DOI: 10.1002/ejoc.200800353

Lewis Acid Catalyzed Addition of Pyrazoles to Alkynes: Selective Synthesis of Double and Single Addition Products

Teruhisa Tsuchimoto,*[a] Kazuki Aoki,[a] Tatsuya Wagatsuma,[a] and Yuichi Suzuki[a]

Keywords: Addition reactions / Alkynes / Nitrogen heterocycles / Regioselectivity / Synthetic methods

Silver and zinc salts were found to efficiently catalyze the addition of an N–H bond of pyrazoles to alkynes. With silver triflate as a catalyst, two pyrazoles regioselectively attacked the same carbon atom of the C≡C bond of aliphatic terminal alkynes to give *gem*-dipyrazolylalkanes predominantly. Replacement of silver triflate with zinc triflate allows us to achieve double addition of pyrazoles to aromatic terminal alkynes. In contrast to the selective double addition, the corresponding single addition of aliphatic and aromatic terminal alkynes exclusively proceeded in the presence of a catalytic amount of silver nitrate. Internal alkynes also participated in the single addition reaction with the aid of silver triflate as a catalyst. The notable feature of this protocol is the utilization of an addition reaction being optimal from environmental and atom-economical points of view. The reaction mechanism is also described.

Introduction

gem-Dipyrazolylalkanes (*gem*-DPAs) are highly attractive units due to their two nitrogen coordination sites. In this context, a large number of main-group and transition-metal complexes coordinated by *gem*-DPAs have been synthesized,[1,2] and some complexes show high catalytic activities for basic organic transformations.[3] Interestingly, platinum derivatives are important as anticancer agents.[4] *gem*-DPAs themselves also exhibit analgesic and anti-inflammatory actions.[5] In addition to the synthetic and biological significances, nickel and group 11 metal complexes show unique optical properties.[6] *gem*-DPAs thus play a vital role in a variety of aspects, but their syntheses have relied mainly on the following four types:[7] (1) Double substitution of dihaloalkanes with metal pyrazolates (metal = Na, K).[8] (2) Brønsted acid catalyzed double substitution of acetals with pyrazoles.[9] (3) Addition and substitution sequence of aldehydes with pyrazoles catalyzed by a Lewis acid.[10] (4) Treatment of dipyrazolyl ketones with aldehydes under cobalt catalysis, releasing CO_2 gas.[11] All these protocols, however, produce their respective byproducts, which is unfavorable in view of atom economy. Among the four types, protocols (1) and (4) seem to have been the most frequently utilized so far. However, the strong basic conditions for type (1) restrict the scope of the dihaloalkanes. In method (4), virulent phosgene is required for making the dipyrazolyl ketones. We thus envisaged that the development of a Lewis acid catalyzed double addition of pyrazoles to alkynes[12,13] would resolve the problems of the previous systems. This report with a metal triflate catalyst (metal = Ag, Zn) proves to be the case. Although hydroamination of alkynes is closely related to the present reaction, double hydroamination of alkynes has no precedent to the best of our knowledge.[14] Notably, use of silver nitrate ($AgNO_3$) as a catalyst was found to change the reaction course drastically, giving only single addition products: pyrazolylalkenes.[15–17] From a synthetic point of view, pyrazolylalkenes are useful frameworks for further organic transformations utilizing their C=C bonds.[18]

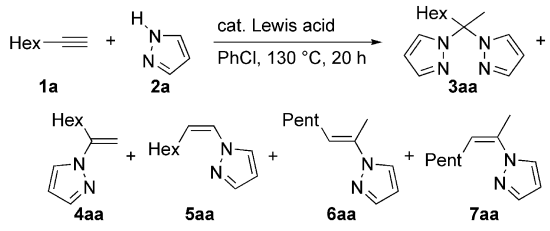
Results and Discussion

We first studied the effect of Lewis acid catalysts in the reaction of 1-octyne (**1a**) with pyrazole (**2a**) (Table 1). Treatment of **1a** and **2a** with 5 mol-% of $In(OTf)_3$ (Tf = SO_2CF_3), which is a prominent catalyst for the double addition of heterocyclic arenes to alkynes,[13] in PhCl at 130 °C for 20 h gave only 2,2-bis(pyrazol-1-yl)octane (**3aa**), albeit in a low yield (Table 1, Entry 1). To our great delight, the yield of **3aa** was improved dramatically by the replacement of $In(OTf)_3$ with AgOTf, though 1:1 adducts of **4aa**–**6aa** were also produced in 13% yield (Table 1, Entry 2). No higher yield of **3aa** was achieved with the increased amount of **2a** (Table 1, Entry 3). The use of 2 mol equiv. of **2a** relative to the amount of **1a** led to nonselective double addition (Table 1, Entry 4). The use of 10 mol-% of $Zn(OTf)_2$ gave **3aa** in a good yield, though its lower loading made the reaction sluggish, where **7aa**, the stereoisomer of **6aa**, was also formed (Table 1, Entries 5 and 6). Other metal triflate cata-

[a] Department of Applied Chemistry, School of Science and Technology, Meiji University,
Higashimita, Tama-ku, Kawasaki, 214-8571, Japan
Fax: +81-44-934-7228
E-mail: tsuchimo@isc.meiji.ac.jp
Supporting information for this article is available on the WWW under http://www.eurjoc.org or from the author.

lysts resulted in lower efficiencies (Table 1, Entries 7–10). The promising activity of AgOTf prompted us to survey the effect of other silver salts. In sharp contrast to the selective double addition observed with AgOTf as well as with $AgClO_4$ and $AgPF_4$, $AgNO_3$ was found to be a crucial catalyst for accessing the single addition, in which **4aa** was selectively obtained among **4aa**–**7aa** (Table 1, Entries 2 and 11–15). No reaction proceeded without a catalyst (Table 1, Entry 16).

