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Ir(I)-Catalyzed Enantioselective Decarboxylative Allylic Etherification: A General Method for the Asymmetric Synthesis of Aryl Allyl Ethers

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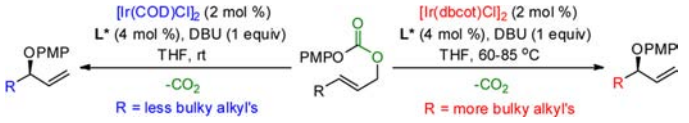
ABSTRACT



Ir(I)-catalyzed enantioselective *decarboxylative* allylic etherification of aryl allyl carbonates provides aryl allyl ethers. Key to the generality and high stereoselection of the reaction is the use of the intramolecular decarboxylative allylation process and $[Ir(dbcot)Cl]_2$ as an Ir(I) source. Ir(I)-catalyzed diastereoselective decarboxylative allylic etherification, combined with asymmetric aldehyde crotylation and cross metathesis, can furnish monoprotected 2-methyl-1,3-diols (starting from simple aldehydes) with high diastereoselectivities.

Enantiomerically enriched aryl allyl ethers are valuable in organic synthesis.[1] Numerous biologically important compounds can be accessed through aryl allyl ethers.[2] Aryl allyl ethers, particularly *p*-methoxylphenyl (PMP-) allyl ethers, can also serve as an alcohol protection group.[3] Moreover, the recent demonstrations of aryl-Claisen [3,3]-sigmatropic rearrangements[4] and Friedel–Crafts type cyclizations[5] of aryl allyl ethers further attest to the importance of aryl allyl ethers in organic synthesis.

Despite such diverse synthetic utility, methods for the asymmetric synthesis of aryl allyl ethers have been sporadically reported, and all reported asymmetric methodologies are based on allylation reactions catalyzed by transition metals such as Pd,[6] Rh,[7] Ru,[8] and Ir.[2c,9] Although these methods sometimes provided aryl allyl ethers at synthetically useful levels of reaction yield and stereoselectivity, they suffered from their own drawbacks requiring (a) preformation of phenoxide anions and proper choice of the counterions for the phenoxide anions,[2c,7,9b,9d] (b) the use of nucleophiles or allylic electrophiles in excess,[6f,8b,9a−9d] and/or (c) the use of optically pure allylic electrophiles (eq 1).[7,8d] Furthermore, when

(1) (a) Trost, B. M.; Crawley, M. L. *Top. Organomet. Chem.* **2011**, *38*, 321. (b) Trost, B. M.; Crawley, M. L. *Chem. Rev.* **2003**, *103*, 2921.

(2) (a) Roughley, S. D.; Jordan, A. M. *J. Med. Chem.* **2011**, *54*, 3451. (b) Clive, D. L. J.; Stoffman, E. J. L. *Org. Biol. Chem.* **2008**, *6*, 1831. (c) He, H.; Ye, K.-Y.; Wu, Q.-F.; Dai, L.-X.; You, S. L. *Adv. Synth. Catal.* **2012**, *354*, 1084. (d) Kompis, I. M.; Islam, K.; Then, R. L. *Chem. Rev.* **2005**, *105*, 593.

(3) Qin, D.; Byun, H.-S.; Bittman, R. *J. Am. Chem. Soc.* **1999**, *121*, 662.

(4) Ramadhar, T. R.; Kawakami, J.-I.; Lough, A. J.; Batey, R. A. *Org. Lett.* **2010**, *12*, 4446.

(5) Medeiros, M. R.; Narayan, R. S.; McDougal, N. T.; Schaus, S. E.; Porco, J. A., Jr. *Org. Lett.* **2010**, *12*, 3222.

(6) (a) Trost, B. M.; Crawley, M. L. *Chem.—Eur. J.* **2004**, *10*, 2237. (b) Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **1999**, *121*, 4545. (c) Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **1998**, *120*, 815. (d) Goux, C.; Massacret, M.; Lhoste, P.; Sinou, D. *Organometallics* **1995**, *14*, 4585. (e) Cannon, J. S.; Olson, A. C.; Overman, L. E.; Solomon, N. S. *J. Org. Chem.* **2012**, *77*, 1961. (f) Kirsch, S. F.; Overman, L. E.; White, N. S. *Org. Lett.* **2007**, *9*, 911.

(7) Evans, P. A.; Leahy, D. K. *J. Am. Chem. Soc.* **2000**, *122*, 5012.

