Regio- and Stereoselective Dimerization of Terminal Alkynes to Enynes Catalyzed by a Palladium/Imidazolium System

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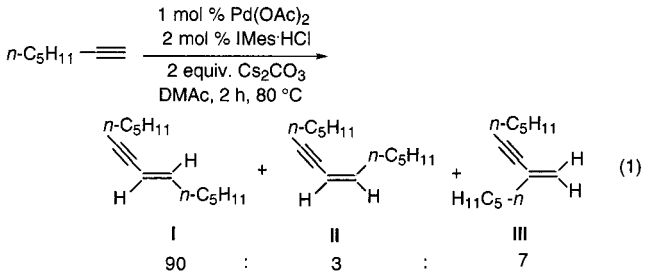
Abstract: A Palladium/imidazolium chloride system has been used to mediate the dimerization of terminal alkynes to enynes. The combination of 1 mol % $Pd(OAc)_2$ and 2 mol % IMes·HCl in the presence of Cs_2CO_3 as base shows high activity and high regio- and steroselectivity for the dimerization of aryl and aliphatic terminal alkynes to enynes.

Transition metal-catalyzed dimerization of terminal alkynes is an attractive method for the synthesis of enynes.[1] It has found increasing application in the construction of key structural moieties in natural products and electronic and optical materials.[2] Usually, the dimeric products include 1,3-disubstituted enynes from the head-to-tail dimerization of alkynes and 1,4-disubstituted enynes from the head-to-head dimerization of alkynes. High regio- and stereoselectivity has been the continued emphasis in the area of alkyne dimerization. Recently, some palladium−phosphine systems have displayed high activity and selectivity in the conversion of alkynes into enynes.[3]

Nucleophilic N-heterocyclic carbenes have attracted considerable attention as "phosphine mimics".[4] High catalytic performances have been achieved by using nucleophilic carbenes in various catalytic reactions such as the Suzuki−Miyaura coupling reaction,[5] the Kumada−Tamao−Corriu coupling reaction,[6] various Heck-type coupling reactions,[7] amination of aryl chlorides,[8] olefin metathesis,[9] and hydrogenation.[10] Most recently, Herrmann has reported a palladium complex with mixed carbene/phosphine ligand showing catalytic activity in the dimerization of phenylacetylene.[11] We wish to now report a regio- and stereoselective dimerization of terminal alkynes catalyzed by a palladium/imidazolium salt system.

We have established that active Pd−carbene species can be formed in situ from a palladium precursor with an imidazolium salt in various C−C coupling reactions under basic conditions.[5b,c,6] In initial experiments, a catalytic system consisting of 1 mol % $Pd(OAc)_2$ and 2 mol % IMes·HCl with 2 equiv of Cs_2CO_3 as base in *N*,*N*-dimethylacetamide (DMAc) at 80 °C was tested for catalytic activity in the dimerization of 1-heptyne (eq 1).

The reaction reached completion in 2 h. The product ratio of *trans*- and *cis*-1,4-disubstituted enyne (I and II) and 1,3-disubstituted enyne (III) is 90:3:7, showing high regio- and stereoselectivity. The stereostructure was determined by the coupling constant between two vinyl protons (J = 16.0 Hz) for *trans*-enyne compared to *cis*-enyne (J = 11.8 Hz).



(1)

In optimization studies, 1-heptyne was used as the model substrate. A survey of solvents for this system showed nearly complete dimerization and similar product distribution in a variety of solvents. Acetonitrile did not appear to be a compatible solvent, presumably in view of its coordinating nature (Table 1). The reaction rates

(1) (a) Straub, T.; Haskel, A.; Eisen, M. S. *J. Am. Chem. Soc.* **1995**, *117*, 6364−6365. (b) Barluenga, J.; González, J. M.; Llorente, I.; Campos, P. J. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 893−894. (c) Horton, A. D. *J. Chem. Soc., Chem. Commun.* **1992**, 185−187. (d) Jun, C.-H.; Lu, Z.; Crabtree, R. H. *Tetrahedron Lett.* **1992**, *33*, 7119−7120. (e) Oshita, J.; Naka, A.; Ishikawa, M. *Organometallics* **1992**, *11*, 602−606. (f) Bianchini C.; Peruzzini, M.; Zanobini, F.; Frediani, P.; Albinati, A. *J. Am. Chem. Soc.* **1991**, *113*, 5453−5454. (g) Ohshita, J.; Furimori, K.; Matsuguchi, A.; Ishikawa, M. *J. Org. Chem.* **1990**, *55*, 3277−3280.