Table 1. Lewis acid catalyzed addition of pyrazole to 1-octyne.[a]

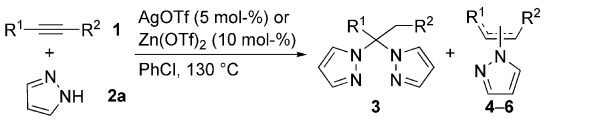


Entry	Lewis acid	Conv. [%] of **1a**[b]	Yield [%] of **3aa**[b]	Yield [%] and ratio of **4aa**–**7aa**[b]
1	$In(OTf)_3$	21	3	<1
2	AgOTf	>99	81	13 (34:54:12:<1)
3[c]	AgOTf	>99	79	11 (30:49:21:<1)
4[d]	AgOTf	>99	39	45 (87:13:<1:<1)
5	$Zn(OTf)_2$[e]	>99	71	18 (7:7:69:17)
6	$Zn(OTf)_2$	65	44	7 (18:12:63:7)
7	$Cu(OTf)_2$	45	19	4 (<1:33:67:<1)
8	$Au(OTf)_3$[f]	>99	58	22 (5:35:49:11)
9	$Bi(OTf)_3$	98	53	15 (8:3:72:17)
10	$Sc(OTf)_3$	84	41	13 (8:25:56:11)
11	$AgClO_4$	>99	75	12 (27:57:16:<1)
12	$AgPF_4$	95	56	28 (70:26:4:<1)
13	$AgSbF_6$	98	41	45 (87:13:<1:<1)
14	AgCl	56	3	13 (91:9:<1:<1)
15	$AgNO_3$	96	1	90 (92:8:<1:<1)
16	None	<1	0	0

[a] **1a**: 0.50 mmol, **2a**: 2.5 mmol, PhCl: 0.5 mL, Lewis acid: 25 μmol. [b] Determined by GC by using *o*-$Cl_2C_6H_4$ as an internal standard. [c] **2a**: 3.0 mmol. [d] **2a**: 1.0 mmol. [e] $Zn(OTf)_2$: 50 μmol. [f] $Au(OTf)_3$ was prepared in situ from $AuCl_3$ (25 μmol) and AgOTf (75 μmol).

With each suitable Lewis acid catalyst for the double or single addition reaction, we next examined the substrate scope for the double addition (Table 2). Besides **1a**, aliphatic terminal alkynes with –Ph, –CN, –OAc, and –PI (PI = phthalimidoyl) groups at the end of the alkyl chain reacted with **2a** predominantly to give **3ba**–**3fa** (Table 2, Entries 1–6). Although the reaction of phenylacetylene (**1g**) with AgOTf resulted predominantly in single addition, $Zn(OTf)_2$ improved the case to afford **3ga** in 70% yield (Table 2, Entries 7 and 8). Various aromatic terminal alkynes **1h**–**1k** also participated in the double addition of **2a** with the aid of $Zn(OTf)_2$ as a catalyst (Table 2, Entries 9–12). The isomer distributions of the 1:1 adducts derived from **1g**–**1j** that are specified in Table 2 should be informative for mechanistic considerations.[19] Among the aromatic alkynes, only **1k** accepted **2a** exclusively at the β-carbon atom of the C≡C bond. The Michael-like addition should be responsible for the negative resonance effect of the 2-pyridyl group that makes the β-carbon atom more electrophilic.[20] The reaction of ethyl propiolate (**1l**) proceeded also in a Michael fashion (Table 2, Entry 13). In addition to **2a**, 4-methylpyrazole (**2b**) added successively to **1a** (Table 2, Entry 14).

Table 2. Lewis acid catalyzed double addition of pyrazoles to alkynes.[a]



