

Palladium-Catalyzed Alkenylation of 1,2,3-Triazoles with Terminal Conjugated Alkenes by Direct C–H Bond Functionalization

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A palladium-catalyzed alkenylation of 1,2,3-triazoles with terminal conjugated alkenes by direct C–H functionalization has been developed in the presence of $\text{Cu}(\text{OAc})_2$ and dioxane. A variety of terminal alkenes such as acrylates and

styrenes can perform the direct oxidative coupling reactions with 1,2,3-triazoles to afford the corresponding alkenylated products in 30–90 % yield.

Introduction

1,2,3-Triazoles are one of the most important N-heterocyclic compounds in organic chemistry due to their inimitable chemical and structural properties, as well as their wide application in agrochemicals and industry such as dyes and corrosion inhibitors.^[1] Since Meldal and Sharpless pioneered the copper-catalyzed Huisgen's 1,3-dipolar [3+2] cycloadditions of azides with alkynes to construct 1,4-disubstituted 1,2,3-triazoles,^[2] the synthesis of highly substituted 1,2,3-triazoles has been of great interest. Known methods for their preparation include transition-metal-catalyzed C-5 functionalization with Pd ^[3,4a,4b] and Cu ^[4c] and Heck-type reactions of prefunctionalized 5-iodo-1,2,3-triazoles with alkenes.^[5] To the best of our knowledge, there are no examples of the direct alkenylation of 1,2,3-triazoles.^[6]

Palladium-catalyzed alkenylation of arenes by C–H bond activation has become a hot topic in recent years.^[7] This method is highly atom economic and has been utilized in intramolecular and intermolecular direct oxidative alkenylation of arenes, thiophenes, furans,^[8] indoles, pyrroles,^[9] and pyrazoles.^[10,11] These facts prompted us to investigate the possibility of alkenylation of 1,2,3-triazoles with alkenes by C–H bond activation. Herein, we report direct oxidative alkenylation in the presence of a $\text{Pd}(\text{OAc})_2/\text{Cu}(\text{OAc})_2/\text{O}_2$ catalytic system for the preparation of highly substituted 1,2,3-triazoles.

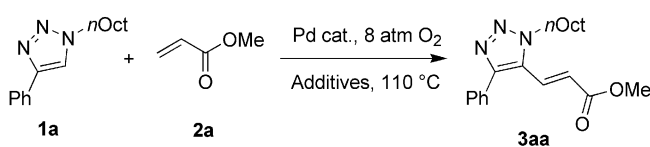
Results and Discussion

Previous research on direct oxidative coupling revealed that acetic acid was an effective solvent.^[7,8a,12] In our initial experiment, when a mixture of 1-octyl-4-phenyl-1*H*-1,2,3-triazole (**1a**), methyl acrylate (**2a**), $\text{Pd}(\text{OAc})_2$ (10 mol-%), and $\text{Cu}(\text{OAc})_2$ (20 mol-%) was heated at 110 °C in AcOH under 8 atm O_2 in an autoclave, no desired product was detected and **1a** was 100% recovered (Table 1, Entry 1). Interestingly, replacement of HOAc with dioxane led target molecule 1,4,5-trisubstituted-1*H*-1,2,3-triazole (**3aa**) in a low yield (Table 1, Entry 2), and the yield of **3aa** increased to 83% when we increased the amount of $\text{Cu}(\text{OAc})_2$ to 2 equivalents (Table 1, Entry 3). Reducing the amount of $\text{Pd}(\text{OAc})_2$ decreased the yield (Table 1, Entry 4). Employing other palladium catalysts, such as PdCl_2 and $\text{Pd}(\text{dba})_2$, also decreased the yields (Table 1, Entries 5 and 6). We also found that the yield decreased without O_2 (Table 1, Entry 7). Replacement of $\text{Cu}(\text{OAc})_2$ with AgOAc , FeCl_3 , or DDQ resulted in only trace amounts of the products (Table 1, Entries 8–10). The addition of base did not promote the coupling reaction under our conditions (Table 1, Entries 11–15). The reaction did not proceed in the absence of $\text{Pd}(\text{OAc})_2$ (Table 1, Entry 16).