(2) (a) Siemesen, P.; Livingston, R. C.; Diederich, F. *Angew. Chem., Int. Ed. Engl.* **2000**, *39*, 2632−2657 and references therein. (b) Trost, B. M. In *Homogeneous Transition Metal Catalyzed Reaction*; Moser, W. R., Slocum, D. W., Eds.; American Chemical Society: Washington, DC, 1992. (c) Grotjahn, D. B. In *Comprehensive Organometallic Chemistry II*; Abel, E. W., Stone, F. G. A., Wilkinson, G., Eds.; Pergamon Press: New York, 1995; Vol. 12. (d) Winter, M. J. In *The Chemistry of the Metal−Carbon Bond*; Hartley, F. R., Patai, S., Eds.; Wiley & Sons: Chichester, U.K., 1985; Vol.3.

(3) (a) Lücking, U.; Pfaltz, A. *Synlett.* **2000**, 1261−1264. (b) Trost, B. M.; Sorum, M. T.; Chan, C.; Harms, A. E.; Rüther, G. *J. Am. Chem. Soc.* **1997**, *119*, 698−708 and references therein. (c) Trost, B. M.; Chan, C.; Rüther, G. *J. Am. Chem. Soc.* **1987**, *109*, 3486−3487.

(4) (a) Bourissou, D.; Guerret, O.; Gabbaï, F. P.; Bertrand, G. *Chem. Rev.* **2000**, *100*, 39−91 and references therein. (b) Chatterjee, A. K.; Grubbs, R. H. *Org. Lett.* **2000**, *2*, 1751−1753. (c) Jafarpour, L.; Schanz, H. J.; Stevens, E. D.; Nolan, S. P. *Organometallics* **1999**, *18*, 5416−5419. (d) Dullius, J. E. L.; Suarez, P. A. Z.; Einloft, S.; de Souza, R. F.; Dupont, J.; Fischer, J.; De Cian, A. *Organometallics* **1998**, *17*, 815−819. (e) Aduengo, A. J., III; Krafczyk, R. *Chem. Z.* **1998**, *32*, 6−14. (f) Herrmann, W. A.; Köcher, C. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2162−2187. (g) Regitz, M. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 725−728.

(5) (a) Böhm, V. P. W.; Gstöttmayr, C. W. K.; Weskamp, T.; Herrmann, W. A. *J. Organomet. Chem.* **2000**, *595*, 186−190. (b) Zhang, C.; Huang, J.; Trudell, M. L.; Nolan, S. P. *J. Org. Chem.* **1999**, *64*, 3804−3805.

(6) Huang, J.; Nolan, S. P. *J. Am. Chem. Soc.* **1999**, *121*, 9889−9890.

(7) (a) Yang, C.; Lee, H. M.; Nolan, S. P. *Org. Lett.* **2001**, *3*, 1511−1514. (b) Yang, C.; Nolan, S. P. *Synlett.* **2001**, 1539−1542. (c) McGuinness, D. S.; Cavell, K. J. *Organometallics* **1999**, *18*, 1596−1605. (d) Herrmann, W. A.; Fischer, J.; Elison, M.; Köcher, C.; Artus, G. R. J. *Chem. Eur. J.* **1996**, *2*, 772−780. (e) Herrmann, W. A.; Elison, M.; Fischer, J.; Köcher, C.; Artus, G. R. J. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2371−2373.

(8) (a) Huang, J.; Grasa, G.; Nolan, S. P. *Org. Lett.* **1999**, *1*, 1307−1309. (b) Stauffer, S. R.; Lee, S.; Stambuli, J. P.; Hauck, S. I.; Hartwig, J. F. *Org. Lett.* **2000**, *2*, 1423−1426. (c) Grasa, G. A.; Viciu, M. S.; Huang, J.; Nolan, S. P. *J. Org. Chem.* **2001**, *66*, 7729−7737.

(9) (a) Huang, J.; Stevens, E. D.; Nolan, S. P.; Peterson, J. L. *J. Am. Chem. Soc.* **1999**, *121*, 2674−2678. (b) Huang, J.; Schanz, H. J.; Stevens, E. D.; Nolan, S. P. *Organometallics* **1999**, *18*, 5375−5380. (c) Scholl, M.; Trnka, T. M.; Morgan, J. P.; Grubbs, R. H. *Tetrahedron Lett.* **1999**, *40*, 2247−2250. (d) Weskamp, T.; Schattenmann, W. C.; Spiegler, M.; Herrmann, W. A. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 2490−2493.