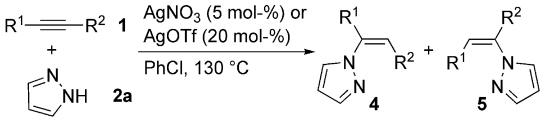
Entry	$R^1C{\equiv}CR^2$ (**1**)	*t* [h]	Yield [%] of **3**[b]	Yield [%] of 1:1 adducts[b]
1	HexC≡CH (**1a**)	20	74 (**3aa**)	12
2	$Ph(CH_2)_2C{\equiv}CH$ (**1b**)	40	73 (**3ba**)	19
3	BnC≡CH[c] (**1c**)	50	79 (**3ca**)	18
4	$NC(CH_2)_3C{\equiv}CH$ (**1d**)	100	70 (**3da**)	15
5	$AcO(CH_2)_3C{\equiv}CH$ (**1e**)	70	65 (**3ea**)	12
6	$PI(CH_2)_3C{\equiv}CH$ (**1f**)	80	72 (**3fa**)	17
7	PhC≡CH (**1g**)	50	12 (**3ga**)	67 (**4ga**, **5ga**)[d]
8	PhC≡CH (**1g**)	50	70 (**3ga**)	23 (**4ga**)
9[e]	4-$ClC_6H_4C{\equiv}CH$ (**1h**)	80	61 (**3ha**)	18 (**4ha**)
10	4-$MeOC_6H_4C{\equiv}CH$ (**1i**)	30	74 (**3ia**)	19 (**4ia**)
11	3-thienyl–C≡CH (**1j**)	45	70 (**3ja**)	14 (**4ja**)
12	HC≡C–2-pyridyl (**1k**)	5	61 (**3ka**)	7
13	$HC{\equiv}CCO_2Et$ (**1l**)	65	82 (**3la**)	2[f]
14[g]	HexC≡CH (**1a**)	20	83 (**3ab**)	9

[a] **1**: 0.50 mmol, **2a**: 2.5 mmol, PhCl: 0.5 mL, AgOTf: 25 μmol for Entries 1–7, 13 and 14, $Zn(OTf)_2$: 50 μmol for Entries 8–12. [b] Isolated yield based on the alkyne. [c] Bn = $PhCH_2$. [d] **4ga**:**5ga** = 50:50. [e] **2a**: 3.5 mmol, $Zn(OTf)_2$: 75 μmol. [f] Ethyl (*E*)-3-(pyrazol-1-yl)-2-propenoate (**8**) was obtained as a single isomer. [g] 4-Methylpyrazole (**2b**) instead of **2a** was used.

As already presented, the $AgNO_3$-catalyzed reaction with the use of 5 mol equiv. of **2a** to **1a** produced a small amount of **3aa** (Table 1, Entry 15). We were, however, pleased to find that **3aa** was reduced to a negligible amount with the use of 2 to 1 molar ratio of **2a** to **1a** (Table 3, Entry 1). We thus applied the conditions to single addition of other alkynes (Table 3). Expectedly, all the reactions of aliphatic and aromatic terminal alkynes provided only pyrazolylalkenes **4** and **5** as a regioisomeric mixture (Table 3, Entries 2–5). In the additions of **2a** to the terminal carbon atom of a C≡C bond, complete *Z* geometry of the products was always observed, that is, the stereoselective formation of **5aa**–**5ja**. These results prove that *anti* addition is involved as a key step in the reaction process. Perfect *anti* addition again took place in the reactions of internal alkynes **1m** and **1n**, where AgOTf is superior to $AgNO_3$ as a catalyst (Table 3, Entries 6 and 7).[21] 3,5-Dimethylpyrazole (**2c**) also is available for the single addition to **1a** (Table 3, Entry 8).

From a mechanistic viewpoint, two routes are possible here. Path A is a route including a cation intermediate and path B proceeds through a concerted mechanism (Scheme 1). On the basis of our previous demonstrations,[13,16] there are some critical differences between the

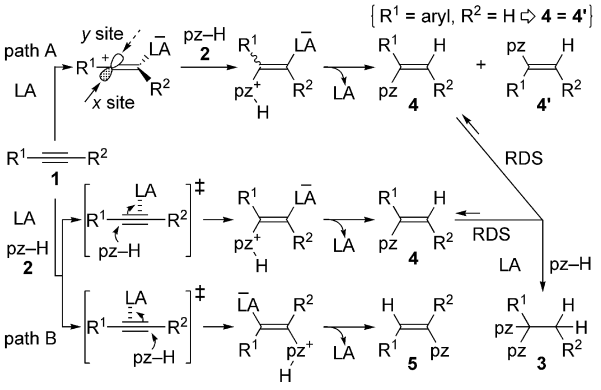
Table 3. Lewis acid catalyzed single addition of pyrazoles to alkynes.[a]



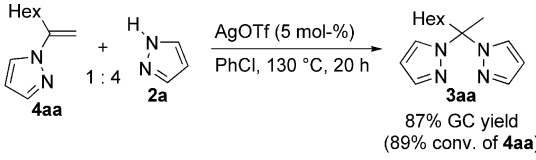
Entry	$R^1C{\equiv}CR^2$ (**1**)	*t* [h]	Yield [%] of **4** and **5**[b]	Ratio of **4**:**5**[c]
1	HexC≡CH (**1a**)	20	86 (**4aa**, **5aa**)	92:8
2	$Ph(CH_2)_2C{\equiv}CH$ (**1b**)	20	95 (**4ba**, **5ba**)	84:16
3	$NC(CH_2)_3C{\equiv}CH$ (**1d**)	20	88 (**4da**, **5da**)	87:13
4	PhC≡CH (**1g**)	20	89 (**4ga**, **5ga**)	48:52
5	3-thienyl–C≡CH (**1j**)	25	56 (**4ja**, **5ja**)	52:48
6[d]	BuC≡CBu (**1m**)	70	51 (**4ma**)	–
7[e]	PhC≡CMe (**1n**)	50	85 (**4na**, **5na**)	15:85
8[f]	HexC≡CH (**1a**)	24	59 (**4ac**, **5ac**)	79:21

