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Pd(0)-Catalyzed Iodoalkynation of Norbornene Scaffolds: The Remarkable Solvent Effect on Reaction Pathway

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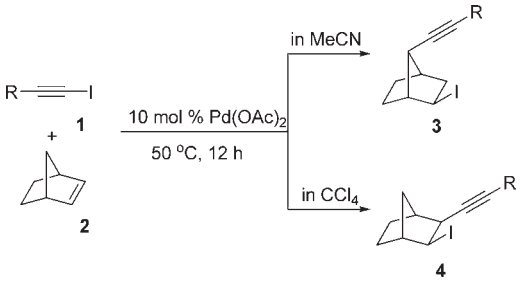
ABSTRACT



A palladium-catalyzed iodoalkynation of norbornene has been realized with the use of alkynyl iodides 1, which is found to be strongly solvent-dependent. MeCN favors 1,7-iodoalkylation product 3 while CCl_4 leads to 1,2-iodoalkylation product 4.

Alkyl halides are versatile intermediates in organic synthesis.[1] In the field of transition-metal catalysis, they are basic starting materials for various organic transformations. However, their halide atoms are always discarded, rendering these transformations nonatom economic. Very recently, we and Lautens et al. independently reported the palladium-catalyzed intramolecular carboiodination of alkenes, which provides a new carbon−carbon bond while retaining the reactive halide of the starting material (Scheme 1a).[2] These results represent a conceptually novel process in palladium catalysis, especially the reductive elimination of alkyl iodide in the involved catalytic cycle.

As part of our ongoing efforts on the metal-catalyzed formation of organic halides,[3] we were devoted to developing the intermolecular carboiodination of alkenes. For the intermolecular variant, we immediately recognized that it would encounter the following dilemma: the polysubstituted alkenes are mandatory to prevent a Heck-type side reaction while their large steric hindrance might hamper the insertion of the related C−Pd bond (Scheme 1b, upper). Norbornene may offer an attractive solution as the corresponding β-H elimination can be completely prohibited due to its rigid structure.[4] On the other hand, we chose iodoalkynes as organic halides with the consideration that they are feasible to undergo oxidative addition to a Pd(0) catalyst.[5] Herein, we report the Pd(0)-catalyzed iodoalkynation of norbornene with iodoalkynes, which features highly selective formation of two different iodoalkylation products depending on the reaction solvent (Scheme 1b, bottom).

First, we used the same conditions[2b] as those for intramolecular carboiodination to investigate the reaction

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(4) For recent reviews, see: (a) Catellani, M.; Motti, E.; Ca', N. D. *Acc. Chem. Res.* **2008**, *41*, 1512. (b) Catellani, M.; Motti, E.; Faccini, F.; Ferraccioli, R. *Pure Appl. Chem.* **2005**, *77*, 1243. (c) Catellani, M. Novel Methods of Aromatic Functionalization Using Palladium and Norbornene as a Unique Catalytic System. In *Palladium in Organic Synthesis*; Tsuji, J., Ed.; Springer: Berlin, 2005; pp 21−53. (d) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174.

(5) For recent examples, see: (a) Damle, S. V.; Seomoon, D.; Lee, P. H. *J. Org. Chem.* **2003**, *68*, 7085. (b) Shi, Y.; Li, X.; Liu, J.; Jiang, W.; Sun, L. *Tetrahedron Lett.* **2010**, *51*, 3626. (c) Kim, S. H.; Chang, S. *Org. Lett.* **2010**, *12*, 1868.