(8) (a) Austeri, M.; Linder, D.; Lacour, J. *Chem.—Eur. J.* **2008**, *14*, 5737. (b) Onitsuka, K.; Okuda, H.; Sasai, H. *Angew. Chem., Int. Ed.* **2008**, *47*, 1454. (c) Mbaye, M. D.; Renaud, J.-L.; Demerseman, B.; Bruneau, C. *Chem. Commun.* **2004**, 1870. (d) Trost, B. M.; Fraisse, P. L.; Ball, Z. T. *Angew. Chem., Int. Ed.* **2002**, *41*, 1059.

(9) (a) Stanley, L. M.; Bai, C.; Ueda, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2010**, *132*, 8918. (b) Leitner, A.; Shu, C.; Hartwig, J. F. *Org. Lett.* **2005**, *7*, 1093. (c) Fischer, C.; Defieber, C.; Suzuki, T.; Carreira, E. M. *J. Am. Chem. Soc.* **2004**, *126*, 1628. (d) Lopez, F.; Ohmura, T.; Hartwig, J. F. *J. Am. Chem. Soc.* **2003**, *125*, 3426.

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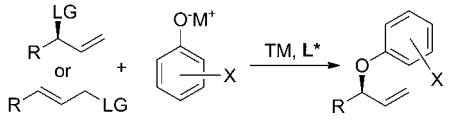
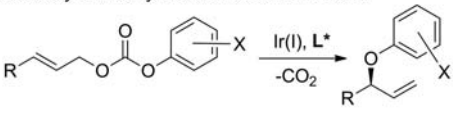
linear allylic electrophiles were used, relatively modest regio- and enantioselectivities were often observed,[6b,6d,8a,8c] and the scope of allylic electrophiles was limited.[6f,8a,8c] Particularly notable in the context of the current work was that only one straight chain aliphatic allylic substrate was used in Ir(I)-catalyzed intermolecular allylic etherification of linear allylic carbonates with phenoxides, and more synthetically useful aliphatic substrates with branched alkyl groups were not reported.[2c,9d] Thus, a general methodology for the asymmetric synthesis of aryl allyl ethers has not been developed. Herein, we describe Ir-catalyzed enantioselective *decarboxylative* allylic etherification as a general method for the asymmetric synthesis of aryl allyl ethers, eliminating all the previous limitations (eqs 1 and 2).[8a,10,11]

Conventional allylic etherification:



(1)

Decarboxylative allylic etherification: this work



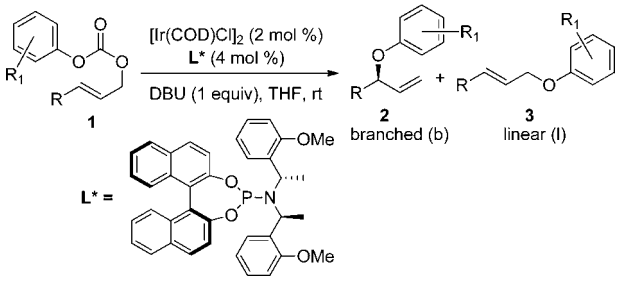
(2)

- Preformation of phenoxide anions (ArO^-) is not required.
- Matching of cation counter-ion (M^+) is not necessary.
- Broad substrate scope accommodating a variety of R-groups including branched R-groups
- High yield as well as good to excellent regio- and enantioselectivity

We recently reported the first Ir(I)-catalyzed enantioselective *decarboxylative* allylic amidation of benzyl allyl imidodicarboxylates by employing a catalytic system involving $[Ir(COD)Cl]_2$, phosphoramidite ligand **L***, DBU, and PS (proton sponge) in THF[12] and wondered if similar catalytic conditions would enable the corresponding enantioselective decarboxylative allylic etherification of aryl allyl carbonates. Initial optimization studies were conducted with phenyl cinnamyl carbonate and phenyl *trans*-2-butenyl carbonate as a representative of aliphatic and aromatic carbonates, respectively. After a variety of bases, phosphoramidite ligands, additives, and solvents were screened, the catalytic conditions employing $[Ir(COD)Cl]_2$ (2 mol %), phosphoramidite ligand **L*** (4 mol %), and DBU (1 equiv) in THF were determined to be optimal, and PS was not necessary.