[a] **1**: 0.250 mmol, **2a**: 0.500 mmol, PhCl: 0.25 mL, $AgNO_3$: 12.5 μmol for Entries 1–5 and 8, AgOTf: 50.0 μmol for Entries 6 and 7. [b] Isolated yield based on the alkyne. [c] Determined by GC analysis. [d] The reaction was performed in the presence of $(i\text{Pr})_2\text{NEt}$ (50.0 μmol). [e] The reaction was carried out in *p*-$MeClC_6H_4$ instead of PhCl at 140 °C. [f] 3,5-Dimethylpyrazole (**2c**) instead of **2a** was used.

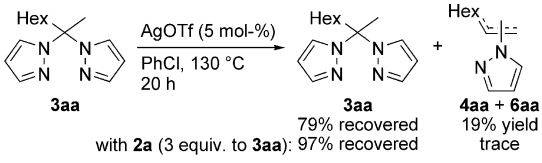
two routes to discriminate which route is operative. Thus, when R^1 or R^2 is aryl or alkyl, respectively, like **1n**, attack of **2** (pz–H) to **1** in path A should proceed regioselectively due to the much higher ability of the aryl group to stabilize positive charges, though a mixture of *anti* and *syn* adducts **4** and **4′** are formed, because the sp-hybridized cation center accepts pz–H from both *x* and *y* sites. On the contrary, path B should provide regioisomeric **4** and **5** by stereoselective *anti* addition because pz–H attacks **1** from the side opposite to a coordinated Lewis acid (LA),[22] where the regioselectivity seems to depend on the nucleophile and/or LA used.[23] According to these considerations, the exclusive *anti* addition to give regioisomers **4** and **5** observed in Table 3 strongly suggests that path B is operative under silver catalysis. Moreover, the formation of **4ga** and **5ga** with AgOTf as a catalyst (Table 2, Entry 7) also supports path B. However, all of the $Zn(OTf)_2$-catalyzed reactions gave only **4** (Table 2, Entries 8–11). Thus, considering that path A works only when $Zn(OTf)_2$ is a catalyst, the perfect regioselectivities should be rationally understood. Although the mechanistic details from **4** to **3** are hard to discuss, the AgOTf-catalyzed reaction of **4aa** with **2a** in PhCl at 130 °C proceeded at almost the same reaction rate as that of **1a** with **2a** (Table 1, Entry 2), giving **3aa** in a higher yield [Equation (1)]. The result suggests that **4** is an intermediate of **3** and that the addition process from **4** to **3** is the rate-determining step (RDS). In addition to this, AgOTf was found to catalyze the elimination of **2a** from **3aa** [Equation (2)]. Because almost no elimination occurs in the presence of **2a**, these results may explain why the successful double addition reaction requires an excess amount of pyrazoles relative to the amount of alkynes. Finally, we investigated a route for the formation of **6** and **7**, and $Zn(OTf)_2$ was used as a catalyst for this purpose, because no **7aa** is generated from the silver-catalyzed reactions of **1a** with **2a** (Table 1, Entries 2–4 and 11–15). Treatment of **4aa** with 10 mol-% of $Zn(OTf)_2$ in PhCl at 130 °C gave a mixture of **6aa** and **7aa** [Equation (3)], which clearly shows that **6** and **7** are formed by isomerization of **4**.



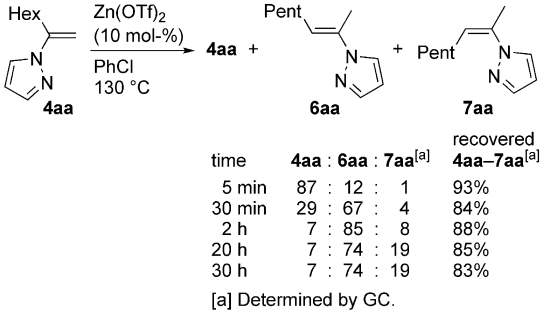
Scheme 1. Proposed routes for the addition of pyrazoles to alkynes.



(1)



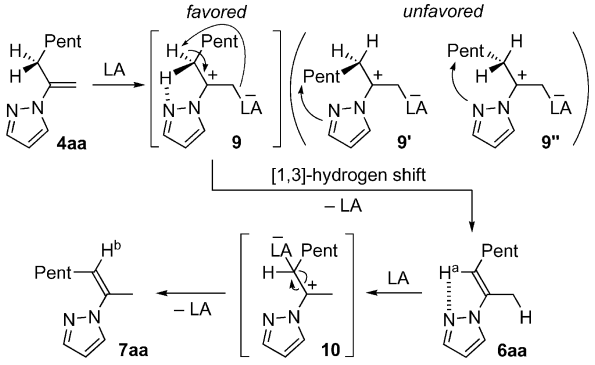
(2)



(3)

