Communication

Palladium-Catalyzed Enantioselective Intermolecular Carboetherification of Dihydrofurans

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J. Am. Chem. Soc., **Just Accepted Manuscript** • DOI: 10.1021/jacs.6b02158 • Publication Date (Web): 15 Mar 2016

Palladium-Catalyzed Enantioselective Intermolecular Carboetherification of Dihydrofurans

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Supporting Information Placeholder

ABSTRACT: A novel enantioselective Pd-catalyzed intermolecular carboetherification of dihydrofurans is reported. The in situ generation of chiral bisphosphinemonooxide (BPMO) ligands is crucial and a general catalytic system has been identified based on this approach. It provides access to a variety of fused tetrahydrofurobenzofurans in consistently high yield and enantiomeric excess.

The 2,3,3a,8a-tetrahydrofuro[2,3-*b*]benzofuran scaffold is frequently found in biologically active compounds such as Asperversin A or Aflatoxin B2, a potent mutagen (Figure 1, A).[1] Nonetheless, direct access to this synthetic motif remains particularly challenging and only a handful of enantioselective approaches has been disclosed.[2] We envisaged that the effective development of a Pd-catalyzed enantioselective intermolecular carboetherification starting from 2,3-dihydrofurans (dhf) and 2-halophenol derivatives would provide direct access to this pattern (**A** on Figure 1, B). Despite recent and remarkable advances in the field, such a process is notably absent from the current portfolio of carboetherification of alkenes.[3] Importantly, most reported examples proceed via *intra*molecular reactions and their enantioselective variants are still scarce.[4] Importantly, we anticipated that the successful realization of this goal would require circumventing the formation of the competing α-etherification and Heck products **B** and **C** that may form under typically basic cross-coupling reaction conditions.[5,6]

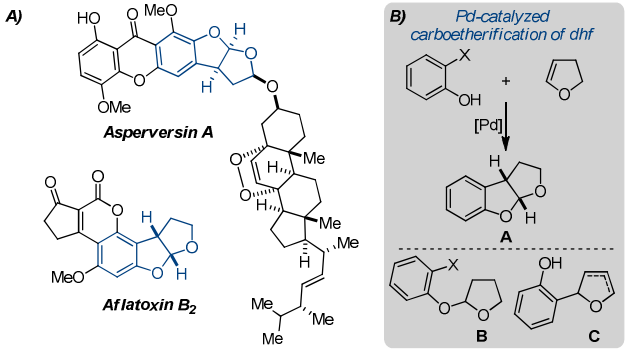
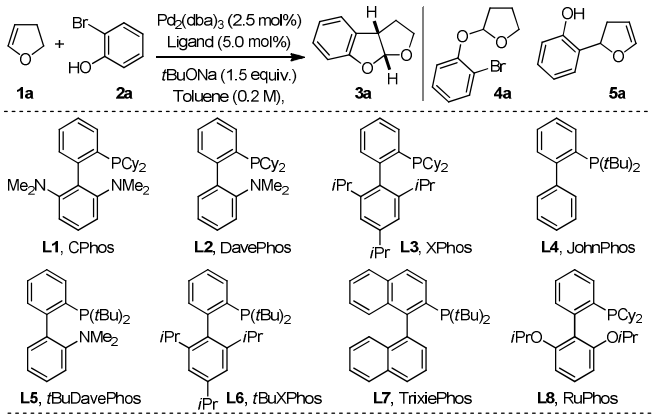


Figure 1. Biologically active tetrahydrofurobenzofurans (A) and proposed intermolecular carboetherification of dihydrofuran (B).

In this communication, we describe the first examples of *enantioselective intermolecular* Pd-catalyzed *syn*-carboetherifications of olefins affording fused tetrahydrofurobenzofurans in good yield and excellent level of enantiomeric excess.