(10) (a) Lee, H. M.; Smith. D. C., Jr.; He, Z.; Stevens, E. D.; Yi, C.; Nolan, S. P. *Organometallics* **2001**, *20*, 794−797. (b) Lee, H. M.; Jiang, T.; Stevens, E. D.; Nolan, S. P. *Organometallics* **2001**, *20*, 1255−1258.

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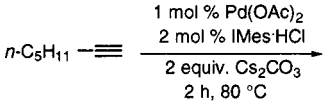
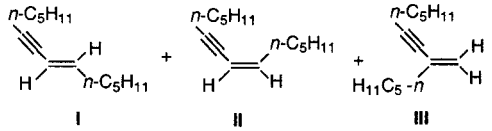
Table 1. Effect of the Solvent on $Pd(OAc)_2$/IMes·HCl-Catalyzed Dimerization of 1-Heptyne[a]





entry	solvent	product ratio[b] I:II:III	yield (%)[c]
1	THF	87:2:11	95
2	dioxane	90:2:8	95
3	CH_3CN	91:0:9	45
4	DMF	90:3:7	94
5	DMAc	90:3:7	97

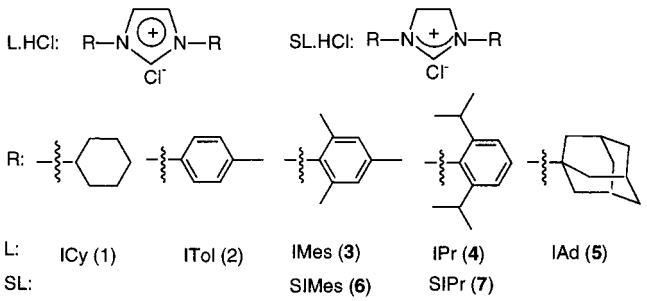
[a] Reaction conditions: 1.0 mmol of 1-heptyne, 2 mL of solvent. [b] Determined by GC. [c] GC yields based on 1-heptyne (an average of two runs).

Table 2. Effect of the Base on $Pd(OAc)_2$/IMes·HCl-Catalyzed Dimerization of 1-Heptyne[a]

entry	base	product ratio[b] I:II:III	yield (%)[c]
1	none	20:8:72	17[d]
2	NaOMe		0
3	KO^{t}Bu		0
4	NaOAc	11:2:87	31
5	K_2CO_3	11:1:89	92
6	Cs_2CO_3	90:3:7	97

[a] Reaction conditions: 1.0 mmol of 1-heptyne, 2 mL of DMAc. [b] Determined by GC. [c] GC yields based on 1-heptyne (an average of two runs). [d] Reaction time 6 h.

Scheme 1. Structures of Imidazolium Salts

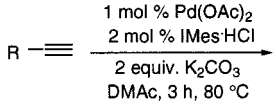


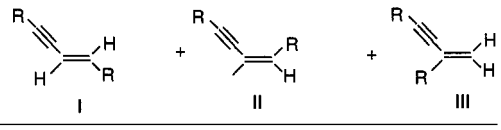
also proved to be significantly influenced by the identity of the base used in the reaction (Table 2). High activity and regio- and stereoselectivity could be achieved with Cs_2CO_3 as the base. In this case, *trans*-1,4-disubstituted enyne was the predominant product. Surprisingly, employing K_2CO_3 as base resulted in a high yield and dramatically influenced the product distribution with 1,3-disubstituted enyne being the dominant product. Strong bases such as NaOMe and KO^{t}Bu did not show any activity in this system.

In an effort to select the most effective imidazolium salts, a series of 1,3-disubstituted imidazolium chlorides (Scheme 1) with different electronic and steric properties were used in the model reaction (Table 3). Use of IMes (**3**), SIMes (**6**), and IPr (**4**) led to highly efficient, regio- and stereoselective dimerization with *trans*-1,4-disubstituted enyne as the major product. Other imidazolium salts showed lower reactivity and regioselectivity.

(11) Herrmann, W. A.; Böhm, V. P. W.; Gstöttmayr, C. W. K.; Grosche, M.; Reisinger, C.-P.; Weskamp, T. *J. Organomet. Chem.* **2001**, *617−618*, 616−628.

