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Palladium-Catalyzed Conjugate Addition of Terminal Alkynes to Enones

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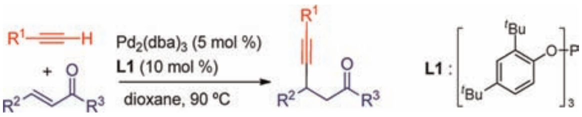
ABSTRACT



A practical protocol for the hydroalkynylation of enones using Pd catalysis is reported. The reaction proceeds efficiently with a variety of alkynes as well as with several cyclic and acyclic enones, providing synthetically relevant β-alkynyl ketones in good to excellent yields.

The transition-metal-catalyzed conjugate addition of organometallic reagents to Michael acceptors is an extremely powerful methodology for the construction of C–C bonds.[1] Particularly interesting is the metal-promoted conjugate addition of terminal alkynes to α,β-unsaturated carbonyl compounds because of the synthetic utility of the resulting β-alkynyl carbonyls. Classical ways to promote these conjugate additions involve the use of stoichiometric amounts of metal alkynylide species,[2] which unavoidably leads to the generation of significant metallic waste.

In this context, the development of alternative, atom-economical approaches, based on the catalytic generation of the reactive organometallic species from terminal alkynes, is a highly desirable goal. Recent advances in this field, including the development of some enantioselective variants, have been achieved using Rh,[3] Cu,[4] Zn,[5] Ru,[6] or Co[7] catalysts. Curiously, and despite the preponderance of Pd in organometallic catalysis, there are very few precedents on the use of Pd complexes to induce 1,4-additions of terminal alkynes to α,β-unsaturated carbonyls.[8,9] Perhaps this could be due to the tendency of terminal alkynes to react with themselves under Pd catalysis.[10] Moreover, the examples reported so far are restricted to the use of β-unsubstituted acyclic enones and acrylates.[8] Herein, we

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(1) (a) Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis*; Tetrahedron Organic Chemistry Series 9; Pergamon Press: Oxford, 1992.

(2) For instance, see: (a) Schwartz, J.; Carr, D. B.; Hansen, R. T.; Dayrit, F. M. *J. Org. Chem.* **1980**, *45*, 3053. (b) Kim, S.; Lee, J. M. *Tetrahedron Lett.* **1990**, *31*, 7627. (c) Sinclair, J. A.; Molander, G. A.; Brown, H. C. *J. Am. Chem. Soc.* **1977**, *99*, 954. (d) Wu, T. R.; Chong, J. M. *J. Am. Chem. Soc.* **2005**, *127*, 3244. (e) Larionov, O. V.; Corey, E. J. *Org. Lett.* **2010**, *12*, 300. (f) Woo, J. C. S.; Cui, S.; Walker, S. D.; Faul, M. M. *Tetrahedron* **2010**, *66*, 4730. (g) Cui, S.; Walker, S. D.; Woo, J. C. S.; Borths, C. J.; Mukherjee, H.; Chen, M. J.; Faul, M. M. *J. Am. Chem. Soc.* **2009**, *132*, 436. For a review, see: (h) Fujimori, S.; Knöpfel, T. F.; Zarotti, P.; Ichikawa, T.; Boyall, D.; Carreira, E. M. *Bull. Chem. Soc. Jpn.* **2007**, *80*, 1635.

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(4) (a) Knopfel, T. F.; Zarotti, P.; Ichikawa, T.; Carreira, E. M. *J. Am. Chem. Soc.* **2005**, *127*, 9682. (b) Knöpfel, T. F.; Carreira, E. M. *J. Am. Chem. Soc.* **2003**, *125*, 6054. (c) Yazaki, R.; Kumagai, N.; Shibasaki, M. *J. Am. Chem. Soc.* **2010**, *132*, 10275. (d) Fujimori, S.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 4964.

(5) (a) Knöpfel, T. F.; Boyall, D.; Carreira, E. M. *Org. Lett.* **2004**, *6*, 2281. (b) Kidwai, M.; Jain, A.; Bhardwaj, S. *Catal. Lett.* **2011**, *141*, 183.