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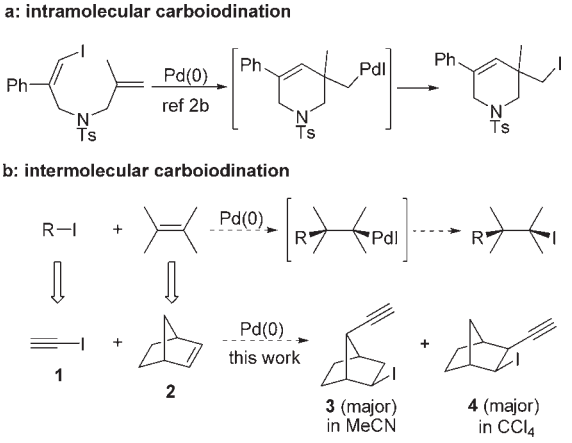
Scheme 1. Design Plan for Intermolecular Iodoalkynation

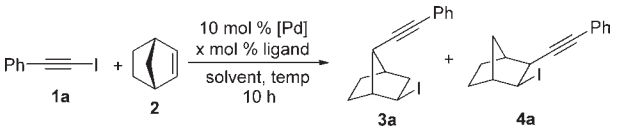


of phenylethynyl iodide **1a** and norbornene **2** (1.2 equiv) (Table 1, entry 1). To our delight, both 1,7-iodoalkylation product **3a**[6] and 1,2-iodoalkylation product **4a**[7] were isolated in a ratio of 60:40, albeit in 10% yield (Table 1, entry 1). The reaction temperature was found to be essential for product yield; the reaction conducted at 50 °C afforded a combined 28% yield of **3a** and **4a** in a ratio of 72:28, while no reaction occurred at room temperature (Table 1, entries 2−3). The ligand effect was further investigated. The reaction was improved in the presence of 20 or 10 mol % DPPF, leading to a combined yield of 36% (Table 1, entry 4) and 53% (Table 1, entry 5), respectively, implying that the additional ligand would impose a negative effect on the overall yield. Indeed, when the reaction was conducted in the absence of ligand, a 69% isolated yield was obtained and the product distribution was also improved to 89:11 (Table 1, entry 6). Afterward, we decided to perform further optimizations with 10 mol % $Pd(OAc)_2$ as catalyst. It was found that the solvent CCl_4 was an optimal one, affording **4a** in 78% yield with a selectivity as high as 96% (Table 1, entry 8). Surprisingly, when a polar solvent was used instead, such as THF, MeCN, DMSO, and DMF, an opposite selectivity was observed, resulting in 1,7-iodoalkynation product **3a** as the majority (Table 1, entries 9−12). MeCN was found to be suitable for practicable synthesis in terms of yield and stereoselectivity. It should be noted that the selectivity of **3a** could be further improved to be 99% in the presence of 20 mol % PPh_3 or with the use of $Pd(PPh_3)_4$ as catalyst (Table 1, entries 13−14). On the basis of these results, we can conclude that the iodoalkynation is strongly affected by the reaction media, with a nonpolar solvent favoring 1,2-selectivity and a polar solvent favoring 1,7-selectivity.

(6) The structure of **3a** was determined by comparision of the authentic samples according to the following paper: Li, Y; Liu, X; Jiang, H; Liu, B; Chen, Z; Zhou, P. *Angew. Chem., Int. Ed.* **2011**, *50*, 6341.

(7) The structure of **4a** was determined according to the authentic sample: Allen, A.; Villeneuve, K.; Cockburn, N.; Fatila, E.; Riddell, N.; Tam, W. *Eur. J. Org. Chem.* **2008**, 4178. The molecular structure of **4a** was further established by X-ray crystallography.

Table 1. Optimization of Reaction Conditions[a]



entry	[Pd]	ligand (x)	Solvent	temp (°C)	yield (%)[b] (**3a**:**4a**)
1	$Pd(OAc)_2$	DPPF (30)	PhMe	120	10 (60:40)
2	$Pd(OAc)_2$	DPPF (30)	PhMe	50	28 (72:28)
3	$Pd(OAc)_2$	DPPF (30)	PhMe	rt	NR
4	$Pd(OAc)_2$	DPPF (20)	PhMe	50	36 (66:34)
5	$Pd(OAc)_2$	DPPF (10)	PhMe	50	53 (69:31)
6	$Pd(OAc)_2$	--	PhMe	50	69 (89:11)
7	$Pd(OAc)_2$	--	PhH	50	61 (89:11)
8	**$Pd(OAc)_2$**	**--**	**CCl_4**	**50**	**78 (96:4)**
9	$Pd(OAc)_2$	--	THF	50	68 (26:74)
10	*$Pd(OAc)_2$*	*--*	*MeCN*	*50*	*82 (3:97)*
11	$Pd(OAc)_2$	--	DMSO	50	31 (1:99)
12	$Pd(OAc)_2$	--	DMF	50	48 (1:99)
13	$Pd(OAc)_2$	PPh_3 (20)	MeCN	50	69 (1:99)
14	$Pd(PPh_3)_4$	--	MeCN	50	25 (1:99)