The scope of Ir-catalyzed enantioselective decarboxylative allylic etherification was studied by varying the aryl part of aryl cinnamyl/*trans*-2-butenyl carbonates, and the results are described in Table 1. It is evident that (a) both electron-donating and -withdrawing groups worked well to give rise to the desired branched allylation products with

Table 1. Ir(I)-Catalyzed Enantioselective Decarboxylative Allylic Etherification of Aryl Allyl Carbonates **1**[a]



entry	R–	R_1–	yield [%][b]	**2**:**3**[c]	*ee* of **2** [%][d]
1	*n*-Pr	H (**a**)	70	92:08	86
2	Ph	H (**b**)	72	>99:01	94
3	*n*-Pr	4-OMe (**c**)	80	94:06	92
4	Ph	4-OMe (**d**)	85	>99:01	>99
5	*n*-Pr	2-OMe (**e**)	78	95:05	93
6	Ph	2-OMe (**f**)	80	>99:01	97
7	*n*-Pr	3,4-$(OMe)_2$ (**g**)	84	97:03	95
8	Ph	3,4-$(OMe)_2$ (**h**)	85	>99:01	nd
9	*n*-Pr	4-Me (**i**)	72	94:06	89
10	Ph	4-Me (**j**)	70	>99:01	98
11	*n*-Pr	2-Me (**k**)	70	94:06	93
12	Ph	2-Me (**l**)	70	>99:01	>99
13	*n*-Pr	2,6-$(Me)_2$ (**m**)	75	98:02	94
14	Ph	2,6-$(Me)_2$ (**n**)	80	>99:01	96
15	*n*-Pr	4-Cl (**o**)	70	89:11	74
16	Ph	4-Cl (**p**)	70	97:03	80
17	*n*-Pr	4-Br (**q**)	80	89:11	75
18	Ph	4-Br (**r**)	78	96:04	76

[a] All reactions were performed at 0.2 mmol scale using 2 mol % $[Ir(COD)Cl]_2$, 4 mol % **L***, and DBU (1 equiv) in 1.5 mL of THF. [b] Isolated yields. [c] Regioselectivities determined by the ^1H NMR spectrum of reaction mixtures. [d] Enantiomeric excesses determined by chiral HPLC.

good to excellent regio- and enantioselectivities, (b) the position of substituents on the phenyl ring exhibited little effect on reaction yield and stereoselectivity, and (c) electron-donating groups showed better regio- and enantioselectivities than electron-withdrawing groups.[13] In general, cinnamyl (R = aromatic) carbonates gave better reaction yields and stereoselectivities than *trans*-2-butenyl (R = aliphatic) carbonates.

Noting that electron-donating substituents gave rise to higher reaction yields and stereoselectivities in the above allylation reactions and that the *p*-methoxyphenyl (PMP) group can serve as a good alcohol protection group,[5] the reaction scope was further explored by employing a wide range of R-groups for the allyl part of aryl allyl carbonates and fixing the aryl part as PMP. As shown in Table 2, synthetically useful levels of reaction yield and

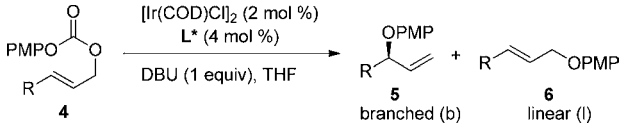
(10) (a) Hartwig, J. F.; Pouy, M. J. *Top. Organomet. Chem.* **2011**, *34*, 169. (b) Helmchen, G.; Dahnz, A.; Düebon, P.; Schelwies, M.; Weihofen, R. *Chem. Commun.* **2007**, 675.

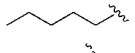
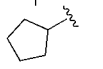
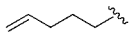
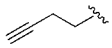
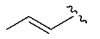
(11) Weaver, J. D.; Recio, A.; Grenning, A. J.; Tunge, J. A. *Chem. Rev.* **2011**, *111*, 1846.

(12) (a) Singh, O. V.; Han, H. *J. Am. Chem. Soc.* **2007**, *129*, 774. (b) Singh, O. V.; Han, H. *Org. Lett.* **2007**, *9*, 4801.

(13) Strongly electron-withdrawing groups did not work well: with 4-CF_3, the allylic etherification reaction proceeded with modest reaction yield (48%) and regioselectivity (7:3), and with 4-NO_2, the desired etherification product did not form, instead cleavage of the carbonate occurred.