Additionally, the fact that the ratio of **6aa** and **7aa** varies depending on the reaction time exhibits that **6aa**, which is gradually isomerized in part to **7aa**, is the kinetically favored isomer. Moreover, no further isomerization of **6aa** to **7aa** after 20 h results from an equilibrium between **6aa** and **7aa** under the reaction conditions, and the resulting higher ratio of **6aa** suggests that **6aa** is also thermodynamically

more stable than **7aa**. A possible isomerization mechanism exemplified by the reaction of **4aa** is summarized in Scheme 2. Thus, formation of alkyl cation **9** by the reaction of **4aa** with a metal triflate (LA) and subsequent [1,3]-hydrogen shift induces the isomerization of **4aa** to **6aa**.[24] Successively, **6aa** is isomerized to **7aa** by generation of cation **10** followed by bond rotation and elimination of LA. Although three conformers, **9**, **9′**, and **9′′**, possibly exist in the isomerization process, conformer **9** without steric hindrance between the pentyl and pyrazolyl groups seems to be the most favorable, which should result in the predominant formation of **6aa**. The hydrogen bonding shown in **9** also might contribute to the formation process of **6aa**. The participation of the hydrogen bonding may be explained by the fact that the H^a signal (δ = 5.87 ppm) appears downfield relative to the corresponding H^b signal (δ = 5.33 ppm) in their ^1H NMR spectra.[25]



Scheme 2. A possible isomerization mechanism.

Conclusions

We have achieved the selective double and single addition of pyrazoles to alkynes, for the first time, by appropriate choice of the Lewis acid catalyst. The highlight of our strategy is attributed to the utilization of an addition scaffold that is environmentally benign and completely atom economical. The wide substrate scope based on the remarkable functional group compatibility enhances the utility of this protocol. Studies on application of single and double addition products are currently underway.

Experimental Section

General Remarks: All manipulations were conducted with standard Schlenk techniques under an argon atmosphere. Nuclear magnetic resonance spectra were taken with a JEOL ECA-400 (^1H, 400 MHz; ^{13}C, 100 MHz) or JEOL ECA-500 (^1H, 500 MHz; ^{13}C, 125 MHz) spectrometer by using tetramethylsilane (^1H) or $CDCl_3$ (^{13}C) as an internal standard. Analytical gas chromatography was performed with a Shimadzu model GC-18A instrument equipped with a capillary column of ID-BPX5 (5% phenyl polysilphenylene-siloxane, 30 m × 0.25 mm × 0.25 μm) with the use of nitrogen as a carrier gas. High-resolution mass spectra (HRMS) were obtained with a Mariner spectrometer. Preparative recycling high-performance liquid chromatography (HPLC) was performed with JAI LC-908 equipped with JAIGEL-SIL S-043–15 column. All melting points were measured with a Yanaco Micro Melting Point apparatus and are uncorrected. Chlorobenzene was distilled under an argon atmosphere from calcium chloride just prior to use. *p*-Chlorotoluene and *N*,*N*-diisopropylethylamine were stored over 4 Å MS before use. All alkynes **1a**–**1n** and pyrazoles **2a**–**2c** were commercially available and used as received.

General Procedure for the Lewis Acid Catalyzed Double Addition of Pyrazole to Alkynes: AgOTf (6.4 mg, 25 μmol) or $Zn(OTf)_2$ (18.2 mg, 50.0 μmol or 27.3 mg, 75.0 μmol) was placed in a 20-mL Schlenk tube, which was heated at 80 °C for 15 min or 150 °C for 2 h under vacuum, respectively. The tube was cooled to room temperature and filled with argon. To this was added pyrazole (170.2 mg, 2.500 mmol or 238.3 mg, 3.500 mmol), chlorobenzene (0.5 mL), and an alkyne (0.500 mmol) successively, and the resulting mixture was stirred at 130 °C. After the time specified in Table 2, saturated $NaHCO_3$ aqueous solution (1 mL) was added, and the mixture was extracted with ethyl acetate (3 × 5 mL). The combined organic layer was dried with anhydrous sodium sulfate. Filtration and evaporation of the solvent followed by column chromatography on silica gel (hexane/ethyl acetate) gave the corresponding *gem*-dipyrazolylalkane **3** and an isomeric mixture of pyrazolylalkenes **4**, **5**, and/or **6**. The double addition of 4-methylpyrazole to 1-octyne presented in Table 2 (Entry 14) was carried out similarly as above. These results are summarized in Table 2. All *gem*-dipyrazolylalkanes were fully characterized by ^1H and ^{13}C NMR spectroscopy and HRMS (see Supporting Information).

General Procedure for the Lewis Acid Catalyzed Single Addition of Pyrazole to Alkynes: $AgNO_3$ (2.12 mg, 12.5 μmol) or AgOTf (12.8 mg, 50.0 μmol) was placed in a 20-mL Schlenk tube, which was heated at 80 °C in vacuo for 15 min. The tube was cooled to room temperature and filled with argon. To this was added pyrazole (34.0 mg, 0.500 mmol), chlorobenzene or *p*-chlorotoluene (0.25 mL), and an alkyne (0.250 mmol) successively, and the resulting mixture was stirred at 130 or 140 °C. After the time specified in Table 3, saturated $NaHCO_3$ aqueous solution (1 mL) was added, and the mixture was extracted with ethyl acetate (3 × 5 mL). The combined organic layer was dried with anhydrous sodium sulfate. Filtration and evaporation of the solvent followed by column chromatography on silica gel (hexane/ethyl acetate) gave the corresponding pyrazolylalkene **4** and/or **5**. The single addition of 3,5-dimethylpyrazole to 1-octyne presented in Table 3 (Entry 8) was carried out similarly as above. In the cases of **4ba** and **5ba**, **4da** and **5da**, **4ga** and **5ga**, and **4ac** and **5ac**, further separation was performed with preparative recycling HPLC. These results are summarized in Table 3. All pyrazolylalkenes appearing in Tables 1–3 were fully characterized by ^1H and ^{13}C NMR spectroscopy and HRMS (see Supporting Information).

