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Catalytic and highly regiospecific carbon–carbon bond formation at α-position of Michael acceptor by palladium complex

Jae-Goo Shim,*[a] Jong Chul Park,[b] Chan Sik Cho,[b] Sang Chul Shim*[b] and Yoshinori Yamamoto[c]

[a] *Environment-Chemistry Group, Korea Electric Power Research Institute (KEPRI), Daejeon 305-380, Korea*

[b] *Department of Industrial Chemistry, College of Engineering, Kyungpook National University, Taegu 702-701, Korea. E-mail: scshim@kyungpook.ac.kr*

[c] *Department of Chemistry, Graduate School of Science, Tohoku University, Sendai 980-8578, Japan*

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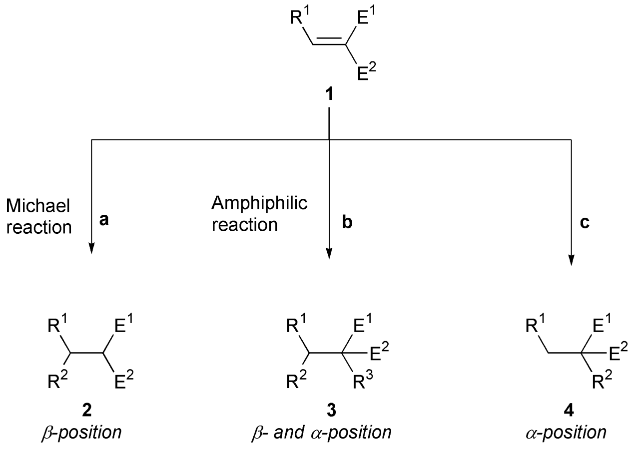
Activated olefins react with allyl acetates and Bu_3SnH in the presence of a catalytic amount of a palladium catalyst to afford the corresponding products which construct a new C–C bond selectively at the α-position of Michael acceptors.

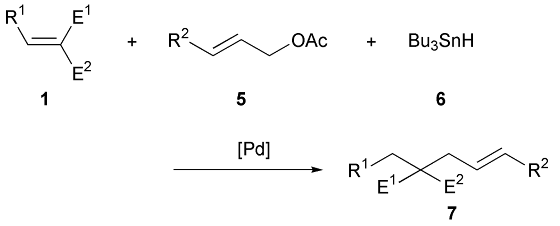
The carbon–carbon bond-forming reaction is one of the most powerful tools for developing creative synthetic methodologies and preparing new compounds. Such a reaction is in general most useful and efficient when conducted catalytically. The use of homogeneous transition metals for a catalytic carbon–carbon bond-forming reaction is quite attractive because the metal activates the ligated organic moiety intrinsically and facilitates the desired reaction. Among the manifold carbon–carbon bond-forming reactions, the Michael reaction between various nucleophiles and activated olefins has been considered as one of the most versatile methods since it gives a new bond selectively at the β-position of activated olefin **1** (route a, Scheme 1).[1]

Recently, Trost and Yamamoto have developed new methods affording two new carbon–carbon bonds successively at the β- and α-positions of Michael acceptors *via* the amphiphilic reaction of activated olefins and bis-π-allylpalladium complex (or its unsymmetric and functionalized derivative) (route b, Scheme 1).[2] These results encouraged us to study highly regiospecific carbon–carbon bond formation at the α-position of activated olefins (route c, Scheme 1).[3] Herein, we describe that palladium-catalysed three component reactions of certain activated olefins **1** with allyl acetates **5** and Bu_3SnH (**6**) afford the corresponding products **7** in good to excellent yields (Scheme 2).[4] In this instance, it is possible to construct a new carbon–carbon bond regioselectively at the *α-position* of activated olefins.

Benzylidenemalononitrile (**1a**) (1 equiv.) reacted at rt with allyl acetate (**5a**) (2.4 equiv.) and **6** (2.4 equiv.) in the presence of $Pd(dba)_2$ (5 mol%) and dppp (10 mol%) under an argon atmosphere in THF (0.25 M) to give the corresponding product **7a** in 97% isolated yield (Table 1, run 1).[5–7] Activated olefin **1b** was enabled to react with **5a** and **6** under the same reaction conditions to produce **7b** in 83% yield (run 2). Starting olefins **1c–e** having electron-rich or electron-neutral substituents reacted effectively with **5a** and **6** to afford the corresponding products **7c–e** in good to excellent yields (runs 3–5). In addition, even Michael acceptor **1f** possessing a sterically bulky alkyl substituent produced **7f** in 72% isolated yield (run 6). The effect of the electron-withdrawing groups of Michael acceptors was investigated. Under the same reaction conditions, Michael acceptors **1g–j** containing CN and CO_2Et or CN and SO_2Ph as electron-withdrawing groups in place of two CN groups were converted smoothly to the corresponding products **7g–j** (runs 7–10). In addition, reaction of **1a** with cinnamyl acetate (**5b**) and **6** afforded **7k** as a single isomer in 82% yield (run 11).†



Scheme 1 Regiospecific C–C bond formation of an activated olefin.