(6) (a) Nishimura, T.; Washitake, Y.; Uemura, S. *Adv. Synth. Catal.* **2007**, *349*, 2563. (b) Uemura, S.; Nishimura, T.; Washitake, Y.; Nishiguchi, Y.; Maeda, Y. *Chem. Commun.* **2004**, 1312. (c) Chang, S.; Na, Y.; Choi, E.; Kim, S. *Org. Lett.* **2001**, *3*, 2089. (d) Picquet, M.; Bruneau, C.; Dixneuf, P. H. *Tetrahedron* **1999**, *55*, 3937.

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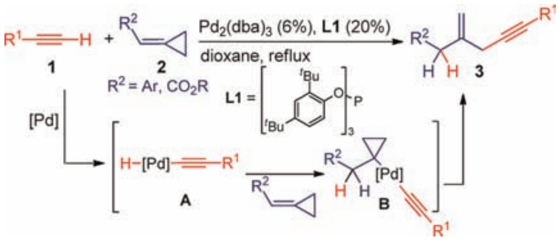
(10) The homodimerization of terminal alkynes is a well-known process. For selected examples, see: (a) Trost, B. M.; Chan, C.; Ruhter, G. *J. Am. Chem. Soc.* **1987**, *109*, 3486. (b) Rubina, M.; Gevorgyan, V. *J. Am. Chem. Soc.* **2001**, *123*, 11107. (c) Nishiura, M.; Hou, Z.; Wakatsuki, Y.; Yamaki, T.; Miyamoto, T. *J. Am. Chem. Soc.* **2003**, *125*, 1184.

10.1021/ol300988n

report a Pd-based catalytic system which promotes efficient conjugate additions of terminal alkynes to a range of α,β-unsaturated carbonyls. Importantly, the reaction also works with prochiral β-substituted acyclic and cyclic enones, therefore allowing the generation of stereocenters in the product. We also include experimental and theoretical data that suggest a mechanistic pathway involving a hydropalladation rather than the more commonly proposed alkene carbopalladation.

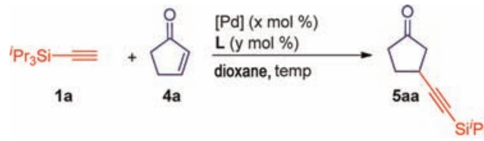
This work emerged in the context of our research in transition-metal-catalyzed alkylidenecyclopropane cycloadditions,[11] in particular after finding that treatment of terminal alkynes (**1**) and alkylidenecyclopropanes (**2**) with specific Pd catalysts generates hydroalkynylated products of type **3** (Scheme 1),[12] instead of the initially expected (3 + 2) cycloadducts.[13] The formation of **3** was explained through an initial C−H activation process that yields a hydroalkynylpalladium(II) species **A**, which subsequently hydropalladates the alkylidenecyclopropane leading to **B**. A β-carboelimination followed by reductive elimination would complete the catalytic cycle.

Scheme 1. Previous Pd-Catalyzed Hydroalkynylations of **2**[12]



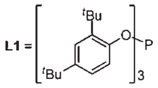
Encouraged by these results, we decided to explore the performance of this Pd catalyst ($Pd_2(dba)_3$/**L1**)[12] in the hydroalkynylation of alkenes lacking the cyclopropane moiety. Thus, in a preliminary screening, we tested the hydroalkynylation of styrene and cyclopenten-2-one (**4a**) using triisopropylsilylacetylene (**1a**) as the alkyne partner. Although styrene did not provide any coupling product,[14] cyclopenten-2-one participated in the reaction, leading to the desired β-alkynyl cyclopentanone **5aa** in a low 20% yield (Table 1, entry 1). Enyne products **6a** and **6a′**, arising from the dimerization of the alkyne **1a**, were detected as major side products.[10] Further optimization of the reaction conditions determined that the use of a Pd/**L1** ratio of 1:1, as well as a slightly lower temperature (90 °C), favors the conjugate addition over the alkyne dimerization, and thus, **5aa** could be obtained in a good 68% yield (entry 2).[15] As can be seen in entries 3 and 4, other Pd/**L1** ratios turned out to be less efficient, providing **5aa** in lower yields. On the other hand, the use of an excess of alkyne (2.5 equiv) was found to be important but not essential for the reaction, as the product could still be obtained in 47% yield using a 1:1 ratio of **1a** and **4a** (entry 5). Other phosphites such as $P(OPh)_3$ or $P(O^iPr)_3$, as well as alternative Pd sources (i.e., $Pd(PPh_3)_4$), were ineffective, leading to the recovery of **4a** and the formation of mixtures of enynes **6a**/**6a′** (entries 6−8). We also tested conditions previously used for the Pd-catalyzed alkynylation of α,β-unsaturated systems: $Pd(OAc)_2/PMe_3$[8] and $Pd(OAc)_2$/tris(2.6-dimethoxyphenyl)phosphine.[9] However, none of the reactions produced the alkyne **5aa** but instead a mixture of side products mostly consisting of alkyne dimers.[16]

