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Palladium-catalysed alkene chain-running isomerization[†]

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We report a method for palladium-catalysed chain-running isomerization of terminal and internal alkenes. Using an air-stable 2,9-dimethylphenanthroline-palladium catalyst in combination with NaBAr₄ promoter, olefins are converted to the most stable double bond isomer at -30 to 20 °C. Silyl enol ethers are readily formed from silylated allylic alcohols. Fluorinated substituents are compatible with the reaction conditions, allowing the synthesis of fluoroenolates. Catalyst loading as low as 0.05% can be employed on a gram scale.

Alkenes are key intermediates in the synthesis of complex organic molecules; consequently, their synthesis and reactivity have been extensively investigated.^{1,2} Less available but more desirable alkenes can often be accessed by isomerization of readily available olefins. Such transition metal-catalysed transformations have been extensively studied and recent investigations have achieved regio- and diastereoselective control.^{3,4}

Alkene isomerization can be coupled with a second transformation that allows trapping of the double bond at a specific position.⁵ Isomerization alone can afford either a kinetic or a thermodynamic product of double bond migration.^{3,4} In the case of kinetic control, linear terminal alkenes are often selectively converted to 2-olefins.⁴ Long-distance chain-running double bond isomerization has been achieved using palladium or nickel catalysis, but it often takes advantage of a thermodynamic driving force to convert the alkene selectively to another functionality such as ketone or aldehyde.^{5a,e-g} A few examples describe efficient long-distance chain-running isomerization that conserves the valuable alkene functionality (Scheme 1).6 In 2000, Mori reported that a ruthenium hydride catalyst at 5 mol% loading performs functionalized, deconjugative alkene isomerization forming silvl enol ethers in refluxing toluene.^{6a} In a further advance, Grotjahn has described a catalyst capable of efficient long-distance olefin isomerization yielding a silyl enol ether. However, branched substrates did not afford silyl enol ether products.^{6b} We report





here that an air-stable 2,9-dimethylphenanthroline-palladium methyl chloride precatalyst in combination with NaBAr₄ as activator isomerizes a range of substrate olefins to the thermodynamically favoured products.

A 1997 mechanistic study showed that phenanthrolinepalladium alkyl cations undergo series of β-hydride eliminations/ reinsertions that constitute the fundamental mechanistic steps involved in olefin isomerization.7 Consequently, a phenanthrolinepalladium catalyst system should be capable of efficient alkene isomerization. A short optimization study showed that 2,9-dimethylphenanthroline palladium methyl chloride complex 3 affords the best combination of reactivity and stability when activated with NaB[C₆H₃(CF₃)₂]₄.⁸ As described below, high efficiency and generality of alkene isomerization is observed, allowing catalytic synthesis of synthetically valuable silvl enol ethers, including fluoroenolates. Simple olefins can be rapidly and efficiently converted to the thermodynamically most stable isomer as well. Disubstituted alkenes are reactive, and efficient chain-running isomerization is possible. More substituted substrates typically require longer reaction times.

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Table 1 Isomerization of simple alkenes^a



^{*a*} Reaction conditions: alkene (0.2 mmol), **3** (0.002 mmol), NaB[C₆H₃(CF₃)₂]₄ (0.008 mmol), CDCl₃ (0.1 mL), 0 $^{\circ}$ C, 16 h. Yields were determined by ¹H NMR with an internal standard. Please see ESI for details. ^{*b*} Reaction time: 2 h. ^{*c*} Reaction time: 1 h. ^{*d*} Reaction time: 3 h.

The isomerization of simple alkenes was investigated using 1% loading of 3 in combination with 4% of NaB[C₆H₄(CF₃)₂]₄ activator at 0 °C (Table 1). Allyl phenyl ether was isomerized to the alkenyl ether in 90% yield giving 2.7/1 product *E*/*Z* selectivity (entry 1). An aromatic bromide substituent is also tolerated (entry 2). Allylbenzenes are converted to the conjugated isomers in excellent yields and *E*/*Z* selectivities (entries 3 and 4). The isomerization of 1-hexene produces a mixture of 2-hexenes and 3-hexenes in nearly a thermodynamic ratio (entry 5).³¹ Isomerization of the disubstituted olefin (entry 6) efficiently produces the trisubstituted alkene.

Next, we investigated base-free synthesis of synthetically useful silyl enol ethers.⁹ While transition metal-catalysed isomerization of *O*-silylated unsaturated alcohols has been reported previously, only a very limited number of substrates have been investigated.^{3*i*,4*d*,*k*,6} Most of the literature examples involve conversion of an unsubstituted allyl moiety to an enol silane functionality.