Scheme 2

Although more detailed study on the mechanism is needed, the proposed pathway is shown in Scheme 3. The oxidative addition of Pd(0) to **5** would lead to the π-allylpalladium acetate complex **8** (route A). Transmetalation of **8** with **6** followed by the hydropalladation of intermediate **10** to activated olefin **1** would afford intermediate **12**. The reductive elimination of Pd(0) from **12** would give a corresponding **7**. There are other possibilities which would be started from the oxidative addition of Pd(0) to **6** giving hydridopalladium complex **9** (route B-1 and B-2).

Table 1 Pd-catalysed regiospecific C–C bond formation at the α-position of activated olefins[a]

	1						
Run	R1	E1	E2		5 (R2 =)	t/h	Yield (%)[b]
1	Ph	CN	CN	(**1a**)	H (**5a**)	6	**7a** (97)
2	2-Furfuryl	CN	CN	(**1b**)	**5a**	8	**7b** (83)
3	3-Tolyl	CN	CN	(**1c**)	**5a**	7	**7c** (97)
4	4-Tolyl	CN	CN	(**1d**)	**5a**	7	**7d** (97)
5	2-Naphthyl	CN	CN	(**1e**)	**5a**	8	**7e** (92)
6	^{t}Bu	CN	CN	(**1f**)	**5a**	11	**7f** (72)
7	2-Anisyl	CN	CO_2Et	(**1g**)	**5a**	28	**7g** (73)
8	3-Anisyl	CN	CO_2Et	(**1h**)	**5a**	21	**7h** (72)
9	Ph	CN	CO_2Et	(**1i**)	**5a**	7	**7i** (77)
10	Ph	CN	SO_2Ph	(**1j**)	**5a**	12	**7j** (91)
11		**1a**			Ph (**5b**)	5	**7k** (82)[c]

[a] All reactions were carried out at rt in the presence of $Pd(dba)_2$ (5 mol%) and dppp (10 mol%) unless otherwise specified. [b] Yields are for isolated materials and are an average of two runs at least. [c] *cis*:*trans* = 0:100.

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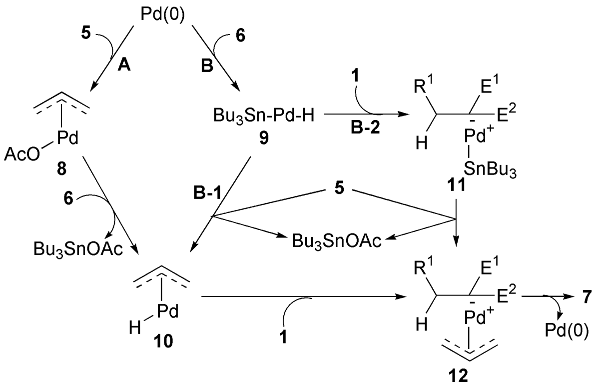
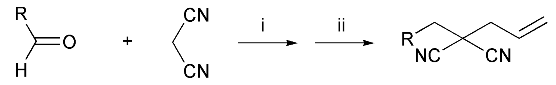


Scheme 3

Next, we attempted the *in situ* generation of the Michael acceptors followed by the palladium-catalysed regiospecific carbon–carbon bond formation (all in one operation) (Scheme 4). This one-pot reaction proceeded smoothly in the presence of H_2O which was produced naturally by the condensation of aldehyde and malononitrile. Benzaldehyde (**13a**) was treated with malononitrile (**14**) in THF in the presence of tetrabutylammonium fluoride (TBAF) (10 mol%) at rt for 1 h. After **14** was consumed completely, 5 mol% of palladium catalyst, **5a** and **6** were added successively. Upon completion of the reaction, the mixture was extracted with ether and concentrated *in vacuo*. After the treatment with a saturated KF solution, the resulting oil gives the desired product **7a** in 94% GLC yield (90% isolated yield) by column chromatography. 4-Tolualdehyde (**13b**) also affords the desired product **7d** in 94% GLC yield by the same reaction conditions. In addition, 2-naphthaldehyde (**13c**) and trimethylacetaldehyde (**13d**) smoothly underwent the condensation and subsequent palladium-catalysed carbon–carbon bond formation to produce the desired products **7e** and **7f**, respectively, in good yields.



13 **14** **7**

a: R = Ph	**a**: R = Ph (94%)
b: R = 4-Tolyl	**d**: R = 4-Tolyl (94%)
c: R = 2-Naphthyl	**e**: R = 2-Naphthyl (76%)
d: R = ^{t}Bu	**f**: R = ^{t}Bu (70%)

Scheme 4 *Reagents and conditions*: i, TBAF (10 mol%), THF, rt; ii, $Pd(dba)_2$ (5 mol%), dppp (10 mol%), **5a** and **6**.