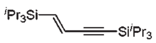
Table 1. Preliminary Screening on the Pd-catalyzed Conjugate Addition of Triisopropylsilylacetylene to Cyclopenten-2-one.[a]

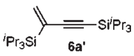


entry	equiv (**1a**)	L (mol %)	[Pd] (mol %)	temp (°C)	yield (%) of **5aa**[b]
1	2.5	**L1** (20)	$Pd_2(dba)_3$ (6)	105	20
2	**2.5**	**L1 (10)**	**$Pd_2(dba)_3$ (5)**	**90**	**68**
3	2.5	**L1** (12.5)	$Pd_2(dba)_3$ (5)	90	40
4	2.5	**L1** (5)	$Pd_2(dba)_3$ (5)	90	36
5	1	**L1** (10)	$Pd_2(dba)_3$ (5)	90	47
6	2.5	$P(OPh)_3$ (10)	$Pd_2(dba)_3$ (5)	90	0[c]
7	2.5	$P(O^iPr)_3$ (10)	$Pd_2(dba)_3$ (5)	90	0[c]
8	2.5	**L1** (0−10)	$Pd(PPh_3)_4$ (5)	90	0[c]

[a] Conditions: **4a** (1 equiv) and **1a** at a concentration of 0.1 M. [b] Isolated yields. [c] Analysis of the crude reaction mixtures indicated the presence of starting materials and enynes **6a** and **6a′** (NMR, GC−MS).




6a


6a'

With optimal conditions in hand, we next screened the addition of triisopropylsilylacetylene (**1a**) to different Michael acceptors (Table 2). Other cyclic enones such as cyclohexen-2-one (**4b**) or cyclohepten-2-one (**4c**) cleanly provided the expected adducts in 70% and 94% yield, respectively (Table 2, entries 2 and 3). Except for two Rh-promoted cases,[3d] results from entries 1−3 represent the only examples reported so far involving a direct catalytic conjugate addition of terminal alkynes to cyclic unsaturated systems. Simple acyclic enones such as methyl vinyl ketone (**4d**) also participated in the process, providing the

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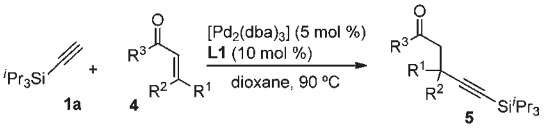
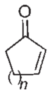
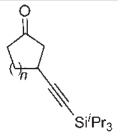
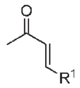
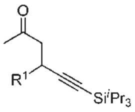
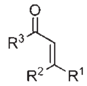
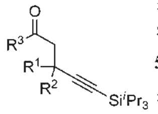
(14) For a Ni-catalyzed hydroalkynylation of styrenes, see: Shirakura, M.; Suginome, M. *Org. Lett.* **2009**, *11*, 523.

(15) The reaction could also be performed in other solvents but **5aa** was obtained in lower yields (toluene: 57% yield; 1,2-DCE: 37% yield).

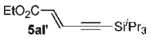
(16) The catalyst reported in ref 14, ($Ni(COD)_2/PMePh_2$), also failed to give **5aa**, leading to mostly enynes **6**.