Using standard conditions, a broad range of silyl allyl ethers can be isomerized to the corresponding enol silanes (Table 2). Unsubstituted *tert*-butyldimethylsilyl allyl ether was converted to the silyl enol ether of propionaldehyde in an 86% yield (entry 1). Disubstituted olefins are reactive as well. Thus, entry 2 shows conversion of a methallylic alcohol derivative to the silyl enol ether of isobutyralde in 87% yield (entry 2). Ketone enolate silyl ethers are formed in good yields (entries 3 and 4). The reaction tolerates aromatic chlorides and protected propiophenone enolate was obtained in 87% yield as a 1.6/1 E/Z isomer mixture (entry 5). Protected butyraldehyde enolate was formed in 93% yield (entry 6). Bis-protected 2-butenediol was converted to 4-hydroxybutyraldehyde enol silane in 62% yield (entry 7). Silyl protected

 Table 2
 Isomerization of silvl allyl ethers^a

R	$\begin{array}{c} 3 \text{ (1 mol%)} \\ R_2 \\ \text{NaB[C_6H_3(CF_3)_2]_4 (4 mol%)} \\ R_4 \\ \text{OTBS} \end{array} \xrightarrow{\text{OTBS}} R_4 \\ \end{array} \xrightarrow{\text{OTBS}} R_5 \\ \end{array}$		
	R ₃	CDCl ₃ , 0 °C	R ₃
Entry	Alkene	Product	Yield, %
1^b	OTBS	Jun OTBS	86 (1.4/1 <i>E</i> / <i>Z</i>)
2	ОТВS	ОТВS	87
3 ^{<i>c</i>}	OTBS	OTBS	60 (4.4:1 <i>E</i> / <i>Z</i>)
4^c	OTBS	OTBS	77 (4.1:1 <i>E</i> / <i>Z</i>)
5 ^{<i>d</i>,<i>e</i>}	OTBS	or CI	87 (1.6:1 <i>E</i> / <i>Z</i>)
6 ^{<i>f</i>}	M OTBS	OTBS	93 (2.0:1 <i>E</i> / <i>Z</i>)
7 ^c	OTBS	OTBS OTBS	62 (1.3 : 1 <i>E</i> / <i>Z</i>)
ď	OTBS	OTBS	51 (4.7:1 <i>E</i> / <i>Z</i>)
85		OTBS	20 (5.6:1 <i>E</i> / <i>Z</i>)
9 ^g	OTBS	OTBS	49 (>50:1 <i>E</i> / <i>Z</i>)

^{*a*} Reaction conditions: alkene (0.2 mmol), catalyst (0.002 mmol), NaB[C₆H₃(CF₃)₂]₄ (0.008 mmol), CDCl₃ (0.1 mL), 0 °C, 16 h. Yields were determined by ¹H NMR with an internal standard. Please see ESI for details. ^{*b*} Time: 2 h. ^{*c*} Time: 3 h. ^{*d*} Time: 22 h. ^{*e*} 30 °C. ^{*f*} Time: 48 h. ^{*g*} Time: 24 h.

3-hydroxyhexene gave a mixture of two possible trisubstituted enolates in 71% combined yield (entry 8). This example shows that reaction does not stop after a enol silane is formed; the double bond can migrate past the silyloxy substituent. The product of entry 9 was obtained by a mono-isomerization followed by a Lewis-acid catalysed allylic rearrangement of a silyloxy group.¹⁰

Targeted transposition of a functional group across many bonds within a molecule presents a useful strategy toward the synthesis of complex molecules. Long distance chain-running isomerization was examined next (Table 3). Both aldehyde and ketone silyl enol ethers can be formed by isomerization of monosubstituted alkenes (entries 1 and 2). Disubstituted double bonds can be subjected to isomerization as well (entries 3 and 4). Interestingly, a disubstituted enol is obtained in preference to trisubstituted olefin (entry 3). By using a more bulky silyl protected group and a different catalyst, Grotjahn was able to change the preference to a trisubstituted alkene.^{6b} Butenyl benzene was converted to the conjugated product in good yield and selectivity (entry 5). Entry 6 shows the result obtained with 0.05 mol% catalyst at room temperature on one gram scale. The isomerization product was isolated in 76% yield as a 2.6/1 E/Z mixture.