Supporting Information (see footnote on the first page of this article): Spectral and analytical data, ^1H and ^{13}C NMR spectra for all compounds.

[1] For a review, see: C. Pettinari, R. Pettinari, *Coord. Chem. Rev.* **2005**, *249*, 663–691.

[2] For selected recent examples, Zn and Cd: a) C. Santini, *Inorg. Chem. Commun.* **2004**, *7*, 834–837; Ru: b) A. Caballero, M. C. Carrión, G. Espino, F. A. Jalón, B. R. Manzano, *Polyhedron* **2004**, *23*, 361–371; Co and Ni: c) X.-Y. Chen, W. Shi, J. Xia, P. Cheng, B. Zhao, H.-B. Song, H.-G. Wang, S.-P. Yan, D.-Z. Liao, Z.-H. Jiang, *Inorg. Chem.* **2005**, *44*, 4263–4269; Mn: d) D. L. Reger, J. R. Gardinier, T. C. Grattan, M. D. Smith, *J. Or-*

ganomet. Chem. **2005**, *690*, 1901–1912; W: e) L.-F. Tang, J. Hong, Z.-K. Wen, *Organometallics* **2005**, *24*, 4451–4453; Cu: f) A. S. Potapov, A. I. Khlebnikov, *Polyhedron* **2006**, *25*, 2683–2690; Ag: g) A. Cerquetella, Effendy, C. Pettinari, R. Pettinari, B. W. Skelton, A. H. White, *Inorg. Chim. Acta* **2007**, *360*, 2265–2270; Re: h) A. R. Cowley, J. R. Dilworth, M. Salichou, *Dalton Trans.* **2007**, 1621–1629; Ni: i) N. Baho, D. Zargarian, *Inorg. Chem.* **2007**, *46*, 299–308; Rh and Ir: j) D. F. Kennedy, B. A. Messerle, M. K. Smith, *Eur. J. Inorg. Chem.* **2007**, 80–89.

[3] Cycloisomerization of 1,6-dienes: a) A. Heumann, M. Moukhliss, *Synlett* **1998**, 1211–1212; epoxidation of alkenes: b) A. M. Santos, F. E. Kühn, K. Bruus-Jensen, I. Lucas, C. C. Romão, E. Herdtweck, *J. Chem. Soc., Dalton Trans.* **2001**, 1332–1337; c) F. E. Kühn, W.-M. Xue, A. Al-Ajlouni, A. M. Santos, S. Zang, C. C. Romão, G. Eickerling, E. Herdtweck, *Inorg. Chem.* **2002**, *41*, 4468–4477; aerobic oxidation of organic molecules: d) M. H. V. Huynh, L. M. Witham, J. M. Lasker, M. Wetzler, B. Mort, D. L. Jameson, P. S. White, K. J. Takeuchi, *J. Am. Chem. Soc.* **2003**, *125*, 308–309; dehydrogenative silylation of alcohols: e) L. D. Field, B. A. Messerle, M. Rehr, L. P. Soler, T. W. Hambley, *Organometallics* **2003**, *22*, 2387–2395; hydroformylation of alkenes: f) E. Teuma, M. Loy, C. L. Berre, M. Etienne, J.-C. Daran, P. Kalck, *Organometallics* **2003**, *22*, 5261–5267; asymmetric Diels–Alder reaction: g) C. Kashima, Y. Miwa, S. Shibata, H. Nakazono, *J. Heterocycl. Chem.* **2003**, *40*, 681–688; intramolecular hydroamination of alkynes: h) S. Burling, L. D. Field, B. A. Messerle, P. Turner, *Organometallics* **2004**, *23*, 1714–1721.

[4] a) J. A. Broomhead, L. M. Rendina, L. K. Webster, *J. Inorg. Biochem.* **1993**, *49*, 221–234; b) N. J. Wheate, B. J. Evison, A. J. Herlt, D. R. Phillips, J. G. Collins, *Dalton Trans.* **2003**, 3486–3492; c) J. G. Collins, N. J. Wheate, *J. Inorg. Biochem.* **2004**, *98*, 1578–1584.

[5] P. T. Pavlov, A. F. Goleneva, A. E. Lesnov, T. S. Prokhorova, *Khim. Farm. Zh.* **1998**, *32*, 28–30.

[6] a) M. J. Calhorda, P. J. Costa, O. Crespo, M. C. Gimeno, P. G. Jones, A. Laguna, M. Naranjo, S. Quintal, Y.-J. Shi, M. D. Villacampa, *Dalton Trans.* **2006**, 4104–4113; b) N. Baho, D. Zargarian, *Inorg. Chem.* **2007**, *46*, 7621–7632.