With the optimized conditions in hand [10 mol-% $\text{Pd}(\text{OAc})_2$, 2 equiv. of $\text{Cu}(\text{OAc})_2$, 110 °C in dioxane under 8 atm O_2], we probed the scope of the direct alkenylation of 1,2,3-triazoles with different alkenes. The results are summarized in Table 2. At first, we examined a variety of 1,2,3-triazoles and methyl acrylate was utilized as the substrate (Table 2, Entries 1–8). 1,2,3-Triazoles bearing large R^2 groups were shown to have a steric effect on the yields. A gradual increase in yield was accompanied by a decrease in the size of the R^2 group (Table 2, Entries 1–3 and 4, 5). Aromatic rings with electron-donating R^1 groups led to moderate yields, which indicated the electronic effect of the

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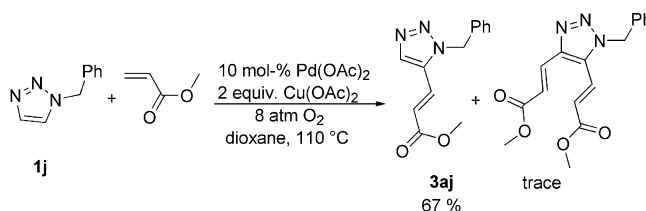
Table 1. Optimization of reaction conditions for the Pd-catalyzed alkenylation of **1a** with **2a**.^[a]


Entry	Catalyst	Additive	Solvent	Yield[%] ^[b]
1	10 mol-% Pd(OAc) ₂	20 mol-% Cu(OAc) ₂	HOAc	n.r. ^[c]
2	10 mol-% Pd(OAc) ₂	20 mol-% Cu(OAc) ₂	dioxane	16
3	10 mol-% Pd(OAc) ₂	2 equiv. Cu(OAc) ₂	dioxane	83 (80)
4	5 mol-% Pd(OAc) ₂	2 equiv. Cu(OAc) ₂	dioxane	59
5	10 mol-% Pd(dba) ₂	2 equiv. Cu(OAc) ₂	dioxane	29
6	10 mol-% PdCl ₂	2 equiv. Cu(OAc) ₂	dioxane	72
7 ^[d]	10 mol-% Pd(OAc) ₂	2 equiv. Cu(OAc) ₂	dioxane	18
8	10 mol-% Pd(OAc) ₂	2 equiv. AgOAc	dioxane	trace
9	10 mol-% Pd(OAc) ₂	2 equiv. FeCl ₃	dioxane	n.r. ^[c]
10	10 mol-% Pd(OAc) ₂	2 equiv. DDQ	dioxane	trace
11	10 mol-% Pd(OAc) ₂	20 mol-% Cu(OAc) ₂ / 2 equiv. K ₂ CO ₃	dioxane	32
12	10 mol-% Pd(OAc) ₂	2 equiv. Cu(OAc) ₂ / 2 equiv. K ₂ CO ₃	dioxane	75
13	10 mol-% Pd(OAc) ₂	2 equiv. Cu(OAc) ₂ / 2 equiv. NaOAc	dioxane	80
14	10 mol-% Pd(OAc) ₂	2 equiv. Cu(OAc) ₂ / 2 equiv. KOH	dioxane	n.r. ^[c]
15	10 mol-% Pd(OAc) ₂	2 equiv. Cu(OAc) ₂ / 2 equiv. DBU	dioxane	n.r. ^[c]
16	—	2 equiv. Cu(OAc) ₂	dioxane	n.r. ^[c]

[a] Reaction conditions: 1,2,3-triazole (0.3 mmol), methyl acrylate (0.6 mmol, 2 equiv.), solvent (2 mL), 110 °C, 8 atm O₂, 20 h. [b] Determined by GC. [c] No reaction. [d] Without O₂.