Table 2. Ir(I)-Catalyzed Enantioselective Decarboxylative Allylic Etherification of PMP Allyl Carbonates **4**[a]



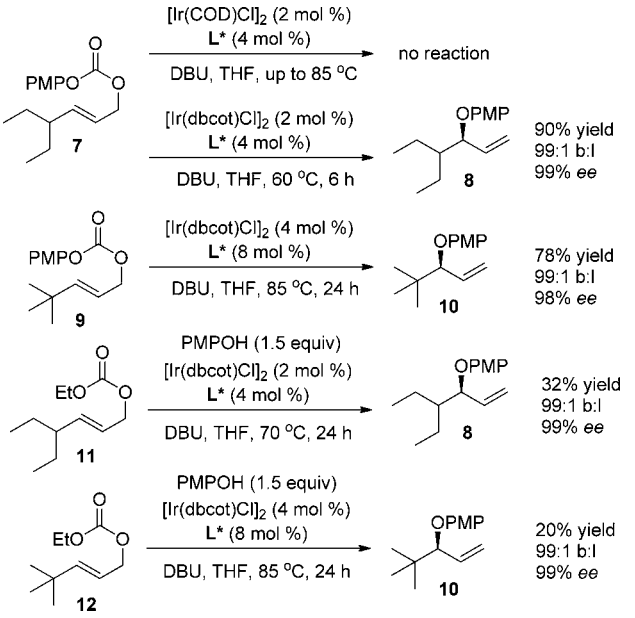
entry	R-	temp [°C]	yield [%][b]	**5**:**6**[c]	*ee* of **5** [%][d]
1	 (**a**)	25	84	96:04	96
2	 (**b**)	25	82	90:10	99
3	 (**c**)	25	84	93:07	99
4	TBDPSO(CH2)3- (**d**)	25	88	92:08	95
5	Br- (**e**)	25	91	87:13	99
6	 (**f**)	25	80	96:04	96
7	 (**g**)	25	83	90:10	95
8	 (**h**)	25	80	93:07	99
9	4-Br-C_6H_4- (**i**)	25	85	99:01	96
10	2-Br-C_6H_4- (**j**)	60	56	99:01	75
11	4-OMe-C_6H_4- (**k**)	25	91	99:01	99
12	2-OMe-C_6H_4- (**l**)	25	78	99:01	99
13	4-*iPr*-C_6H_4- (**m**)	25	75	99:01	98

[a] All reactions were performed at 0.2 mmol scale using 2 mol % $[Ir(COD)Cl]_2$, 4 mol % **L***, and DBU (1 equiv) in 1.5 mL of THF. [b] Isolated yields. [c] Regioselectivities determined by the ^1H NMR spectrum of reaction mixtures. [d] Enantiomeric excesses determined by chiral HPLC.

stereoselectivity were obtained in all cases studied. Linear alkyl (entry 1), branched alkyl (entry 2), and cyclic alkyl (entry 3) groups proceeded with good to excellent regio- and enantioselectivities, as did functionalized alkyl groups with ether, halide, double bond, and triple bond functionalities (entries 4–8). A variety of aryl groups with an electron-donating or -withdrawing group (entries 9 and 11–13) also worked well. The position of those substituents had little effect on reaction yield and stereoselectivity, except one case (R = 2-Br-C_6H_4) that required elevated temperature and proceeded with relatively modest enantioselectivity (entry 10, *ee* = 75%).

Encouraged by the excellent enantioselectivities observed with branched aliphatic alkyl groups (entries 2 and 3 in Table 2), Ir(I)-catalyzed enantioselective decarboxylative allylic etherification reactions of PMP allyl carbonates **7** and **9** with the bulkier branched alkyl groups were studied. As shown in Scheme 1, when **7** was subjected to the catalytic conditions, the desired allylic etherification reaction did not occur and the starting material remained unreacted up to 85 °C for 25 h. Based on the reasoning that

Scheme 1. Ir(I)-Catalyzed Enantioselective Decarboxylative Allylic Etherification Reactions of Allyl Carbonates **7** and **9** with a Bulky Alkyl Side Chain as well as the Corresponding Intermolecular Versions



the active catalyst generated from $[Ir(COD)Cl]_2$ might not survive under elevated temperatures for prolonged reaction times and that $[Ir(dbcot)Cl]_2$ would generate the more robust catalysts,[14] the catalytic conditions using $[Ir(dbcot)Cl]_2$ instead of $[Ir(COD)Cl]_2$ were attempted for the allylic etherification of **7**. Gratifyingly, the reaction proceeded cleanly at 60 °C to give the desired branched allylation product **8** in 6 h with excellent reaction yield and stereoselectivities (Scheme 1). Remarkably, the modified catalytic conditions employing $[Ir(dbcot)Cl]_2$ enabled the enantioselective allylic etherification of even bulkier carbonate **9** with the allyl part bearing a *t*-Bu group in 24 h. To our knowledge, enantioselective installation of a C–O bond at such a neopentyl carbon by transition metal catalyzed allylation of linear allylic substrates has never been accomplished before.[15]