Table 2. Pd-Catalyzed Conjugate Addition of Triisopropylsilylacetylene to α,β-Unsaturated Carbonyls[a]



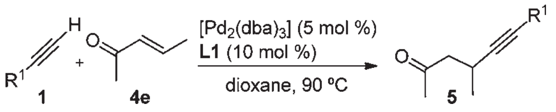
entry	α,β-unsaturated carbonyl, 4		addition product, 5		yield (%)[b]
1		n = 1, **4a**		**5aa**	68
2		n = 2, **4b**		**5ab**	70
3		n = 3, **4c**		**5ac**	94
4		R^1 = H, **4d**		**5ad**	92
5		R^1 = Me, **4e**		**5ae**	90
6		R^1 = ^{i}Pr, **4f**		**5af**	81
7		R^1 = ^{n}Bu, **4g**		**5ag**	72
8		R^1 = (CH$_2$)$_4$OTBS, **4h**		**5ah**	60
9		R^{1,2,3} = Me, **4i**		**5ai**	0[c]
10		R^{1,2} = H, R^3 = Et, **4j**		**5aj**	94
11		R^1 = Me, R^{2,3} = H, **4k**		**5ak**	38
12		R^{1,2} = H, R^3 = CO$_2$Et, **4l**		**5al**	65[d]

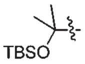
[a] Conditions: **1a** (2.5 equiv), **4** (1 equiv), Pd$_2$(dba)$_3$ (5%), and **L1** (10%) in dioxane (0.1 M) at 90 °C for 16–24 h, unless otherwise noted. [b] Isolated yields. [c] Analysis of the crude reaction mixtures indicated the presence of starting materials and enynes **6a** and **6a′** (NMR, GC–MS). [d] Yield corresponds to a 3:1 mixture of **5al** and **5al′**.



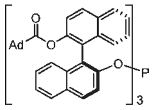
5al′

Table 3. Pd-Catalyzed 1,4-Addition of Terminal Alkynes to **4e**[a]



entry	alkyne (R^1)	(1)	product, 5	yield (%)[b]
1	Ph	(**1b**)	**5be**	0[c,d]
2	Ph	(**1b**)	**5be**	50
3	o-Me-C$_6$H$_4$	(**1c**)	**5ce**	98
4	m-Me-C$_6$H$_4$	(**1d**)	**5de**	82
5	p-Me-C$_6$H$_4$	(**1e**)	**5ee**	69
6	p-OMe-C$_6$H$_4$	(**1f**)	**5fe**	79
7	p-CF$_3$-C$_6$H$_4$	(**1g**)	**5ge**	45
8	TBSO-CH$_2$	(**1h**)	**5he**	17
9	 TBSO	(**1i**)	**5ie**	89
10[c,e]	TIPS	(**1a**)	**5ae**	96, 39% ee
11[e]	Ph	(**1b**)	**5be**	50, 38% ee

[a] Conditions: **1a** (2.5 equiv) added over 10 h to a solution of **4** (1 equiv), Pd$_2$(dba)$_3$ (5%), and **L1** (10%) in dioxane (0.1 M) at 90 °C, unless otherwise noted. Reaction times: 16–24 h. [b] Isolated yields. [c] Alkyne **1b** was added in one portion. [d] Analysis of the crude reaction mixtures indicated the presence of starting materials and enynes **6b** and **6b′**. [e] Carried out with **L2** (20%) and Pd$_2$(dba)$_3$ (5%).



L2; Ad = adamantyl

addition product **5ad** in an excellent 92% yield (entry 4). More significantly, β-substituted acyclic enones (**4e**–**4h**) reacted with **1a** to give the corresponding addition products **5ae**–**ah** in good to excellent yields (60–92% yield, entries 5–8). However, further substitution in the β-position of the enone, such as in **4i**, precludes the coupling reaction (entry 9).[17] Ethyl vinyl ketone (**4j**) is also an excellent addition partner for **1a**, providing the ketone **5aj** in 94% yield (entry 10). Interestingly, the conjugate addition of **1a** is not limited to α,β-unsaturated ketones; thus, more challenging enals and enoates like **4k** or **4l** can also participate in the process,[18] leading to synthetically appealing β-alkynyl aldehydes and esters, albeit with modest yields (entries 11 and 12).