substrate (Table 2, Entries 4–6). The yield decreased to 56% when an electron-withdrawing group was present as R¹ on the aromatic ring (Table 2, Entry 7). Substrates with alkyl groups as R¹ also afforded products in moderate yield (Table 2, Entry 8). On the other hand, when less reactive alkenes such as styrene were chosen, homocoupling by-products were generated under the same reaction conditions. The yields of the desired products were low until we increased the reaction time to 40 h (Table 2, Entries 10–14). There are similar steric and electronic effects on the formation of **3ca**, **3cc**, and **3cd**, resulting in yields of 61, 44, and 39%, respectively (Table 2, Entries 10–12). 1-Fluoro-4-vinylbenzene afforded the product in a yield of 51%, because the electron-withdrawing group might improve the activity of styrene (Table 2, Entry 13). 1-Methyl-4-vinylbenzene seemed less susceptible than 1-fluoro-4-vinylbenzene to undergo the reaction, which led to a lower yield of **3eh**. Finally, we employed other terminal alkenes such as acrylonitrile and acrylamide, but only trace amounts of products were detected by GC–MS. In addition, internal alkenes like methyl but-2-enoate or ethyl cinnamate were not suitable for the reaction. This suggested the substituted group on the C–C double bond inhibited the reaction. Finally, we increased the scale of the reaction to 1 mmol, and the yield of **3aa** decreased slightly, but an acceptable result of 71% was still obtained.

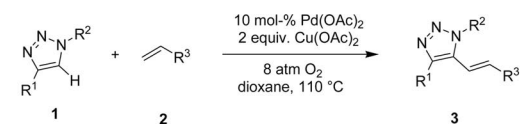
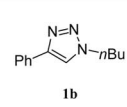

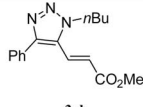
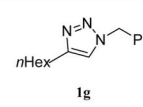

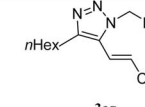
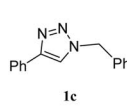

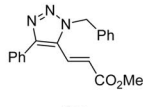
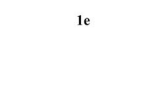

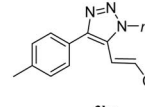
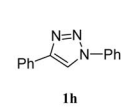

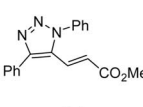
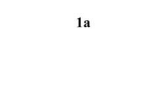

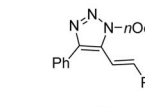
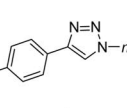

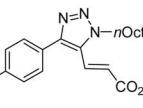
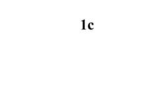

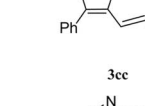
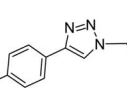

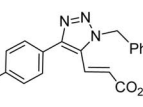
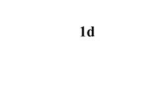

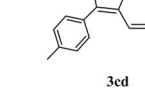
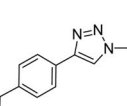

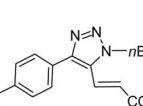
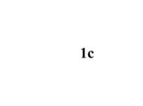

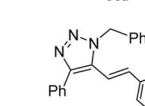
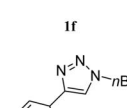

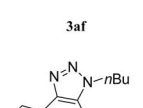
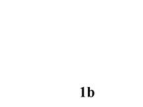

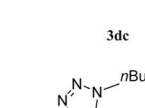
In order to examine the regioselectivity of the triazoles, *N*-monosubstituted triazole **1j** was used as a substrate (Scheme 1). To our delight, highly regioselective 1,5-disubstituted triazole **3aj** was the major product along with only trace amounts of the fully substituted triazole.^[13] These results are similar to those reported.^[3,4b]



Scheme 1. Palladium-catalyzed alkenylation of monosubstituted triazoles.

Although a detailed mechanism still remains elusive, we propose a reaction path similar to that proposed by Fujiwara (Scheme 2).^[7b] Initially, electronic attack of Pd^{II} on the triazole forms intermediate **A**. Active intermediate **A** then inserts into the alkene to form intermediate **B**, which rapidly decomposes through β -elimination to afford the target products and an active palladium species. More recently, Ishii reported a new hydropalladation mechanism in a related coupling reaction, and this may also explain our reaction. (Scheme 2, path B).^[12b] According to the mechanism of Ishii, vinyl palladium species **A'** is formed by the vinyl species and Pd(OAc)₂. Then, insertion into the Pd–vinyl bond leads to σ -Pd complex **B'**, and after β -elimination the same products as those afforded in Path A are obtained. Finally, Pd⁰ is recycled by the cooperation of Cu^{II} and O₂. According to the result in Table 1, a higher pressure of O₂ may promote the regeneration of Cu^{II} from Cu^I.