To assess the advantages of decarboxylative allylic etherification over traditional intermolecular allylic etherification, the corresponding intermolecular versions of the above two reactions were studied under otherwise identical conditions except that 1.5 equiv of PMPOH were externally added to ethyl allyl carbonates **11** and **12** (Scheme 1). Similar levels of enantio- and diastereoselectivities were observed from these reactions, but reaction yields dropped significantly to 32% and 20%, respectively, even after heating at

(14) Spiess, S.; Welter, C.; Frank, G.; Taquet, J.-P.; Helmchen, G. *Angew. Chem., Int. Ed.* **2008**, *47*, 7652.

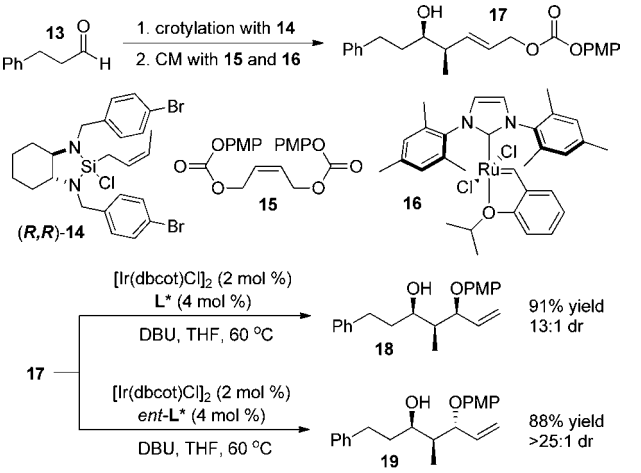
(15) In ref 9a, the Hartwig group reported that an Ir-catalyzed intermolecular allylic etherification reaction between NaOPh and a branched allylic benzoate in which the allyl unit is substituted with a *t*-Bu group occurred at 50 °C to give the desired allyl aryl ether product. However, when the corresponding linear allylic benzoate (which is known to be less reactive than the branched isomer) was used, the allylic etherification reaction did not occur.

higher temperatures for 24 h. These results, taken together with those in Tables 1 and 2, demonstrate the clear advantage of Ir-catalyzed enantioselective decarboxylative allylic etherification over the intermolecular counterpart.[16]

To highlight a synthetic utility of the Ir(I)-catalyzed decarboxylative allylic etherification, we chose to synthesize monoprotected 2-methyl-1,3-diols, which are common structural motifs in natural products.[17,18] Asymmetric crotylation of hydrocinnamaldehyde (**13**) by (*R,R*)-**14**[19] followed by cross-metathesis (CM) of the resulting alkene with **15** in the presence of Hoveyda–Grubbs second–generation catalyst **16** delivered PMP allyl carbonate **17** in 83% yield and with >25:1 *E*/*Z* selectivity (Scheme 2).[20] When **17** was subjected to the catalytic conditions employing **L***, aryl allyl ether **18** was obtained in 91% yield and with 13:1 diastereoselectivity. On the other hand, the use of *ent*-**L*** in otherwise identical conditions gave rise to the corresponding diastereomer **19** in 88% yield and with >25:1 diastereoselectivity. These results clearly indicate that the stereochemical outcome of the Ir(I)-catalyzed decarboxylative allylic etherification is predominantly governed by the stereochemistry of a phosphoramidite ligand used (reagent-controlled), and the existing chiral center has little effect on reaction stereochemistry.

In summary, we have developed the Ir-catalyzed enantioselective *decarboxylative* allylic etherification as a general method for the asymmetric synthesis of aryl allyl ethers and demonstrated that the substrate scope of the reaction is greatly expanded by using $[Ir(dbcot)Cl]_2$ as an Ir(I) source. The method, combined with other transition metal catalyzed allylation reactions for the asymmetric synthesis of alkyl allyl ethers,[21] allylic alcohols,[22] and allylic esters,[23] should be able to provide a convenient synthetic tool box for the enantioselective introduction of an allylic C–O bond. Also developed is a very efficient synthetic strategy consisted of asymmetric aldehyde crotylation, CM, and the Ir(I)-catalyzed decarboxylative allylic etherification for the asymmetric synthesis of monoprotected 2-methyl-1,3-diol motifs.