Table 1. Reaction optimization[a]



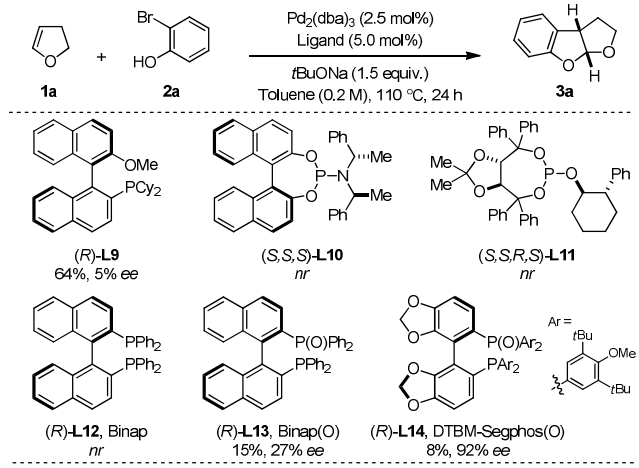
entry	ligand	t (h)	T (°C)	yield (%)[b]
1	**L1** (CPhos)	24	110	56
2	**L2** (DavePhos)	24	110	nr
3	**L3** (XPhos)	24	110	nr
4	**L4** (JohnPhos)	24	110	nr
5	**L5** (*t*BuDavePhos)	24	110	45
6	**L6** (*t*BuXPhos)	24	110	68
7	**L7** (TrixiePhos)	24	110	36
8	**L8** (RuPhos)	24	110	73
9	**L8** (RuPhos)	4	50	traces
10	**L8** (RuPhos)	6	110	56[c]
11	**L8** (RuPhos)	4	80	73

[a] Reaction conditions: **1** (1.0 mmol), **2a** (0.2 mmol). [b] Determined after purification by column chromatography. [c] Using 2-chlorophenol.

In our exploratory experiments, we investigated the coupling between 2,3-dihydrofuran **1a** and 2-bromophenol **2a** using CPhos (**L1**), a prototypical monodentate biarylphosphine ligand (Table 1, Entry 1).[7] After a rapid survey of various reaction parameters, we were delighted to

find that **3a** could be formed exclusively and isolated in 56% yield after heating at 110°C a toluene solution for 24 h using *t*BuONa (1.5 equiv.) and $Pd_2(dba)_3$ (2.5 mol%). In an attempt to improve reactivity, additional Buchwald-type phosphine ligands were evaluated next. Whereas **L2** (DavePhos), **L3** (XPhos) and **L4** (JohnPhos) did not prove competent for this transformation, the sterically demanding **L5** (*t*BuDavePhos), **L6** (*t*BuXPhos) and **L7** (TrixiePhos) all afforded **3a** in moderate to acceptable yield (45%, 68% and 36% yield respectively; Table 1, Entry 2-7). Satisfactorily, with **L8** (RuPhos), the yield was improved to 73%. This performance could be maintained even when the reaction was performed at lower temperature and in a much reduced time (80°C, 4 h; Table 1, Entry 11). Of note, products **4a** and **5a** were only detected when other bases or ligands were employed. Higher yields were obtained using a 5:1 stoichiometry between 2,3-dhf **1a** and 2-bromophenol **2a** (see Supporting Information for details).

Table 2. Chiral ligand survey[a]

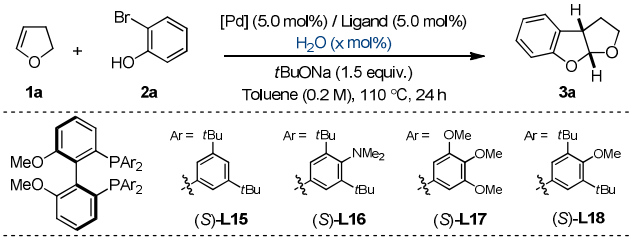


[a] Reaction conditions: **1a** (1 mmol), **2a** (0.2 mmol). Yields of isolated products after purification. Enantioselectivity determined by HPLC using a chiral column.