Table 2. Pd-catalyzed coupling of 1,4-disubstituted-1*H*-1,2,3-triazoles with alkenes.^[a]

									
Entry	Triazole	Alkene	Product	Yield ^[b,d] [%]	Entry	Triazole	Alkene	Product	Yield ^[b,d] [%]
1				90	8				64
2				70	9				63
3				31	10				61 ^[c]
4				55	11				44 ^[c]
5				30	12				39 ^[c]
6				75	13				51 ^[c]
7				56	14				42 ^[c]

[a] Reaction conditions: triazole (0.3 mmol), alkene (0.6 mmol, 2 equiv.), dioxane (2 mL), Pd(OAc)₂ (10 mol-%), Cu(OAc)₂ (2 equiv.), 110 °C, 8 atm O₂, 20 h. [b] Isolated yields. [c] After 40 h. [d] When using acrylate as alkene, no more than 3% of the (*Z*) diastereomer was detected by GC–MS, whereas, when styrene derivatives were used the alkene, the (*E*) diastereomer was exclusively formed.

Conclusions

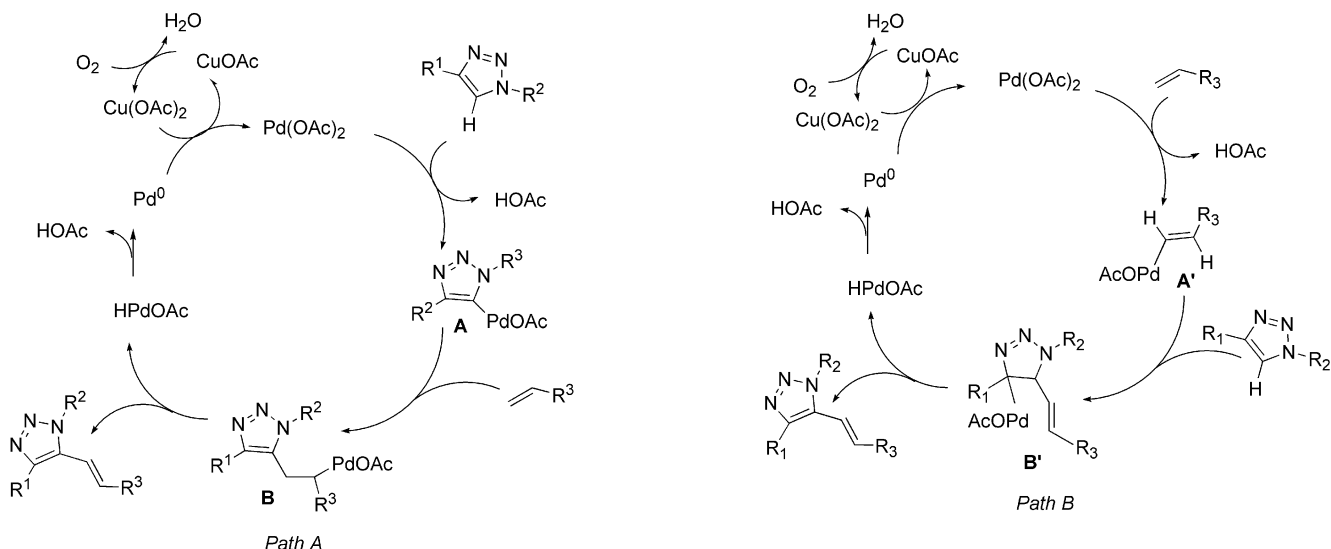
In summary, we have developed an efficient and new method for the palladium-catalyzed dehydrogenative coupling of triazoles and terminal alkenes. The method provides trisubstituted 1,4,5-trisubstituted-1*H*-1,2,3-triazoles in reasonable to excellent yields and with high regio- and stereoselectivities. It should be mentioned that these highly substituted-1*H*-1,2,3-triazoles might show potential biological activities and be utilized in agrochemical and pharmaceutical industries.