[7] For reviews, see: a) D. L. Jameson, R. K. Castellano, *Inorg. Synth.* **1998**, *32*, 51–63; b) A. Otero, J. Fernández-Baeza, A. Antiñolo, J. Tejeda, A. Lara-Sánchez, *Dalton Trans.* **2004**, 1499–1510. See also ref.[1]

[8] For selected examples, see: a) S. Juliá, P. Sala, J. M. del Mazo, M. Sancho, C. Ochoa, J. Elguero, J.-P. Fayet, M.-C. Vertut, *J. Heterocycl. Chem.* **1982**, *19*, 1141–1145; b) R. M. Claramunt, H. Hernandez, J. Elguero, S. Juliá, *Bull. Soc. Chim. Fr.* **1983**, 5–10; c) S. Juliá, J. M. del Mazo, L. Avila, J. Elguero, *Org. Prep. Proced. Int.* **1984**, *16*, 299–307; d) E. Díez-Barra, A. de la Hoz, A. Sánchez-Migallón, J. Tejeda, *Heterocycles* **1992**, *34*, 1365–1373; e) A. Beck, B. Weibert, N. Burzlaff, *Eur. J. Inorg. Chem.* **2001**, 521–527. See also ref.[2a,2f,3e,3g]

[9] For selected examples, see: a) S. Trofimenko, *J. Am. Chem. Soc.* **1970**, *92*, 5118–5126; b) D. L. Jameson, S. E. Hilgen, C. E. Hummel, S. L. Pichla, *Tetrahedron Lett.* **1989**, *30*, 1609–1612.

[10] For selected examples, see: a) P. Ballesteros, J. Elguero, R. M. Claramunt, *Tetrahedron* **1985**, *41*, 5955–5963; b) P. Ballesteros, R. M. Claramunt, T. C. López, J. Elguero, G. Gómez-Alarcón, *Chem. Pharm. Bull.* **1988**, *36*, 2036–2041.

[11] For selected examples, see: a) K. I. Thé, L. K. Peterson, *Can. J. Chem.* **1973**, *51*, 422–426; b) K. I. Thé, L. K. Peterson, E. Kiehlmann, *Can. J. Chem.* **1973**, *51*, 2448–2451; c) P. K. Byers, A. J. Canty, R. T. Honeyman, *J. Organomet. Chem.* **1990**, *385*, 417–427; d) T. C. Higgs, C. J. Carrano, *Inorg. Chem.* **1997**, *36*, 291–297; e) T. C. Higgs, D. Ji, R. S. Czernuszewicz, B. F. Matzanke, V. Schunemann, A. X. Trautwein, M. Helliwell, W. Ramirez, C. J. Carrano, *Inorg. Chem.* **1998**, *37*, 2383–2392; f) T. C. Higgs, C. J. Carrano, *Eur. J. Org. Chem.* **2002**, 3632–3645. See also ref.[2b,2d]

[12] Only highly electrophilic alkynes, 3-butyn-2-one, methyl propiolate, and dimethyl acetylenedicarboxylate have been used for the previous double addition: a) H. Winckler, E. Peterson, *Justus Liebigs Ann. Chem.* **1932**, *498*, 1–15; b) R. M. Acheson, P. W. Poulter, *J. Chem. Soc.* **1960**, 2138–2140; c) H. Reimlinger, C. H. Moussebois, *Chem. Ber.* **1965**, *98*, 1805–1813; d) S. Hoffmann, E. Mühle, *Z. Chem.* **1968**, *8*, 458–459; e) J. Elguero, A. de la Hoz, C. Pardo, *J. Chem. Soc. Perkin Trans. 2* **1985**, 427–431; f) E. Díez-Barra, J. Guerra, V. Hornillos, S. Merino, J. Tejeda, *Tetrahedron Lett.* **2004**, *45*, 6937–6939.

[13] We have demonstrated that alkynes accept two molecules of electron-rich heterocyclic arenes such as pyrroles, furans, and thiophenes assisted by indium triflate as a catalyst: T. Tsuchimoto, K. Hatanaka, E. Shirakawa, Y. Kawakami, *Chem. Commun.* **2003**, 2454–2455.

[14] For selected recent reports on hydroamination of alkynes, see: a) R. S. Robinson, M. C. Dovey, D. Gravestock, *Tetrahedron Lett.* **2004**, *45*, 6787–6789; b) R. S. Robinson, M. C. Dovey, D. Gravestock, *Eur. J. Org. Chem.* **2005**, 505–511; c) Y. Luo, Z. Li, C.-J. Li, *Org. Lett.* **2005**, *7*, 2675–2678; d) N. Lingaiah, N. S. Babu, K. M. Reddy, P. S. S. Prasad, I. Suryanarayana, *Chem. Commun.* **2007**, 278–279; e) A. V. Lee, L. L. Schafer, *Eur. J. Inorg. Chem.* **2007**, 2243–2255; f) Y. Zhang, J. P. Donahue, C.-J. Li, *Org. Lett.* **2007**, *9*, 627–630; g) X.-Y. Liu, P. Ding, J.-S. Huang, C.-M. Che, *Org. Lett.* **2007**, *9*, 2645–2648; h) P. J. Donoghue, E. Kieken, P. Helquist, O. Wiest, *Adv. Synth. Catal.* **2007**, *349*, 2647–2654; i) P. H. Cebrowski, J.-G. Roveda, J. Moran, S. I. Gorelsky, A. M. Beauchemin, *Chem. Commun.* **2008**, 492–493. See also a recent review: j) R. Severin, S. Doye, *Chem. Soc. Rev.* **2007**, *36*, 1407–1420.