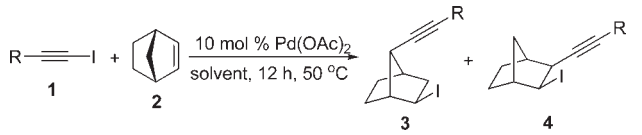
[a] Reaction conditions: **1a** (68.4 mg, 0.3 mmol), **2** (33.8 mg, 0.36 mmol), $Pd(OAc)_2$ (6.8 mg, 0.03 mmol). [b] Isolated yield. The ratio was determined according to ^1H NMR analysis.

With the optimized conditions in hand, we then investigated the reaction scope with various iodoalkynes, and the results are summarized in Table 2. In general, the reactions of (iodoethynyl)aromatics smoothly proceeded in either CCl_4 or MeCN, affording 1,2- and 1,7-iodoalkynation products, respectively, in good to excellent yields (Table 2, entries 1−9). In contrast, only a moderate yield was obtained in the case of (iodoethynyl)alkyl substrates, regardless of whether CCl_4 or MeCN was used (Table 2, entries 10 and 11). With respective to selectivity, good to excellent results were obtained for (iodoethynyl)aromatic substrates in either CCl_4 or MeCN solvent. Again, for (iodoethynyl)alkyl substrates, a much lower 1,7-selectivity was obtained in the solvent MeCN. The stereochemistry of other products was tentatively assigned by comparing their CHI peak from ^1H NMR to that of **3a** and **4a**, respectively.

To extend the scope of this transformation, (bromoethynyl)benzene **5** was employed as the substrate. To our delight, it was also active enough for Pd-catalyzed 1,7-bromoalkynation in MeCN to give compound **6** in 80% yield with 98% selectivity (Scheme 2a). It should be noted that bromoalkyne **5** was found to be inert in solvent CCl_4. When the reaction of **1a** and norbornene derivative **7** was conducted in solvent MeCN, to our surprise, 1,2-iodoalkynation product **8** was instead obtained in 72% yield with 97% selectivity (Scheme 2b).[8] This result implied that 1,2- and 1,7-iodoalkynation probably involved a common intermediate and the latter could be diminished due to

(8) Compound **7** is not dissolved in CCl_4 even at 50 °C, which is a possible reason for the failure of the reaction of **7** in CCl_4.

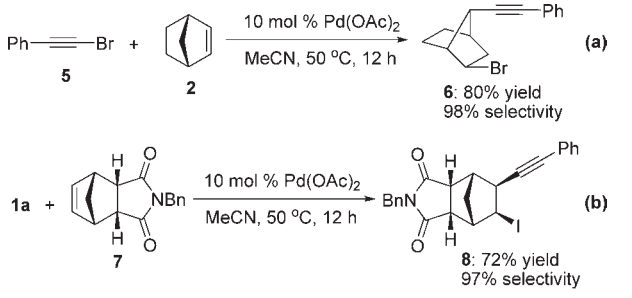
Table 2. Reaction Scope[a]