We next turned to the development of an enantioselective version of this intermolecular carboetherification reaction using the same model reaction between **1a** and **2a** (Table 2). Reasoning that the MOP-type ligands originally designed by Hayashi may constitute closely related structural analogues of RuPhos, ligand **L9** was evaluated first.[8] After 24 h at 110°C, **3a** was isolated in reasonable yield but in almost racemic form (64% yield, 5% *ee*). The less basic Binol-based phosphoramidite ligand (**L10**) and Taddol-based phosphite ligand (**L11**) which were recently found to be suitable ligands in a related intramolecular carboalkoxylation of alkenes only generated traces of the carboetherification product **3a** along with minute amount of **5a**.[4g] Interestingly, whereas Binap (**L12**) was ineffective in the carboetherification reaction, its corresponding monoxide Binap(O) (**L13**) delivered **3a** in 15% yield and 27% *ee*. These results are consistent with the notion that Binap(O) is a hemilabile ligand that behaves temporarily as a monodentate chiral phosphine ligand.[9-11] With another member of this ligand class, DTBM-Segphos(O) (**L14**), **3a** was still obtained in modest yield but in excellent enantiomeric excess (92% *ee*).[12]

To ensure rapid identification of a lead structure we next focused on the development of a protocol that would enable in situ generation of chiral bis-monophosphine oxide ligands (BMPO) starting from their commercially available bisphosphine precursors (Table 3). Our approach was inspired by the seminal contributions of Ozawa and Hayashi who demonstrated that Binap(O) could be generated in situ under basic conditions using Pd(OAc)2 and controlled amount of added water.[13] Very recent reports from Li and Belik, and Eastgate and Blackmond are also in line with this approach.[14-15]

Table 3. Effect of added water and final evaluation of chiral ligands[a]



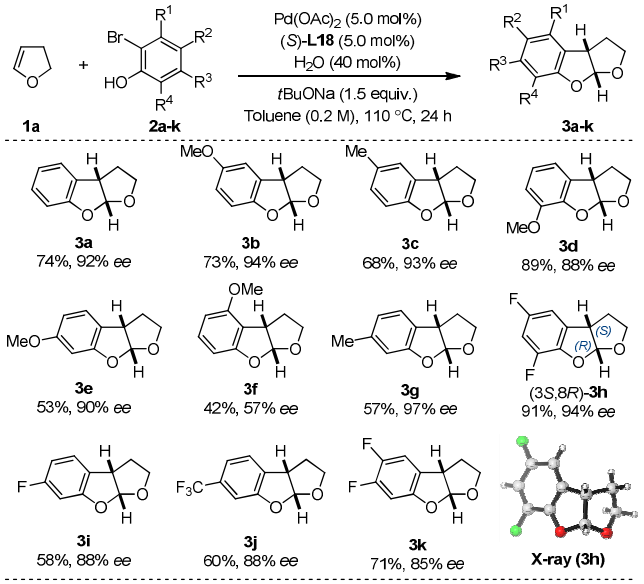
entry	ligand (5 mol%)	[Pd] (5 mol%)[b]	H2O (mol%)	yield (%)[c]	*ee* (%)[d]
1	DTBM-Segphos	Pd2(dba)3	-	*nr*	*nd*
2	**L14**	Pd2(dba)3	-	8	92
3	DTBM-Segphos	Pd(OAc)2	-	16	90
4	DTBM-Segphos	Pd(OAc)2	20	31	83
5	DTBM-Segphos	Pd(OAc)2	40	40	85
6	DTBM-Segphos	Pd(OAc)2	60	35	81
7	**L15**	Pd(OAc)2	40	76	90
8	**L16**	Pd(OAc)2	40	66	90
9	**L17**	Pd(OAc)2	40	31	65
10	**L18**	Pd(OAc)2	40	74	92

[a] Reaction conditions: **1a** (1 mmol), **2a** (0.2 mmol). [b] Concentration in Pd. [c] After purification by chromatography. [d] Determined by HPLC using a chiral column.