The scope of the reaction with respect to the alkyne component was studied using (*E*)-pent-3-en-2-one (**4e**) as the alkene partner (Table 3). Although the treatment of phenylacetylene (**1b**) with this enone under standard conditions produced only undesired alkyne dimers (entry 1), slow addition of the alkyne to the reaction mixture allowed us to obtain the product **5be** in 50% yield (entry 2). Using this modified protocol, the addition of other aryl-substituted alkynes, incorporating methyl groups at the *ortho*, *meta*, and *para* positions, as well as electron-donating or -withdrawing groups, proceeded satisfactorily, and the corresponding addition products could be isolated in yields ranging from 45% to 98% (entries 3–7). Remarkably, while the silyl-protected prop-2-yn-1-ol derivative **1h** gave a poor yield of the desired product (entry 8), the bulkier analogue **1i** gave the desired adduct in excellent yield (89%, entry 9), probably because the steric bulk minimizes the homodimerization process.

At this point, we performed a preliminary test on the viability of rendering the methodology asymmetric by using chiral phosphorus ligands. Among several chiral phosphines, phosphites, or phosphoramidites tested, only phosphite **L2**[19] was able to promote the conjugate addition reaction of **1a** to **4e**. Thus, the catalyst generated from Pd$_2$(dba)$_3$ (5%) and **L2** (20%) afforded **5ae** in an excellent 96% yield, whereas ketone **5be**, resulting from the addition of **1b** to **4e**, could be isolated in 50% yield (entries 10, 11).[20] The enantiomeric excesses of the products in both cases are promising (ca. 40% ee), thus warranting further investigations in this area.

When deuterated phenylacetylene (**1b**-*d*) was treated with **4e** under the reaction conditions, the corresponding monodeuterated product **5be**-*d* was obtained (deuterium content: 40%).[21,22] This result is consistent with a reaction mechanism involving insertion of Pd(0) into the alkyne *sp*-C–H bond, followed by either hydropalladation or carbopalladation of the enone and final reductive elimination.

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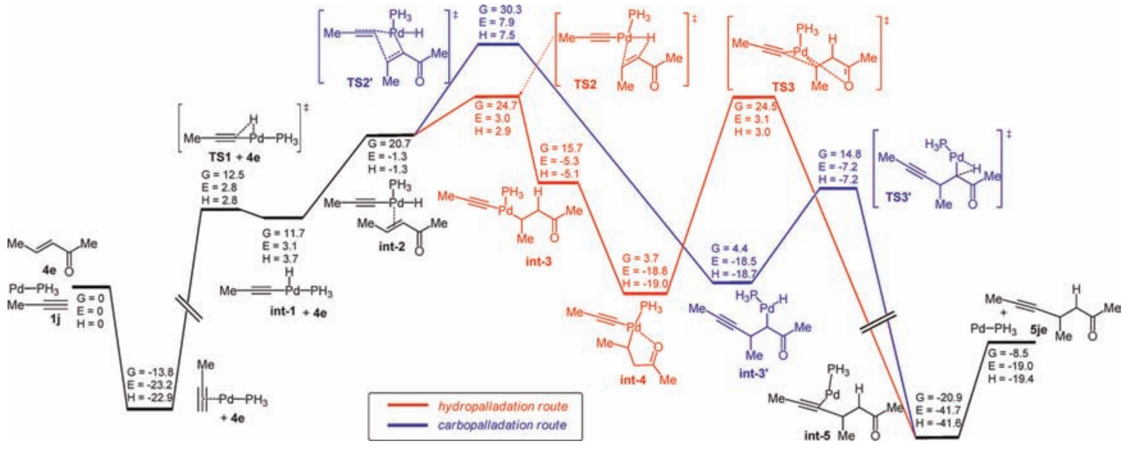
(17) Preliminary tests indicated that α-substituted enones were also unreactive under these conditions.

(18) There are very few precedents in the direct alkynylation of these types of Michael acceptors. See references 3c (enals) 4c, (thioamides), and 6a and 8a (acrylates).

(19) Reetz, M. T.; Guo, H.; Ma, J.-A.; Goddard, R.; Mynott, R. J. *J. Am. Chem. Soc.* **2009**, *131*, 4136.