Table 3. Dimerization of 1-Heptyne Using $Pd(OAc)_2$ with Different Imidazolium Chlorides[a]

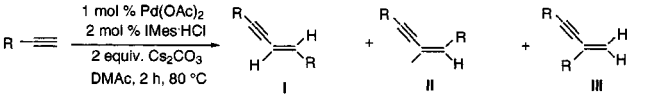




entry	L·HCl	product ratio[b] I:II:III	yield (%)[c]
1	none	39:15:46	27[d]
2	ICy (**1**)	40:0:60	34
3	ITol (**2**)	47:6:47	34
4	IMes (**3**)	90:3:7	97
5	IPr (**4**)	88:1:11	76
6	IAd (**5**)	47:3:50	45
7	SIMes (**6**)	92:1:7	88
8	SIPr (**7**)	54:10:36	14

[a] Reaction conditions: 1.0 mmol of 1-heptyne, 2 mL of DMAc. [b] Determined by GC. [c] GC yields based on 1-heptyne (an average of two runs). [d] Reaction time 6 h.

Table 4. Dimerization of Terminal Alkynes to Enynes Catalyzed by the $Pd(OAc)_2$/IMes·HCl/Cs_2CO_3 System[a]

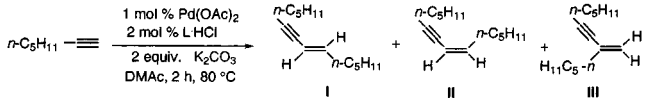


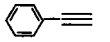
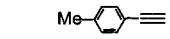
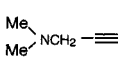
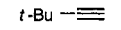
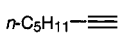
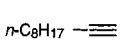
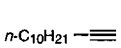
entry	alkyne	product ratio[b] I:II:III	yield (%)[c]
1		97:3:0	100(98)[d,e]
2		94:6:0	100(97)[e]
3		92:1:7	99(90)
4	*n*-Bu—	91:3:6	97(85)
5	*t*-Bu—	99:1:0	99(90)
6	n-C_5H_{11}—	90:3:7	97(84)
7	n-C_5H_{11}—	91:0:9	57[f]
8		100:0:0	98(87)
9	n-C_8H_{17}—	89:3:8	98(82)
10	n-$C_{10}H_{21}$—	91:3:6	98(90)

[a] Reaction conditions: 1.0 mmol of alkyne, 2 mL of DMAc. [b] Determined by GC. [c] GC yields based on alkyne are an average of two runs (numbers in parentheses are isolated yields). [d] 0.5 mol % $Pd(OAc)_2$, 1 mol % IMes·HCl. [e] Reaction time 0.5 h. [f] 1 mol % $Pd(dba)_2$ as Pd source.

Under optimized conditions (1 mol % $Pd(OAc)_2$, 2 mol % IMes·HCl, 2 equiv of Cs_2CO_3, DMAc, 80 °C), excellent yields of regio- and stereocontrolled dimeric products could be obtained from a wide array of terminal alkynes in a short time (Table 4). For aryl terminal alkynes, complete conversion to 1,4-disubstituted enynes could be achieved in 0.5 h (entries 1, 2). For aliphatic terminal alkynes, reactions reached near completion in 2 h with the 1,4-disubstituted enynes being the predominant product (entries 3−6, 8−10). The length of the aliphatic chain did not affect the reactivity and selectivity. Sterically demanding substrates favored the formation of 1,4-disubstituted products via head-to-head dimerization (entries 1, 2, 5, 8). The dimerization in a head-to-head mode is reasonable in view of steric requirements associ-

Table 5. Dimerization of Terminal Alkynes to Enynes Catalyzed by the $Pd(OAc)_2$/IMes·HCl/K_2CO_3 System[a]



entry	alkyne	product ratio[b] I:II:III	yield (%)[c]
1		69:5:26	100[d]
2		61:5:34	100[d]
3		24:0:76	92
4		9:0:91	89
5		44:4:52	48
6		11:1:88	92
7		11:0:89	85
8		17:0:83	85

[a] Reaction conditions: 1.0 mmol of alkyne, 2 mL of DMAc. [b] Determined by GC. [c] GC yields based on alkyne (an average of two runs). [d] Reaction time 1 h.

ated with congested terminal alkynes. It is noteworthy that the catalytic system shows excellent stereoselectivity with the *trans*-enynes being the dominant product over *cis*-enynes (only 1−6%). Substitution of $Pd(OAc)_2$ with $Pd(dba)_2$ led to a significant decrease in reactivity but still high regio- and stereoselectivity (entry 7).