The model reaction between **1a** and **2a** was therefore carried out using the bisphosphine ligand DTBM-Segphos (5 mol%), Pd(OAc)2 (5 mol%) and variable amounts of water (0-60 mol%). Although reactivity was observed in the absence of water, the optimal result was obtained when 40 mol% of water were added in the mixture (entry 3-6). The yield in carboetherification product **3a** was significantly improved while the erosion in enantioselectivity remained acceptable. Subsequently, a range of commercially available bisphophines was evaluated (see SI for details). From this screening, it clearly appeared that ligands of the Biphep family (**L15-18**) with sterically demanding and electron-rich aryl substituents were particularly well-suited candidates (Table 3, entry 7-10).[12] Gratifyingly, with **L18** the carboetherification product **3a** was isolated in 74% yield and 92% *ee*.

The scope of the reaction was delineated with **L18** using the protocol for in situ mono-oxidation of the ligand (Table 4). Overall, both electron-rich and electron-deficient 2-bromophenols participated efficiently in the *syn*-carboetherification of 2,3-dihydrofuran **1a**, delivering the product in consistently good yield and high level of enantio-

Table 4. Scope of the enantioselective intermolecular carboetherification of 2,3-dihydrofuran[a]



[a] Reaction conditions: **1a** (1 mmol), **2a-k** (0.2 mmol). Yields of isolated products after purification. Enantioselectivity determined by HPLC or GC using a chiral column. Absolute configuration of all products is as shown and was assigned by analogy with the X-ray crystallography analysis of (3*S*,8*R*)-**3h**.[16]

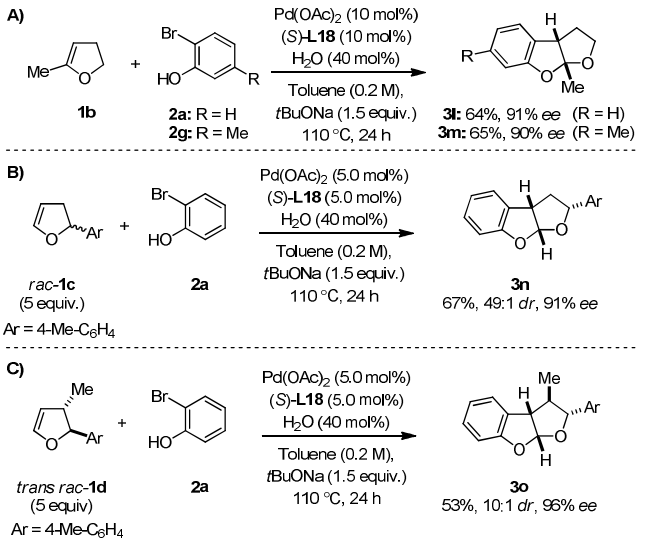


Figure 2. Variation of the dihydrofuran structure. Reaction conditions: **1b-d** (1 mmol), **2a** or **2g** (0.2 mmol). Yields of isolated product. Enantioselectivity determined by HPLC or GC using a chiral column. Diastereomeric ratio measured by ^{1}H NMR of the crude reaction mixture. A) Using 5-methyl-2,3-dihydrofuran **1b**. B) Using *rac* 2-(*p*-tolyl)-2,3-dihydrofuran **1c**. Recovered **1c**: 37% yield, 12% *ee*, yield based on *rac*-**1c**. C) Using *rac trans*-3-methyl-2-(*p*-tolyl)-2,3-dihydrofuran **1d**. Recovered **1d**: 64% yield, 8% *ee*, yield based on *rac*-**1d**.[17]

-selectivity (10 examples: **3a-e**,**g-k** 53-91% yield; 85-97% *ee*). Interestingly, an electron-withdrawing or an electron-donating group can be placed indifferently in *para* position with respect to the bromine atom or the -OH functionality without noticeable effect on the reaction outcome. However, when 2-bromo-3-methoxyphenol **2f** was employed, both the reactivity and the enantioselectivity were affected significantly (**3f**: 42% yield, 57% *ee*).

