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Iodoetherification of unactivated alkenes catalyzed by diphosphine palladium(II) complexes

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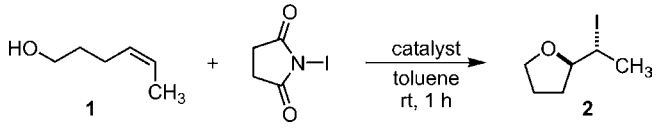
ABSTRACT

A palladium-catalyzed intramolecular iodoetherification of alkenes is reported. The reaction is efficient and highly diastereoselective for disubstituted alkenes. The tether length between the alcohol and alkene can be varied to produce tetrahydrofuran and tetrahydropyran rings. Diphosphine palladium(II) salts are highly active catalysts enabling future studies on the development of an enantioselective process.

Reactions that operate on unactivated alkenes are important in organic synthesis. The addition of an oxygen nucleophile and halogen atom across alkenes, haloetherification,[1] falls squarely into this category. Intramolecular and intermolecular examples have been well established with new methods of catalyzing the reaction being reported in recent years.[2] An intramolecular haloetherification can be applied to the synthesis of tetrahydrofurans,[3] commonly found in pharmaceuticals and complex natural products. Development of novel catalytic methods for haloetherification can provide opportunity for enantiocontrol. Whereas transition-metal catalysts for the enantioselective iodoetherification of alkenes have been developed, few are late transition metals.[4] Application of late transition-metal catalysis to haloetherification opens access to a broad ligand set for controlling reactivity and stereochemistry. We became interested in palladium(II) complexes as competent catalysts for the intramolecular iodoetherification, a currently undeveloped process.

Recently, a growing interest in the palladium(II/IV) catalyst cycle has produced a variety of important new methods. One class of reactions has focused on C–H activation,[5] while another has demonstrated successful activation of alkenes.[6] In the latter case, Michael et al. have realized an intramolecular aminochlorination of alkenes,[7] a valuable method for the synthesis of N-protected, halogenated pyrrolidines. Though most of the research has focused on nitrogen nucleophiles, oxygen nucleophiles have been employed in an intramolecular aminoetherification reaction producing 2-aminotetrahydrofurans.[8] Despite the intense research in palladium(II/IV) catalysis, the development of a palladium-catalyzed iodoetherification remains absent.

Table 1
Optimization of catalyst conditions



Entry	Catalyst[f]	Mol %	Yield[a] (%)
1	None	0	13
2	None	0	95[b]
3	$(MeCN)_2PdCl_2$	5	87
4	$(cod)PdCl_2$	5	88
5	$Pd(OAc)_2$	5	71
6	$Pd_2(dba)_3$	2.5	71
7	$(cod)PdCl_2 + PPh_3$[c]	5	93
8	$(dppe)PdCl_2$	5	45
9	**$(dppf)PdCl_2$**	**5**	**95**
10	$(cod)PdCl_2$	1	41
11	$(dppf)PdCl_2$	1	60
12	$(cod)PdCl_2$	5	55[d]
13	$(cod)PdCl_2$	5	94[e]

[a] Yield determined by GC using 1-iodohexane as an internal standard.
[b] Reaction performed in THF.
[c] 0.15 equiv of PPh_3 used.
[d] Pyridine (1.2 equiv) added.
[e] Sodium bicarbonate (3 equiv) added.
[f] cod = 1,5-cyclooctadiene; dba = dibenzylideneacetone; dppe = 1,2-bis(diphenylphosphino)ethane; dppf = 1,1′-bis(diphenylphosphino)ferrocene.

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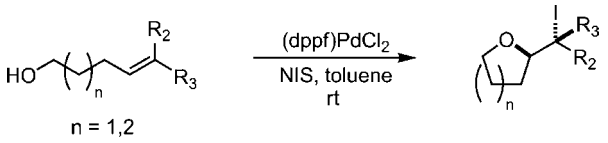
Here we report the development of a highly diastereoselective palladium-catalyzed iodoetherification of alkenes with the ultimate goal of asymmetric catalysis in mind. Alkenes containing a tethered oxygen nucleophile were initially chosen for development. The intramolecular cyclization generates oxygen-containing heterocycles which are common motifs in bio-active small molecules and marine natural products, including examples incorporating a pendant halogen.[9]

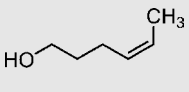
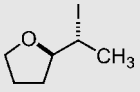
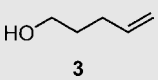
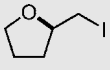
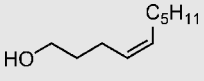
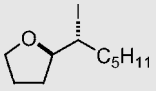
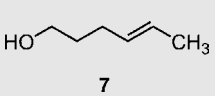
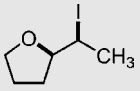
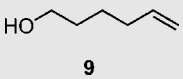
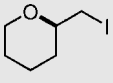
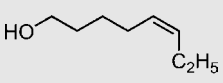
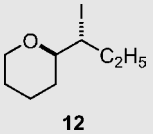
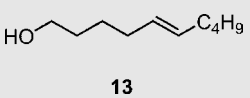
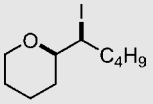
Studies on catalysis were initiated with *cis*-4-hexen-1-ol (**1**). Treatment of the alkene with *N*-iodosuccinimide (NIS) in a variety of polar solvents led to rapid, uncatalyzed cyclization to **2** after 1 h. The high reactivity of this substrate may help explain the lack of research on catalysis of this reaction. We were interested to find that reactivity was greatly reduced in non-polar solvents, such as toluene. In fact, only 13% of **2** was produced in 1 h compared to 95% in the more polar THF (Table 1, entries 1 and 2). With the rate of background reaction reduced, an opportunity for catalysis was present. In toluene, common palladium(II) precursors showed high catalytic activity over the 1 h time frame (entries 3–5). A palladium(0) source (entry 6) also shows catalysis presumably following oxidation to palladium(II) in situ. Reactivity of the palladium center was unhindered by the addition of phosphine ligands. Surprisingly, ligands enhanced reactivity with (dppf)$PdCl_2$ providing the best catalytic activity (entries 7–9). Since the reactions were generally suspensions, we attempted to lower catalyst loadings. Even at 1 mol % catalyst loading, iodoetherification still occurred in 1 h, but at a lower rate (entries 10 and 11).