^{*a*} Reaction conditions: alkene (0.2 mmol), catalyst (0.002 mmol), NaB[C₆H₃(CF₃)₂]₄ (0.008 mmol), CDCl₃ (0.1 mL), 0 °C, 3 h. Yields in entries 1, 2, 4, and 5 were determined by ¹H NMR with an internal standard. Yields in entries 3 and 6 are isolated yields of pure product. Please see ESI for details. ^{*b*} Time: 48 h. ^{*c*} Time: 24 h. ^{*d*} Room temperature. ^{*e*} Scale: 2.0 mmol. ^{*f*} Alkene (4.6 mmol), catalyst (0.0023 mmol), NaB[C₆H₃(CF₃)₂]₄ (0.01 mmol), CH₂Cl₂ (0.115 mL).

The chain-running isomerization procedure can be used to synthesize fluorinated silyl enol ethers that are valuable synthetic precursors but are difficult to access (Scheme 2).¹¹ Isomerization of alkenyl fluoride **4** resulted in formation of **5** in 78% yield. A silane activator was necessary in this case, presumably due to weak coordination of the fluorine-substituted olefin to palladium.^{4/,7} Furthermore, isomerization of **6** to 7 produces a fluoromethyl-substituted enol ether in moderate isolated yield.

The reaction likely commences with halide abstraction from dimethylphenanthroline-palladium methyl chloride complex. The formed cationic palladium species coordinates alkene substrate. Migratory insertion followed by β -hydride elimination gives the active cationic palladium hydride complex, which after coordination of substrate and a series of migratory insertion/ β -hydride elimination steps releases the product.



Scheme 2 Synthesis of fluorinated enol ethers.

In conclusion, we have shown that an air- and moisture stable, easily prepared 2,9-dimethylphenanthroline palladium catalyst 3 in combination with NaBAr₄ as promoter in chloroform or dichloromethane converts alkenes to the most stable double bond isomer at room temperature or below. Silyl enol ethers are readily formed from silylated allylic alcohols. Long-distance double bond chain-running can afford enol silanes as well. Fluorinated substituents are compatible with the reaction conditions, allowing the synthesis of protected fluoroenolates. Catalyst loadings as low as 0.05% can be employed in gram scale reactions and turnover numbers as high as *ca.* 1520 were demonstrated.

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Conflicts of interest

There are no conflicts to declare.