Substituted dihydrofurans are notoriously more difficult to engage in cross-coupling reactions than their unsubstituted counterparts.[18] Therefore, the influence of substitution on various positions of the dihydrofuran ring was investigated next (Figure 2). When 5-methyl-2,3-dihydrofuran **1b** was subjected to the optimized reaction conditions, increasing the catalyst loading to 10 mol% was required to maintain a reasonable level of reactivity. The corresponding fused tetrahydrofurobenzofurans **3l-m** with a fully substituted congested acetal carbon stereocenter were isolated in good yields and excellent levels of enantioselectivity (Figure 2, A). Interestingly, 2-(*p*-tolyl)-2,3-dihydrofuran **1c** – obtained from an independent Heck cross-coupling reaction[5,19] – also proved a competent partner delivering **3n** as a single diastereoisomer in 67% yield and 91% *ee* (Figure 2, B). More remarkably, *trans*-3-methyl-2-(*p*-tolyl)-2,3-dihydrofuran **1d**[19,20] afforded the corresponding carboetherification product **3o** with four contiguous stereocenters in 53% yield, 10:1 *dr* and 96% *ee* (Figure 2, C). Of note, an optically active tetrahydrofurobenzofurans with such a level of stereochemical complexity would certainly be difficult to prepare by conventional methods.[21]

In conclusion, we have developed a very general and unprecedented enantioselective Pd-catalyzed intermolecular *syn*-carboetherification of dihydrofurans using in situ generated chiral bis-monophosphine oxide ligands. The method gives readily access to synthetically relevant and stereochemically complex fused tetrahydrofurobenzofurans in high yield, diastereoselectivity and enantioselectivity. Further mechanistic studies into the origin of the reactivity and selectivity of this catalytic system are ongoing in our laboratories.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization of all new compounds, spectral data and X-ray data for compound **3h** (CCDC 1455966).This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interests.

ACKNOWLEDGMENT

This work was supported by the University of Geneva and the Swiss National Science Foundation. S. Rosset is acknowledged for technical assistance, Dr. C. Besnard for assistance with X-ray analysis, crystallographic data collection and refinement. Johnson-Matthey is acknowledged for a generous gift of palladium precursors. This article is

dedicated to Prof. Andreas Pfaltz on the occasion of his retirement.

REFERENCES

(1) (a) Bräse, S.; Encinas, A.; Keck, J.; Nising, C. F. *Chem. Rev.* **2009**, *109*, 3903; (b) Miao, F.-P.; Li, X.-D.; Liu, X.-H.; Cichewicz, R. H.; Ji, N.-Y. *Mar. Drugs* **2012**, *10*, 131.

(2) (a) Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **2003**, *125*, 3090; (b) Zhou, G.; Corey, E. J. *J. Am. Chem. Soc.* **2005**, *127*, 11958.