We considered that the iodoetherification reaction could be catalyzed by protic acid generated in situ by advantageous water. Two experiments were conducted under basic conditions to ensure the reaction was catalyzed by the palladium metal center. Reaction yield was reduced by the addition of pyridine, but catalysis still occurred (Table 1, entry 12). It is believed that the reduction in yield is linked to pyridine consumption of NIS. In the case of an insoluble inorganic base (entry 13), the rate and yield were unaffected. Though not definitive, the data suggest that a protic acid-catalyzed reaction is not occurring.

The (dppf)$PdCl_2$ catalyst was chosen from optimization studies for the investigation of substrate structure on cyclization. Alkenes were generally treated with 3 mol % of catalyst in toluene at room temperature for 90 min in the presence of a slight excess of NIS.[10]

Table 2
Substrate effect on iodoetherifications[11]



Entry	Alkene	Product	Mol % Pd	Time (h)	dr	Yield[a] (%)
1	 **1**	 **2**	3	1.5	>20:1	70
2	 **3**	 **4**	3	1.5	—	51
3	 **5**	 **6**	3	1.5	>20:1	92
4	 **7**	 **8**	3	1.5	>20:1	70[b]
5	 **9**	 **10**	5	6	—	55
6	 **11**	 **12**	5	6	>20:1	61
7	 **13**	 **14**	5	6	>20:1	67

[a] Average isolated yield of two or more experiments carried out with 0.3 mmol of alkene.
[b] Product isolated as an inseparable mixture contained 13% of the regioisomer resulting from 6-endo cyclization.

No work-up was required and products were purified by silica gel chromatography. *cis*-Alkenes (Table 2, entries 1 and 3) participate in the cyclization, generating product in high yield with >20:1 diastereoselectivity.[11] A terminal alkene (entry 2) reacts readily to give a 51% yield of iodotetrahydrofuran **4**. The moderate yield is attributed to product volatility since the ^{1}H NMR spectrum of an unpurified sample showed clean product formation. A *trans*-alkene also undergoes stereospecific iodocyclization in excellent yield (entry 4). Iodide **8** was isolated as a 7:1 mixture of inseparable compounds, which is attributed to formation of the 6-endo cyclization product.

We were delighted to find that tetrahydropyran formation was also possible. The reactions were slower than 5-membered ring formation, so catalyst loading was increased to 5 mol % and reaction time was extended to 6 h. Terminal alkene **9** cyclized to give tetrahydropyran **10** in moderate yield (Table 2, entry 5). Again, product volatility played a role in isolation. The *trans*- and *cis*-alkenes cyclized to give a single stereoisomer of tetrahydropyran in good yield (entries 6 and 7).

In summary, we have developed a palladium-catalyzed intramolecular iodoetherification reaction. Incorporation of diphosphine ligands is promising for the development of a catalytic, enantioselective process. Further investigation into catalysts for enantiocontrol and the reaction mechanism are underway.

Acknowledgments

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10. *General procedure*: An oven-dried vial containing a Teflon-coated stir bar was charged with 7.3 mg (0.009 mmol) of dichloro[1,2-bis(diphenylphosphino)ferrocene]palladium(II) dichloromethane adduct on the benchtop. The vial was purged with argon, and the solid was suspended in 1.5 mL of dry toluene. *N*-Iodosuccinimide (81 mg, 0.36 mmol) was transferred as a solid to the vial. Fifty–five microliters (0.3 mmol) of *cis*-4-decen-1-ol (**5**) were added to the suspension via syringe. The mixture was stirred at room temperature under argon for 90 min. After this time, the suspension was loaded directly onto a silica gel column. The crude mixture was purified by flash chromatography with 50 mL of hexanes followed by 15:1 hexanes/ether. Tetrahydrofuran **6** (78 mg, 92%) was isolated as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.13–4.08 (ddd, 1H), 4.00–3.94 (dt, 1H), 3.87–3.81 (ddd, 1H), 3.77–3.72 (ddd, 1H), 2.12–1.82 (m, 4H), 1.77–1.55 (m, 3H), 1.47–1.21 (m, 5H), 0.90 (t, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 82.4, 68.9, 42.8, 36.3, 31.0, 30.8, 29.4, 26.2, 22.5, 14.0.
11. Products **2**, **4**, **6**, and **10** displayed characterization data identical to literature values. Major diastereomer assignment was based on products **2** and **6**.