In conclusion, we have developed the first transition metal-catalysed hydrocarbonation[8] of an activated olefin to give a new carbon–carbon bond at the α-position. The present result seems to be quite useful for the *catalytic* and *regiospecific* construction of a new carbon–carbon bond at the α-position of Michael acceptors in one operation and excludes the use of stoichiometric amounts of a base which was necessarily to activate the C–H bond at the α-position of activated olefins in classical methods.[9]

Notes and references

† *Typical experimental procedure*: to a solution of **1a** (0.077 g, 0.5 mmol), $Pd(dba)_2$ (0.014 g, 5 mol%) and dppp (0.021 g, 10 mol%) in THF (2 ml) was added **5a** (0.129 ml, 1.2 mmol) and **6** (0.323 ml, 1.2 mmol) successively at room temperature under an Ar atmosphere and the reaction mixture was stirred for 6 h at that temperature. The reaction mixture was quenched with water and then extracted with ether. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The resulting crude oil was treated with ethyl acetate and a saturated KF solution. The mixture was stirred for 5 h and then extracted with ether. The organic layer was washed with a saturated NaCl solution, dried over $MgSO_4$ and concentrated *in vacuo*. The product **7a** was isolated in 97% yield (0.097 g) by column chromatography (silica gel, ethyl acetate : hexane = 1 : 10).

1 P. Perlmutter, *Conjugate Addition Reactions in Organic Synthesis*, Pergamon, Oxford, 1992; M. E. Jung, *Comprehensive Organic Synthesis*, ed. B. M. Trost, I. Fleming and M. F. Semmelhack, Pergamon, Oxford, 1992, vol. 4, pp. 1–67; V. J. Lee, ref. 1b, pp. 69–137.

2 B. M. Trost and C.-J. Li, *Tetrahedron Lett.*, 1993, **34**, 2271; H. Nakamura, J.-G. Shim and Y. Yamamoto, *J. Am. Chem. Soc.*, 1997, **119**, 8113; J.-G. Shim, H. Nakamura and Y. Yamamoto, *J. Org. Chem.*, 1998, **63**, 8470; H. Nakamura, H. Shibata and Y. Yamamoto, *Tetrahedron Lett.*, 2000, **41**, 2911.

3 Except for this report, several methods are known for regioselective carbon–carbon bond formation at the α-position of activated olefins: E. J. Enholm and P. E. Whitely, *Tetrahedron Lett.*, 1996, **37**, 559; Y. Shvo and A. H. I. Arisha, *J. Org. Chem.*, 2001, **66**, 4921.

4 Cu-catalysed carbon–carbon bond formation at the α-position of α,β-unsaturated carbonyl compounds at −50 °C was reported: T. Tsuda, H. Satoni, T. Hayashi and T. Saegusa, *J. Org. Chem.*, 1987, **52**, 439.

5 When other ester-based activated olefins, such as $RCH{=}CHCO_2Et$ and $RCH{=}C(CO_2Et)_2$ were used, the desired products were not obtained and the starting olefins were recovered quantitatively. Accordingly, a CN group in two electron-withdrawing groups is required to accomplish the present reaction. Complete coplanarity of two esters is difficult due to the steric repulsion of electron-withdrawing groups although the small and linear cyano group leads much less disruption than that of ester overlap. This phenomenon is in accord with Boeckman's and Shim and Yamamoto's previous results: R. K. Boeckmann and S. S. Ko, *J. Am. Chem. Soc.*, 1982, **104**, 1033; J.-G. Shim and Y. Yamamoto, *J. Org. Chem.*, 1998, **63**, 3067.

6 Other palladium complexes, such as $PdCl_2(PPh_3)_2$, $Pd(PPh_3)_4$, $Pd(dba)_2$-dppe also catalysed this reaction, however, the yield of **7a** in these cases were somewhat lower.

7 Replacement of **5a** with other allyl sources resulted in the decrease of the reaction speed and yield. These phenomena may be caused by the differences of leaving group effect and transmetalation rate of allyl sources.

8 Yamamoto and his coworkers have opened these types of chemistry, hydrocarbonation of pronucleophiles with certain unactivated carbon–carbon multiple bond in the absence of base: Y. Yamamoto and U. Radhakrishnan, *Chem. Soc. Rev.*, 1999, **28**, 199 and references cited therein.

9 According to the previous report, it was impossible to construct a new C–C bond at the α-position of an activated olefin through the hydrocarbonation of certain activated olefins with pronucleophiles in the presence of a palladium complex: M. Meguro and Y. Yamamoto, *J. Org. Chem.*, 1999, **64**, 694.