Experimental Section

General: ¹H NMR spectra were recorded in CDCl₃ at 400 MHz and ¹³C NMR spectra were recorded at 100 MHz; chemical shifts

were referenced to TMS. GC–MS was obtained by using electron ionization (EI). TLC was performed by using commercially prepared 100–400 mesh silica gel plates (GF₂₅₄), and visualization was effected at 254 nm. All the other chemicals were purchased from Aldrich Chemicals.

Typical Experimental Procedure for Pd-catalyzed Alkenylation of 1a with 2a: A mixture of 1-octyl-4-phenyl-1*H*-1,2,3-triazole (**1a**; 77.1 mg, 0.3 mmol), methyl acrylate (**2a**; 51.6 mg, 0.6 mmol), Pd(OAc)₂ (6.7 mg, 0.03 mmol), and Cu(OAc)₂ (108.9 mg, 0.6 mmol) in dioxane (2 mL) was added to a HF-10 autoclave, and then oxygen gas was pumped into the autoclave by a cooling pump until the desired pressure (8 atm) was reached. The autoclave was heated at 110 °C by oil bath under magnetic stirring for the desired time. After the reaction finished, the autoclave was allowed to cool to room temperature. O₂ was vented and the surplus was filtered and condensed under reduced pressure. The solvent was subjected



Scheme 2. Plausible reaction pathway for the alkenylation of triazoles.

to isolation by TLC (GF₂₅₄), eluting with petroleum ether/dichloromethane to give compound **3aa**. ¹H NMR (400 MHz, CDCl₃, 25 °C): δ = 0.86 (t, *J*_{H,H} = 6.8 Hz, 3 H, 3-CH₂CH₃), 1.23–1.37 (m, 10 H, 10 × CH₂CH₂CH₂CH₂CH₂CH₃), 1.90–1.93 (m, 2 H, 2-CH₂CH₂C₆H₁₃), 3.78 (s, 3 H, 3-OCH₃), 4.43 (t, *J*_{H,H} = 7.4 Hz, 2 H, 2-NCH₂), 6.31 (d, *J*_{H,H} = 16.4 Hz, 1 H, CH=CHCOOCH₃), 7.37–7.46 (m, 3 H, 3-C₆H₅), 7.61–7.63 (m, 2 H 2-C₆H₅), 7.62 (d, *J*_{H,H} = 16.4 Hz, 1 H, CH=CHCOOCH₃) ppm. ¹³C NMR (100 MHz, CDCl₃, 25 °C): δ = 14.0, 22.6, 26.5, 28.9, 29.0, 30.0, 31.7, 49.3, 52.1, 122.6, 126.7, 127.7, 128.0, 128.2, 128.4, 128.6, 128.8, 128.9, 130.6, 147.8, 166.3 ppm. MS (EI, 70 eV): *m/z* (%) = 341 (5) [M]⁺, 213 (100), 228 (36). IR (KBr): ν̄ = 3029, 2925, 2858, 1725, 1645, 1502, 1460, 1355, 1273, 1177, 972, 771, 697 cm⁻¹. C₂₀H₂₇N₃O₂ (341.06): calcd. C 70.35, H 7.97, N 12.31; found C 70.16, H 8.04, N 12.22.

Supporting Information (see footnote on the first page of this article): Analytical and spectroscopic data for compounds **3aa–3aj**.

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- [1] Reviews on 1,2,3-triazoles: a) H. Dehne in *Methoden der Organischen Chemie (Houben-Weyl)* (Ed.: E. Schumann), Thieme, Stuttgart, **1994**, vol. 8, p. 305; b) H. Wamhoff in *Comprehensive Heterocyclic Chemistry* (Eds.: A. R. Katritzky, C. W. Rees), Pergamon, Oxford, **1984**, vol. 5, p. 669; c) P. Desai, K. Schildknecht, K. A. Agrios, C. Mossman, G. Milligan, J. Aube, *J. Am. Chem. Soc.* **2000**, *122*, 7226–7232.
- [2] a) C. Tornøe, C. Christensen, M. Meldal, *J. Org. Chem.* **2002**, *67*, 3057–3064; b) V. V. Rostovtsev, L. G. Green, V. V. Fokin, K. B. Sharpless, *Angew. Chem. Int. Ed.* **2002**, *41*, 2596–2599.
- [3] S. Chuprakov, N. Chernyak, A. S. Dudnik, V. Gevorgyan, *Org. Lett.* **2007**, *9*, 2333–2336.