To investigate the scope of the opposite regio-selectivity when using K_2CO_3 as base, we tested the generality of this observation on a series of terminal alkynes (Table 5). In these experiments, good to excellent yields were obtained. For less hindered substrates, the 1,3-disubstituted enynes via a head-to-tail dimerization are the prevailing products (entries 3, 4, 6, 7, 8). For more congested substrates, the 1,4-disubstituted enynes formed by a head-to-head dimerization are the major products (entries 1, 2). The highly hindered substrate *tert*-butylacetylene suffered from low reactivity and low regioselectivity (entry 5). However the ratio of 1,3-disubstituted enynes obviously increased compared to the case when Cs_2CO_3 was used as base.

Most recently, Trost has reported a palladium-catalyzed highly regio- and stereoselective cross-dimerization of terminal alkynes and internal alkynes.[3b,c] We also attempted to apply the optimized protocol effective to self-dimerization to cross-dimerization. Preliminary results showed that the self-dimerization products were still major products.

In summary, a Pd/imidazolium salt system has been successfully applied to the dimerization of terminal alkynes. $Pd(OAc)_2$/IMes·HCl has been shown to be a highly efficient and regio- and stereoselective catalytic system in the dimerization of a variety of aryl and aliphatic terminal alkynes. The role of the base in controlling product distribution represents an interesting observation that we are presently exploring. Using Cs_2CO_3 as base, *trans*-1,4-disubstituted enynes, from the head-to-head dimerization, are the predominant products. Replacement of Cs_2CO_3 with K_2CO_3 results in a significant increase of 1,3-disubstituted enynes from the head-to-tail dimerization. For less hindered alkynes, the 1,3-disubstituted enynes become the dominant product. In both cases (Cs_2CO_3 or K_2CO_3 as base), sterically demanding substrates prefer to form 1,4-disubstituted products. The catalytic system also shows excellent stereoselectivity with *trans*-enynes being the almost exclusive product over *cis*-enynes. The Pd complexes usually dimerize terminal alkynes to branched enynes,[3] while, in this work, the Pd/imidazolium system provide linear enynes as predominant products. Elaboration of this methodology and investigation of other catalytic applications using nucleophilic carbenes, as ligands, are ongoing.

Experimental Section

General Considerations. All terminal alkynes (Aldrich), $Pd(dba)_2$ (Strem), $Pd(OAc)_2$ (Strem), and *N*,*N*-dimethylacetamide (Aldrich, anhydrous) were used as received. Flash chromatography was performed on silica gel 60 (230−400 mesh) (Natland International Corp.). Imidazolium salts L·HCl (L = ICy (**1**), ITol (**2**), IMes (**3**), IPr (**4**), IAd (**5**), SIMes (**6**), and SIPr (**7**)) were synthesized according to the literature procedure.[12,13] ^1H NMR spectra were recorded using a Varian 400 MHz spectrometer. GC analyses were performed on an Agilent 6890 GC spectrometer with an FID detector and an HP-5 column. GC-MS analyses were performed on a MicroMass AutoSpec instrument.

Catalytic Dimerization Reactions. In a typical catalytic run, a scintillation vial equipped with a cap and a septum was charged with $Pd(OAc)_2$ (0.01 mmol), IMes·HCl (0.02 mmol), Cs_2CO_3 (2.0 mmol), and 2.0 mL of *N*,*N*-dimethylacetamide in a glovebox. The mixture was stirred for 10 min. Then 1.0 mmol of alkynes was added to the vial. The reaction mixture was allowed to stir in an oil bath at 80 °C. The product yields were monitored and determined by GC analyses. The product distribution was determined by GC and confirmed by ^1H NMR. The workup procedure was as follows: 30 mL of water was added to the reaction mixture, followed by extraction with diethyl ether. The combined organic layer was dried over $MgSO_4$ and filtered, and ether was evaporated to give a crude product. The pure product was obtained by flash chromatography (eluent: hexane). The product identity was confirmed by GC-MS and ^1H NMR as well as by comparison with literature data.

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Supporting Information Available: Text providing experimental procedures, details of reaction conditions, and ^1H NMR spectroscopic data for the dimerization products. This material is available free of charge via the Internet at http://pubs.acs.org.

JO010837S

(12) Arduengo, A. J., III. U.S. Patent 5 077 414, 1991.
(13) Arduengo, A. J., III; Dias, H. V. R.; Harlow, R. L.; Kline, M. *J. Am. Chem. Soc.* **1992**, *114*, 5530−5534.