(3) Recent reviews: (a) Wolfe, J. P. *Eur. J. Org. Chem.* **2007**, 571; (b) Wolfe, J. P. *Synlett* **2008**, 2913; Schultz, D. M.; Wolfe, J. P. *Synthesis* **2012**, 351; (c) Wolfe, J. P. *Top. Heterocycl. Chem.* **2013**, *32*, 1. Recent examples: Cobalt-catalyzed carboetherifications: (d) Fries, P.; Halter, D.; Kleinscheck, A.; Hartung, J. *J. Am. Chem. Soc*. **2011**, *133*, 3906; (e) Schuch, D.; Fries, P.; Donges, M.; Menéndez Pérez, B.; Hartung, J. *J. Am. Chem. Soc*. **2009**, *131*, 12918; (f) Palmer, C.; Morra, N. A.; Stevens, A. C.; Bajtos, B.; Machin, B. P.; Pagenkopf, B. L. *Org. Lett*. **2009**, *11*, 5614; Gold-catalyzed carboetherifications: (g) Zhang, G.; Cui, L.; Wang, Y.; Zhang, L. *J. Am. Chem. Soc*. **2010**, *132*, 1474; (h) Melhado, A. D.; Brenzovich, W. E.; Lackner, A. D.; Toste. F. D. *J. Am. Chem. Soc*. **2010**, *132*, 8885; (i) Ball, L. T.; Green. M.; Lloyd-Jones, G. C.; Russell, C. A. *Org. Lett*. **2010**, *12*, 4724; (j) Brenzovich, W. E., Brazeau, J.-F; Toste, F. D. *Org. Lett*. **2010**, *12*, 4728; Palladium-catalyzed carboetherifications: (k) Satterfield, A. D.; Kubota, A.; Sanford, M. S. *Org. Lett*. **2011**, *13*, 1076; (l) Hayashi, S.; Yorimitsu, H.; Oshima, K. *J. Am. Chem. Soc*. **2009**, *131*, 2052; (m) Nakhla, J. S.; Kampf, J. W.; Wolfe. J. P. *J. Am. Chem. Soc*. **2006**, *128*, 2893; (n) Hay, M. B.; Wolfe, J. P. *J. Am. Chem. Soc*. **2005**, *127*, 16468; (o) Wolfe, J. P.; Rossi, M. A. *J. Am. Chem. Soc*. **2004**, *126*, 1620; (q) Kiss, L.; Antus, S. *Heterocyclic Commun.* **2000**, *6*, 309; (r) Kiss, L.; Papp, G.; Joó, F.; Antus, S. *Heterocyclic Commun.* **2001**, *7*, 417; (s) Kiss, L.; Kurtan, T.; Antus, S. Brunner, H. *Arkivoc* **2003**, 69.

(4) (a) Catalytic enantioselective alkene carboetherifications: (a) Tietze, L. F.; Sommer, K. M.; Zinngrebe, J.; Stecker, F. *Angew. Chem. Int. Ed.* **2005**, *44*, 257; (b) Pathak, T. P.; Gligorich, K. M.; Welm, B. E.; Sigman, M. S. *J. Am. Chem. Soc.* **2010**, *132*, 7870; (c) Arai, M. A.; Kuraishi, M.; Arai, T.; Sasai, H. *J. Am. Chem. Soc.* **2001**, *123*, 2907; (d) Kawamura, Y.; Kawano, Y.; Matsuda, T.; Ishitobi, Y.; Hosokawa, T. *J. Org. Chem.* **2009**, *74*, 3048; (e) Burke, S. D.; Jiang, L. *Org. Lett.* **2001**, *3*, 1953; (f) Bovino, M. T.; Liwosz, T. W.; Kendel, N. E.; Miller, Y.; Tyminska, N.; Zurek, E.; Chemler, S. R. *Angew. Chem. Int. Ed.* **2014**, *53*, 6383; (g) Hopkins, B. A.; Garlets, Z. J.; Wolfe, J. P. *Angew. Chem. Int. Ed.* **2015**, 54, 13390.

(5) *The Mizoroki–Heck Reaction*; Oestreich, M., Ed.; Wiley: New York, **2009.**

(6) For a related Heck/cyclization sequence leading to indoline derivatives: Hyde, A. M.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2008**, *47*, 177.

(7) Reviews: (a) Martin, R.; Buchwald, S. L. *Acc. Chem. Res.* **2008**, *41*, 1461; (b) Surry, D. S.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2008**, *47*, 6338; (c) Surry, D. S.; Buchwald, S. L. *Chem. Sci.* **2011**, *2*, 27.