[15] Except for one article with phenylacetylene (ref.[14c]), alkynes available for single addition have been limited to activated ones as the previous double addition: a) H. Reimlinger, J. F. M. Oth, *Chem. Ber.* **1964**, *97*, 331–338; b) R. Huisgen, B. Giese, H. Huber, *Tetrahedron Lett.* **1967**, *8*, 1883–1888; c) P. Bourgeois, J. Lucrece, J. Dunogués, *J. Heterocycl. Chem.* **1978**, *15*, 1543–1545; d) A. de la Hoz, E. Díez-Barra, M. C. Pardo, J. P. Declerq, G. Germain, M. V. Meerssche, J. Elguero, *Tetrahedron* **1983**, *39*, 2193–2200; e) A. G. Mal′kina, V. V. Nosyreva, E. I. Kositsyna, B. A. Trofimov, *Russ. J. Org. Chem.* **1997**, *33*, 399–402; f) K. Gu, G. Yang, W. Zhang, X. Liu, Z. Yu, X. Han, X. Bao, *J. Organomet. Chem.* **2006**, *691*, 1984–1992. See also ref.[12a–12e]

[16] We have reported that metal triflates catalyze single addition of arenes to alkynes: T. Tsuchimoto, T. Maeda, E. Shirakawa, Y. Kawakami, *Chem. Commun.* **2000**, 1573–1574.

[17] Our report on the synthesis of (hetero)aryl-annulated[*a*]carbazoles including a process of single addition of indole derivatives to alkynes: T. Tsuchimoto, H. Matsubayashi, M. Kaneko, E. Shirakawa, Y. Kawakami, *Angew. Chem. Int. Ed.* **2005**, *44*, 1336–1340.

[18] For recent examples, see: a) O. Iran, F. Holger, M. Dirk, M. Manfred, Q. Jose, P. Klaus, *Z. Naturforsch., B: Chem. Sci.* **2005**, *60*, 1175–1185; b) G. B. Bagdasaryan, P. S. Pogosyan, G. A. Panosyan, G. V. Asratyan, M. G. Indzhikyan, *Russ. J. Gen. Chem.* **2006**, *76*, 1324–1326; c) B. Iddon, J. E. Tønder, M. Hosseini, M. Begtrup, *Tetrahedron* **2007**, *63*, 56–61; d) A. de la Hoz, A. Díaz, J. Elguero, A. Jiménez, A. Moreno, A. Ruiz, A. Sánchez-Migallón, *Tetrahedron* **2007**, *63*, 748–753; e) M. J. Alves, A. G. Fortes, F. T. Costa, V. C. M. Duarte, *Tetrahedron* **2007**, *63*, 11167–11173.

[19] Detailed information concerning isomer distributions in addition to spectral and analytical data of 1:1 adducts produced in the reactions of Table 2, Entries 1–6 and 12–14 are provided in the Supporting Information.

[20] a) T. Sakamoto, H. Nagata, Y. Kondo, K. Sato, H. Yamanaka, *Chem. Pharm. Bull.* **1984**, *32*, 4866–4872; b) T. Sakamoto, Y. Kondo, M. Shirakawa, H. Yamanaka, *Synthesis* **1984**, 245–247.

[21] The single addition of **1m** and **1n** with the use of 20 mol-% of $AgNO_3$ instead of AgOTf also proceeded in comparable yields

(50% yield from **1m**, 76% yield from **1n**). However, an isomer of **4ma** in the reaction of **1m** was produced in a small amount (1% yield) together with **4ma**. In the case of **1n**, a mixture of four isomers including **4na** and **5na** was produced.

[22] For *anti* addition through a concerted mechanism, see: H. M. Weiss, K. M. Touchette, *J. Chem. Soc., Perkin Trans. 2* **1998**, 1523–1528.

[23] In ref.[13], *N*-methylpyrrole goes mainly to the Ph-attached carbon atom of **1n**, contrary to the regioselectivity observed in Table 3, Entry 7.

[24] For LA-catalyzed isomerization of C=C bonds through [1,3]-hydrogen shift, see: M. Rubina, M. Conley, V. Gevorgyan, *J. Am. Chem. Soc.* **2006**, *128*, 5818–5827.

[25] Proton signals that participate in hydrogen bonding such as C–H···X (X = heteroatom) are known to be shifted downfield in ^{1}H NMR spectra. For example, see: H. Kawasaki, G. Sakane, T. Shibahara, *Inorg. Chem. Commun.* **2005**, *8*, 777–781.

Received: April 7, 2008
Published Online: July 4, 2008