(20) Yields of these two examples are equivalent to those with phosphite **L1**, see table 2, entry 5, and table 3, entry 2.

Scheme 2. DFT Profile of the Pd-Catalyzed Conjugate Addition of **1j** to **4e**



To distinguish between the hydro- or the carbometalation alternative, as well as to obtain a more reliable mechanistic picture of the process, we performed preliminary DFT calculations using enone **4e**, prop-1-yne (**1j**), and Pd(PH_3) as model reactant and catalyst (Scheme 2).[23] The computed data indicate that the reaction starts with the coordination of the Pd catalyst to the C−C triple bond prior to an oxidative addition to the *sp*-C−H bond. This process, which proceeds through transition state **TS1**, involves an energy barrier of 26.3 kcal/mol (ΔG value) and yields a hydroalkynylpalladium(II) intermediate **int-1**. Coordination of the enone followed by carbopalladation generates **int-3′** through **TS2′** (energy barrier of 9.6 kcal/mol). Alternatively, hydropalladation through **TS2** would generate intermediate **int-3**, which gains stability by coordination of the carbonyl oxygen to the Pd center to give **int-4**. The hydropalladation process presents an energy cost of 4.0 kcal/mol and, therefore, seems to be kinetically favored over the carbometalation. Finally, reductive elimination from **int-4** or **int-3′** leads to the final adduct **5je**.[24] Although the reductive elimination from the carbopalladation intermediate **int-3′** is favored compared to that from **int-4**, overall the higher energy cost associated to the carbopalladation pathway (via **TS2′**) suggests that, at least in this model system, the hydropalladation route might be preferred.[25] This mechanistic scenario is therefore different from that proposed for other metal-catalyzed alkynylations of α,β-unsaturated carbonyls,[3−8] which have been suggested to proceed via carbometalation pathways.[26] The structures of the key stationary points of the current pathway can be seen in Figure S1 and S2 of the Supporting Information.

In summary, we have developed a simple and practical Pd-catalyzed methodology for the conjugate addition of terminal alkynes to Michael acceptors that is particularly efficient in the case of enones. Worth mentioning are the additions to prochiral β-substituted enones, which had no precedents using Pd catalysts, as well as the additions to cyclic enones for which only two isolated examples using a Rh catalyst had been reported.[3d] The development of a highly asymmetric variant, based on our preliminary findings, is under investigation.

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Supporting Information Available. Experimental procedures, spectroscopy data, DFT calculations, energies, and Cartesian coordinates. This material is available free of charge via the Internet at http://pubs.acs.org The authors declare no competing financial interest.

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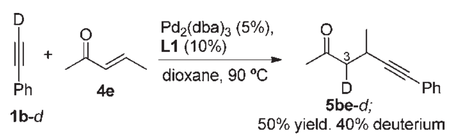
(21) (a) Reaction of **1b**-d with **4e**:



(22) ^{2}H NMR confirmed that deuterium was only incorporated at the internal α position of the ketone **5be**-*d*.

(23) (a) All the calculations were carried using the Gaussian 03 rev. D.01 suite of programs. ZPE-corrected energies (B3LYP/6-31G(d) + LANL2DZ for Pd). Energy values (kcal/mol) are referred to **1j**+**Pd-(PH_3)**+**4e**. Gibbs energy is considered for drawing. For more computational details, see the Supporting Information. (b) We also performed DFT calculations with a Pd catalyst incorporating two PH3 ligands. However, after the initial C-H activation, the hydro-or carbo-palladation must proceed with just one PH_3 attached to the Pd like in the scheme 2. See the Supporting Information for further details.

(24) Reductive elimination from **int-3**, which lacks the carbonyl-Pd coordination, is 5.2 kcal more costly than that from **int-4**.

(25) In qualitative agreement with the experimental results, the theoretical calculations also predict that a hydropalladation of enone **4i**, disubstituted at the β-position, is more difficult.

(26) Related hydrometalation pathways have only been previously suggested in a Rh- and a Ru-catalyzed process, see references 3a and 6d.

The authors declare no competing financial interest.