(8) (a) Hayashi, T. *Acc. Chem. Res.* **2000**, *33*, 354; (b) Xie, X.; Zhang, T. Y.; Zhang, Z. *J. Org. Chem.* **2006**, *71*, 6522.

(9) (a) Grushin, V. V. *Chem. Rev.* **2004**, *104*, 1629; (b) Grushin, V. V. *Organometallics* **2001**, *20*, 3950.

(10) (a) Shimizu, I.; Matsumoto, Y.; Shoji, K.; Ono, T.; Satake, A.; Yamamoto, A. *Tetrahedron Lett.* **1996**, *37*, 7115; (b) Wöste, T. H.; Oestreich, M. *Chem. Eur. J.* **2011**, *17*, 11914; (c) Wöste, T. H.; Oestreich, M. *ChemCatChem* **2012**, *4*, 2096.

(11) The carboetherification product **3a** was not formed when Binap(O)2 was employed as ligand.

(12) Shimizu, H.; Nagasaki, I.; Matsumura, K.; Sayo, N.; Saito, T. *Acc. Chem. Res.* **2007**, *40*, 1385.

(13) Ozawa, F.; Kubo, A.; Hayashi, T. *Chem. Lett.* **1992**, 2177.

(14) (a) Ji, Y.; Plata, E.; Regens, C. S.; Hay, M.; Schmidt, M.; Razler, T.; Qiu, Y.; Geng, P.; Hsiao, Y.; Rosner, T.; Eastgate, M. D.; Blackmond, D. G. *J. Am. Chem. Soc.* **2015**, *137*, 13272; (b) Li, H.; Belyk, K. M.; Yin, J.; Chen, Q.; Hyde, A.; Ji, Y.; Oliver, S.; Tudge, M. T.; Campeau, L.-C.; Campos, K. R. *J. Am. Chem. Soc.* **2015**, *137*, 13728.

(15) For other relevant contributions, see: (a) Fors, B. P.; Krattiger, P.; Strieter, E.; Buchwald, S. L. *Org. Lett.* **2008**, *10*, 3505; (b) Boezio, A. A.; Pytkowicz, J.; Côté, A.; Charette, A. B. *J. Am. Chem. Soc.* **2005** *125*, 14260; (c) Jian, H.; Hirao, H.; Li, Y.; Zhou, J. *Angew. Chem. Int. Ed.* **2013**, 52, 8676; (d) Hu, J.; Lu, Y.; Li, Y.; Zhou, J. *Chem. Commun.* **2013**, *49*, 9425; (e) Wu, C.; Zhou J. *J. Am. Chem. Soc.* **2014**, *136*, 650

(16) The molecular structure of **3h** was generated using CYLview (Legault, C. Y.: CYLview, version 1.0.561b; Université de Sherbrooke: Sherbrooke, QC, 2009, http://www.cylview.org.

(17) Byproducts resulting from the isomerization of **1c** or **1d** were detected in the ^{1}H NMR analysis of the crude reaction mixtures. These compounds decomposed upon attempt purification by column chromatography.

(18) a) Tschoerner, M.; Pregosin, P. S.; Albinati, A. *Organometallics* **1999**, *18*, 670; b) Borrajo-Calleja, G. M.; Bizet, V.; Bürgi, T.; Mazet, C. *Chem. Sci.* **2015**, *6*, 4807; c) Zhang, Q.-S.; Wan, S.-L.; Chen, D.; Ding, C.-H.; Hou, X.-L. *Chem. Commun.* **2015**, *51*, 12235.

(19) See Supporting Information for details.

(20) Hillers, S.; Reiser, O. *Synlett* **1995**, 153.

(21) Dihydropyrans, 4-substituted-2,3-dihydrofurans and vinyl ethers such as 1-methoxycyclopent-1-ene have not been engaged successfully in the present carboetherification reaction.

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