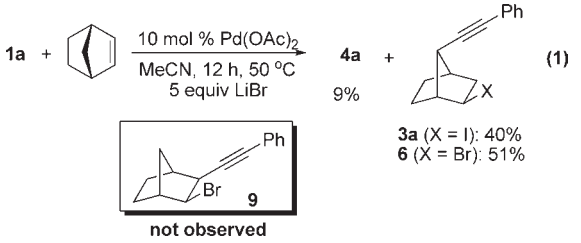
		In CCl_4		In MeCN	
entry	R	**4** (yield)[b]	**4:3**	**3** (yield)[b]	**3:4**
1	Ph	**4a** (75%)	98:2	**3a** (82%)	97:3
2	4-Me-C_6H_4	**4b** (73%)	99:1	**3b** (75%)	99:1
3	3-Me-C_6H_4	**4c** (62%)	88:12	**3c** (58%)	96:4
4	4-MeO-C_6H_4	**4d** (58%)	89:11	**3d** (61%)	92:8
5	2-Br-C_6H_4	**4e** (97%)	94:6	**3e** (95%)	99:1
6	4-Br-C_6H_4	**4f** (65%)	91:9	**3f** (64%)	96:4
7	4-Cl-C_6H_4	**4g** (70%)	97:3	**3g** (86%)	98:2
8	4-F-C_6H_4	**4h** (52%)	97:3	**3h** (58%)	97:3
9	2-thietyl	**4i** (66%)	98:2	**3i** (73%)	96:4
10	*n*-Bu	**4j** (31%)	94:6	**3j** (41%)	80:20
11	$BnOCH_2$-	**4k** (36%)	82:18	**3k** (56%)	81:19
12	TMS	**41** (58%)	81:19	**31** (64%)	98:2

[a] Reaction conditions: **1** (0.3 mmol), **2** (33.8 mg, 0.36 mmol), $Pd(OAc)_2$ (6.8 mg, 0.03 mmol). [b] Isolated yield. The ratio was determined according to ^1H NMR analysis (see Supporting Information).

Scheme 2. Extension of Reaction Scope

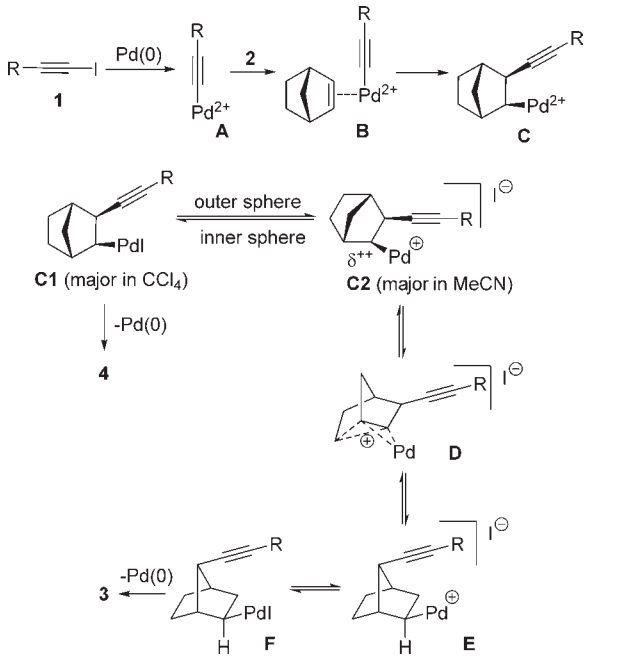


inhibited rearrangement imposed by the molecular structure, such as compound **7**.



To obtain insight into the reaction mechanism, the $Pd(OAc)_2$-catalyzed reaction of **1a** and norbornene was re-evaluated with LiBr (5 equiv) as an additive in MeCN solvent (eq 1). The ^1H NMR analysis of the reaction mixture disclosed that 1,7-bromoalkylation product **6** was yielded along with iodoalkylation products **4a** and **3a**. It should be noted that the corresponding 1,2-bromoalkynation product **9** was not detected at all. The presence of compound **6** indicated that the exchange between iodide and bromine ions would take place before the formation of 1,7-haliodoalkynation products. On the other hand, the absence of compound **9** implied that the process of 1,2-iodoalkynation might not involve a similar exchange.