- [4] a) L. Ackermann, H. K. Potukuchi, D. Landsberg, R. Vicente, *Org. Lett.* **2008**, *10*, 3081–3084; b) L. Ackermann, R. Vicente, R. Born, *Adv. Synth. Catal.* **2008**, *350*, 741–748; c) L. Ackermann, R. Vicente, *Org. Lett.* **2009**, *11*, 4922–4925; d) L. Ackermann, A. Althammer, S. Fenner, *Angew. Chem. Int. Ed.* **2009**, *48*, 201–204.
- [5] J. Deng, Y. M. Wu, Q. Y. Chen, *Synthesis* **2005**, *16*, 2730–2738.
- [6] E. M. Beccalli, G. Brogini, M. Martinelli, S. Sottocornola, *Chem. Rev.* **2007**, *107*, 5318–5365.
- [7] a) I. Moritani, Y. Fujiwara, *Tetrahedron Lett.* **1967**, *8*, 1119–1122; b) Y. Fujiwara, I. Moritani, S. Danno, S. Teranishi, *J. Am. Chem. Soc.* **1969**, *91*, 7166–7169; c) Y. Fujiwara, O. Maruyama, M. Yoshidomi, H. Taniguchi, *J. Org. Chem.* **1981**, *46*, 851–855; d) C. G. Jia, T. Kitamura, Y. Fujiwara, *Acc. Chem. Res.* **2001**, *34*, 633–639.
- [8] a) Y. Fujiwara, R. Asano, I. Moritani, S. Teranishi, *J. Org. Chem.* **1976**, *41*, 1681–1683; b) C. G. Jia, W. J. Lu, T. Kitamura, Y. Fujiwara, *Org. Lett.* **1999**, *1*, 2097–2100; c) A. Maehara, T. Satoh, M. Miura, *Tetrahedron* **2008**, *64*, 5982–5986; d) J. L. Zhao, L. H. Huang, K. Cheng, Y. H. Zhang, *Tetrahedron Lett.* **2009**, *50*, 2758–2761.
- [9] For intermolecular direct alkenylation reactions of indoles and pyrroles, see: a) N. P. Grimster, C. Gauntlett, C. R. A. Godfrey, M. J. Gaunt, *Angew. Chem. Int. Ed.* **2005**, *44*, 3125–3129; b) E. M. Beck, N. P. Grimster, R. H. Hatley, M. J. Gaunt, *J. Am. Chem. Soc.* **2006**, *128*, 2528–2529; c) E. M. Beck, R. Hatley, M. J. Gaunt, *Angew. Chem. Int. Ed.* **2008**, *47*, 3004–3007.
- [10] T. Itahara, K. Kawasaki, F. Ouseto, *Bull. Chem. Soc. Jpn.* **1984**, *57*, 3488–3493.
- [11] For intramolecular direct alkenylation reactions examples, see: a) H. Zhang, E. M. Ferreira, B. M. Stoltz, *Angew. Chem. Int. Ed.* **2004**, *43*, 6144–6148; b) H. Iida, Y. Yuasa, C. Kibayashi, *J. Org. Chem.* **1980**, *45*, 2938–2942; c) H. J. Knölker, N. O'Sullivan, *Tetrahedron* **1994**, *50*, 10893–10908.
- [12] a) T. Yokota, M. Tani, S. Sakaguchi, Y. Ishii, *J. Am. Chem. Soc.* **2003**, *125*, 1476–1477; b) Y. Hatamoto, S. Sakaguchi, Y. Ishii, *Org. Lett.* **2004**, *6*, 4623–4625; c) T. Yamada, S. Sakaguchi, Y. Ishii, *J. Org. Chem.* **2005**, *70*, 5471–5474.
- [13] The structure of **3aj** was determined by NOESY. See Supporting Information for details.

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