon and heated to 120 °C for 24 h, unless otherwise noted. ^b Determined by ¹H NMR of the crude reaction mixture. ^c 5 equiv of LiCl was added. ^d L = tri(2,4,6-trimethoxyphenyl)phosphine. ^e 0.2 mL of CH₂Cl₂ was added first at rt; 0.8 mL toluene was added when heated to 120 °C. ^f Without prestirring. ^g 150 °C. ^h 100 °C.

formed during the prestirring in toluene. Different solvents were examined to facilitate the formation of the active catalyst in situ by dissolving the residue, and it was found that a combination of methylene chloride (0.2 mL) and toluene (0.8 mL) gave the best yield at 120 °C (Table 1, entries 15–18). Either increase or decrease of the reaction temperature decreased the product yield (Table 1, entries 19 and 20). With the optimized conditions, we then examined the scope of this reaction (Table 2).

The reaction worked well for various aliphatic aldehydes and alkynes. Excellent yields could be obtained for aliphatic alkynes with a high boiling point (Table 2, entries 1 and 2), while 1-hexyne gave a 75% yield (Table 2, entry 3). Aromatic alkynes also worked in this reaction system but gave only moderate yield (Table 2, entries 4 and 5). Functional groups, such as halides, ester and methoxy groups, could well be tolerated by the reaction (Table 2, entries 6–9), and all these substrates gave excellent yields of the olefination products. Phenylacetaldehyde derivatives led to a moderate yield, (Table 2, entries 10 and 11), possibly due to the increased steric hindrance on the reacting carbon centers. In a sharp contrast to our previous reports, aromatic aldehydes remain virtually unreactive under the present conditions (Table 2, entry 12). Triisopropylsilyl acetylene also failed to react under this catalytic conditions (Table 2, entry 13), most likely due to steric effect. To further explore this complete switch of chemoselectivity, we run a competition experiment involving both aliphatic and aromatic

Table 2. Substrate Scope of the Decarbonylative Aldehyde–Alkyne Addition Reaction^a

entry	aldehyde	alkyne	product	yield ^b [%]	E/Z ^c
1		1-decyne	3a	90%	1 : 1.5
2		1-tetradecyne	3b	85%	1 : 1.3
3		1-hexyne	3c	75%	1 : 1.2
4	CH ₃ (CH ₂) ₈ CHO		3d	50%	1.5 : 1
5	CH ₃ (CH ₂) ₄ CHO		3e	44%	1.5 : 1
6		1-decyne	3f	90%	1 : 2.1
7		1-decyne	3g	91%	1 : 1
8		1-decyne	3h	92%	1 : 1.3
9			3i	88%	1 : 1
10		1-decyne	3j	60%	1 : 1.1
11		1-hexyne	3k	45%	1 : 1.3
12		1-decyne	3m	2%	
13		≡—TIPS	no reaction		

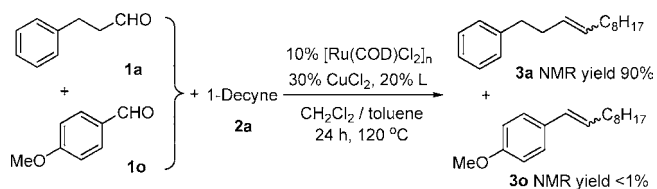
^a Conditions: the reaction was prestirred with 10% [Ru(COD)Cl₂]_n, 30% CuCl₂, 20% tri(2,4,6-trimethoxyphenyl)phosphine in 0.2 mL of CH₂Cl₂ under argon at rt for 24 h. Then **1** (0.2 mmol), **2** (0.8 mmol), and toluene (0.8 mL) were added under argon and heated to 120 °C for 24 h. ^b Total isolated yield of both the *E* and *Z* isomers. ^c The *E/Z* ratio was determined by ¹³C NMR analysis.

aldehydes. The product (**3a**) generated from aliphatic aldehyde was formed in a 90% NMR yield, while less than 1% corresponding aromatic alkene was observed (Scheme 2), which provided an exclusive chemoselectivity.

As a simple test of the potential utility of this novel olefination reaction, we applied this reaction in the synthesis of (*Z*)-9-nonadecene, an extract of sex pheromone glands of female

(8) Koike, K.; Takaiwa, M.; Kimura, Y.; Inoue, S.; Ito, S. *Biosci. Biotechnol. Biochem.* **2000**, *64*, 1064.

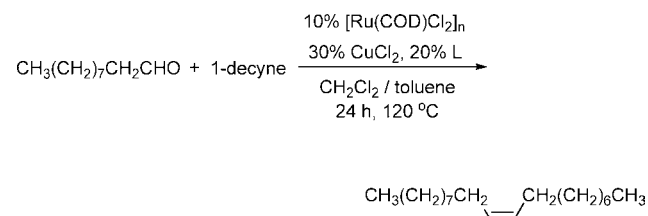
Scheme 2. Competition Experiment between Aliphatic and Aromatic Aldehydes^a



^a Conditions: **1a** (0.2 mmol), **1o** (0.2 mmol), **2a** (0.8 mmol), [Ru(COD)Cl₂]_n 0.02 mmol; conversions and yields were determined by ¹H NMR.

Sabulodes caberata Guenée. The reaction provided the alkene in a 55% NMR yield in one step, albeit as a mixture of *Z* and *E* isomers (Scheme 3).⁸

Scheme 3. Synthesis of (*Z*)-9-Nonadecene



^a *Z:E* = 1:1, determined by GC-MS analysis.

In summary, we have discovered a novel method of C=C double bond formation, specifically for aliphatic aldehydes and alkynes via a decarbonylative addition reaction. Different functionalized substrates were examined, and good to excellent yields were obtained. An unprecedented complete switch of aromatic–aliphatic selective reactivity was observed. A tentative mechanism similar to the one in our earlier paper⁷ is proposed also for this reaction. The role of copper may be either to assist the departure of CO from the ruthenium catalyst center or to alter the nature of the phosphine ligand, which are ongoing investigations. Further efforts to characterize the active catalyst and to optimize the stereoselectivity based on decarbonylative addition in terms of reaction temperature and functional group tolerance are currently underway in our laboratory.

Acknowledgment. We are grateful to the Canada Research Chair (Tier I) Foundation (to C.J.L.), CFI, and NSERC for support of our research.

Supporting Information Available: Typical experimental procedure and characterization data for all products. This material is available free of charge via the Internet at <http://pubs.acs.org>.

OL101107W