Notes and references

- 1 (a) P. W. N. M. van Leeuwen, *Homogeneous Catalysis*, Kluwer Academic Publishers, 2004, pp. 125–138; (b) J. Prunet, *Angew. Chem., Int. Ed.*, 2003, **42**, 2826.
- 2 (a) S. J. Connon and S. Blechert, Angew. Chem., Int. Ed., 2003,
 42, 1900; (b) D. A. Colby, A. S. Tsai, R. G. Bergman and J. A. Ellman, Acc. Chem. Res., 2012, 45, 814; (c) H. H. Brintzinger, D. Fischer, R. Mülhaupt, B. Rieger and R. M. Waymouth, Angew. Chem., Int. Ed., 1995, 34, 1143; (d) R. I. McDonald, G. Liu and S. S. Stahl, Chem. Rev., 2011, 111, 2981.
- 3 (a) S. W. M. Crossley, F. Barabé and R. A. Shenvi, J. Am. Chem. Soc., 2014, 136, 16788; (b) F. Weber, A. Schmidt, P. Röse, M. Fischer, O. Burghaus and G. Hilt, Org. Lett., 2015, 17, 2952; (c) A. Wille, S. Tomm and H. Frauenrath, Synthesis, 1998, 305; (d) L.-G. Zhuo, Z.-K. Yao and Z.-X. Yu, Org. Lett., 2013, 15, 4634; (e) G. Erdogan and D. B. Grotjahn, J. Am. Chem. Soc., 2009, 131, 10354; (f) G. Erdogan and D. B. Grotjahn, Org. Lett., 2014, 16, 2818; (g) A. Scarso, M. Colladon, P. Sgarbossa, C. Santo, R. A. Michelin and G. Strukul, Organometallics, 2010, 29, 1487; (h) P. J. Perez, J. C. Calabrese and E. E. Bunel, Organometallics, 2001, 20, 337; (i) D. Gauthier, A. T. Lindhardt, E. P. K. Olsen, J. Overgaard and T. Skrydstrup, J. Am. Chem. Soc., 2010, 132, 7998; (j) P. Mamone, M. F. Grünberg, A. Fromm, B. A. Khan and L. Gooßen, J. Org. Lett., 2012, 14, 3716; (k) C. Su and P. G. Williard, Org. Lett., 2010, 12, 5378; (l) M. S. Winston, P. F. Oblad, J. A. Labinger and J. E. Bercaw, Angew. Chem., Int. Ed., 2012, 51, 9822; (m) K. Curran, W. Risse, M. Hamill, P. Saunders, J. Muldoon, R. A. de la Rosa and I. Tritto, Organometallics, 2012, 31, 882.
- 4 (a) C. Chen., T. R. Dugan, W. W. Brennessel, D. J. Weix and P. L. Holland, J. Am. Chem. Soc., 2014, 136, 945; (b) Y. Wang, C. Qin, X. Jia, X. Leng and Z. Huang, Angew. Chem., Int. Ed., 2017, 56, 1614; (c) C. R. Larsen, G. Erdogan and D. B. Grotjahn, J. Am. Chem. Soc., 2014, 136, 1226; (d) T. Kobayashi, H. Yorimitsu and K. Oshima, Chem. Asian. J., 2009, 4, 1078; (e) A. Schmidt, A. R. Nödling and G. Hilt, Angew. Chem., Int. Ed., 2015, 54, 801; (f) A. L. Kocen, K. Klimovica, M. Brookhart and O. Daugulis, Organometallics, 2017, 36, 787; (g) S. Y. Y. Yip and C. Aïssa, Angew. Chem., Int. Ed., 2015, 54, 6870; (h) C. Larsen and D. B. Grotjahn, J. Am. Chem. Soc., 2012, 134, 10357; (i) H. J. Lim, C. R. Smith and T. V. RajanBabu, J. Org. Chem., 2009, 74, 4565; (j) M. Mayer, A. Welther and A. J. von Wangelin, ChemCatChem, 2011, 3, 1567; (k) T. Ohmura, Y. Shirai, Y. Yamamoto and N. Miyaura, Chem. Commun., 1998, 1337.
- 5 (a) J.-H. Francisco, T. Moragas, J. Cornella and R. Martin, *Nature*, 2017, 545, 84; (b) R. A. Widenhoefer and N. S. Perch, *Org. Lett.*, 1999, 1, 1103; (c) C. Zhang, C. B. Santiago, L. Kou and M. S. Sigman, *J. Am. Chem. Soc.*, 2015, 137, 7290; (d) T. Kochi, T. Hamasaki, Y. Aoyama, J. Kawasaki and F. Kakiuchi, *J. Am. Chem. Soc.*, 2012, 134, 16544;

(e) T. Hamasaki, Y. Aoyama, J. Kawasaki, F. Kakiuchi and T. Kochi, J. Am. Chem. Soc., 2015, **137**, 16163; (f) E. Larionov, L. Lin, L. Guénée and C. Mazet, J. Am. Chem. Soc., 2014, **136**, 16882; (g) L. Lin, C. Ramano and C. Mazet, J. Am. Chem. Soc., 2016, **138**, 10344.

- 6 (a) H. Wakamatsu, M. Nishida, N. Adachi and M. Mori, J. Org. Chem., 2000, 65, 3966; (b) D. B. Grotjahn, C. R. Larsen, J. L. Gustafson, R. Nair and A. Sharma, J. Am. Chem. Soc., 2007, 129, 9592; (c) D. P. Ojha, K. Gadde and K. R. Prabhu, J. Org. Chem., 2017, 82, 4859.
- 7 A. M. LaPointe, F. C. Rix and M. Brookhart, J. Am. Chem. Soc., 1997, 119, 906.
- 8 Please see ESI† for details.
- 9 (a) R. Mahrwald, Chem. Rev., 1999, 99, 1095; (b) I. Fleming, A. Barbero and D. Walter, Chem. Rev., 1997, 97, 2063.
- 10 B. K. Shull, T. Sakai and M. Koreeda, J. Am. Chem. Soc., 1996, 118, 11690.
- 11 (a) E. Bélanger, M.-F. Pouliot, M.-A. Courtemanche and J.-F. Paquin, J. Org. Chem., 2012, 77, 317; (b) F.-M. Liao, Z.-Y. Cao, J.-S. Yu and J. Zhou, Angew. Chem., Int. Ed., 2017, 56, 2459; (c) J.-S. Yu, F.-M. Liao, W.-M. Gao, K. Liao, R.-L. Zuo and J. Zhou, Angew. Chem., Int. Ed., 2015, 54, 7381.