Scheme 3. Proposed Mechanism



Recently, Jiang and co-workers reported[9] a $Pd(OAc)_2$-catalyzed iodoalkynation of alkyne, which is proposed to be initiated by oxidative addition of $Pd(OAc)_2$ to iodoalkyne, leading to a key Pd(IV) intermediate.[10] The present iodoalkynation, however, is believed to be initiated by a Pd(0) species based on the fact that the classic Pd(0)-systems, such as the combination of $Pd(OAc)_2$ and phosphine ligand as well as $Pd(PPh_3)_4$, are proven to work well. With the combination of the above-mentioned considerations and observations, a proposed reaction mechanism is present in Scheme 3. First, oxidative addition of the Pd(0) species to iodoalkyne forms Pd(II)-acetylide intermediate **A**. Then, the olefin of norbornene coordinates to the Pd(II) center with its *exo*-face, which is followed by *cis*-insertion to gerenate **C** with well-defined stereochemistry. The strong effect of solvent on the reaction pathways inspired us to postulate that intermediate **C** might be represented by an equilibrium between inner form **C1** and outer form **C2** (Scheme 3). Inner form **C1** is believed to have a neutral palladium center while outer form **C2** is a cationic palladium species. Thus, **C1** is overwhelming in a nonpolar

(9) Li, Y.; Liu, X.; Jiang, H.; Feng, Z. *Angew. Chem., Int. Ed.* **2010**, *49*, 3338.

(10) Canty, A. J.; Rodemann, T.; Skelton, B. W.; White, A. H. *Organometallics* **2006**, *25*, 3996.

solvent, such as CCl_4, which undergoes reductive elimination (RE) to form 1,2-alkynation product **4** with retention of the stereochemistry (Scheme 3).[11] In contrast, polar solvent, such as MeCN, could stabilize the ionic species thus rendering **C2** as the majority. As a result, the corresponding norbornene fragment becomes more positively charged to initiate a nonclassical "norbornonium" rearrangement[12] via "bridging" palladium complex **D**, leading to intermediate **E**. Subsequently, the iodide ligand recoordinates to the cation palladium center to form neutral palladium intermediate **F** which undergoes a direct alkyl iodide RE to yield 1,7-iodoalkynation product **3** and regenerates the Pd(0) catalyst. It should be mentioned that no rearrangement was observed in the case of $Pd[P(t\text{-}Bu)_3]_2$-catalyzed iodoaromatization of norbornene with aryl iodides.[2a] We believed that the bulky ligand $P(t\text{-}Bu)_3$ might enforce the alkyl iodide RE to be more rapid, diminishing the possibility of rearrangement. For the case of (iodoethynyl)alkyl substrates, the coordination of an alkyne moiety to the Pd(II) center may be present in intermediate **C2**. Thus, the rearrangement might be partially inhibited, resulting in lower selectivity (Table 2, entries 10 and 11). While the mechanism lacks solid evidence, it does account for the observed chemical outcome, especially the "abnormal" 1,7-iodoalkynation. Nevertheless, the exact catalytic mechanism still needs more investigation.

It should be mentioned that during our preparation of this munascript, Jiang and co-workers have reported a similar 1,7-bromoalkynation with the use of bromoalkyne in MeCN at room temperature, which inspired us to propose a similar mechanism depicted in Scheme 3.[6] However, their selectivity is lower than ours, indicating that a higher reaction temperature could promote "norbornonium" rearrangement.

In summary, we have reported the iodoalkynation of norbornene with the use of iodoalkyne in the presence of a simple palladium catalyst. This transformation is found to be solvent-dependent. Nonpolar solvents favor 1,2-iodoalkynation while polar solvents lead to unexpected 1,7-iodoalkynation. The fact that the norbornene structure undergoes facile "norbornonium" rearrangement might afford a reasonable explanation for 1,7-iodoalkynation. Further investigations of the reaction mechanism and synthetic transformation are currently underway in our laboratory.

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Supporting Information Available. Experimental procedures and full spectroscopic data for all new compounds, as well as X-ray crystal data of compound **4a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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