Scheme 2. Asymmetric Synthesis of Monoprotected 2-Methyl-1,3-diols **18** and **19**



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Supporting Information Available. Experimental procedures and spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(16) Similar advantages were observed in Pd-catalyzed allylation: (a) Trost, B. M.; Schäffner, B.; Osipov, M.; Wilton, D. A. A. *Angew. Chem., Int. Ed.* **2011**, *50*, 3548. (b) Trost, B. M.; Xu, J.; Schmidt, T. *J. Am. Chem. Soc.* **2009**, *131*, 18343.

(17) (a) Paterson, I.; Paquet, T.; Dalby, S. M. *Org. Lett.* **2011**, *13*, 4398. (b) Paterson, I.; Razzak, M.; Anderson, E. A. *Org. Lett.* **2008**, *10*, 3295. (c) Lanners, S.; Norouzi-Arasi, H.; Salom-Roig, X. J.; Hanquet, G. *Angew. Chem., Int. Ed.* **2007**, *46*, 7086.

(18) For recent synthetic approaches, see: (a) Gao, X.; Han, H.; Krische, M. J. *J. Am. Chem. Soc.* **2011**, *133*, 12795. (b) Ichibakase, T.; Nakajima, M. *Org. Lett.* **2011**, *13*, 1579. (c) Dorgan, P. D.; Durrani, J.; Cases-Thomas, M. J.; Hulme, A. N. *J. Org. Chem.* **2010**, *75*, 7475. (d) Rohr, K.; Herre, R.; Mahrwald, R. *J. Org. Chem.* **2009**, *74*, 3744. (e) Mlynarski, J.; Rakiel, B.; Stodulski, M.; Suszczyńska, A.; Frelek, J. *Chem.—Eur. J.* **2006**, *12*, 8158. (f) Gnanadesikan, V.; Horiuchi, Y.; Oshima, T.; Shibasaki, M. *J. Am. Chem. Soc.* **2004**, *126*, 7782. (g) Mascarenhas, C. M.; Miller, S. P.; White, P. S.; Morken, J. P. *Angew. Chem., Int. Ed.* **2001**, *40*, 601.

(19) (a) Leighton, J. L. *Aldrichimica Acta* **2010**, *43*, 3. (b) Kim, H.; Ho, S.; Leighton, J. L. *J. Am. Chem. Soc.* **2011**, *133*, 6517.

(20) (a) Kingsbury, J. S.; Harrity, J. P. A.; Bonitatebus, P. J., Jr.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1999**, *121*, 791. (b) Hoveyda, A. H.; Lombardi, P. J.; O'Brien, R. V.; Zhugralin, A. R. *J. Am. Chem. Soc.* **2009**, *131*, 8378. (b) Vougioukalakis, G. C.; Grubbs, R. H. *Chem. Rev.* **2010**, *110*, 1746.

(21) (a) Roggen, M.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2011**, *50*, 5568. (b) Ueno, S.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2008**, *47*, 1928. (c) Evans, P. A.; Leahy, D. K. *J. Am. Chem. Soc.* **2002**, *124*, 7882.

(22) (a) Gärtner, M.; Mader, S.; Seehafer, K.; Helmchen, G. *J. Am. Chem. Soc.* **2011**, *133*, 2072. (b) Kanbayashi, N.; Onitsuka, K. *Angew. Chem., Int. Ed.* **2011**, *50*, 5197.

(23) (a) Fischer, C.; Defieber, C.; Suzuki, T.; Carreira, E. M. *J. Am. Chem. Soc.* **2004**, *126*, 1628. (b) Cannon, J. S.; Kirsch, S. F.; Overman, L. E. *J. Am. Chem. Soc.* **2010**, *132*, 15185. (c) Takii, K.; Kanbayashi, N.; Onitsuka, K. *Chem. Commun.* **2012**, *48*, 3872. (d) Geurts, K.; Fletcher, S. P.; Feringa, B. L. *J. Am. Chem. Soc.* **2006**, *128*, 15572. (e) Koschker, P.; Lumbroso, A.; Breit, B. *J. Am. Chem. Soc.* **2011**, *133*, 20746. (f) Lumbroso, A.; Koschker, P.; Vautravers, N. R.; Breit, B. *J. Am. Chem. Soc.* **2011**, *133*, 2386. (g) Kanbayashi, N.; Onitsuka, K. *J. Am. Chem. Soc.* **2010**, *132*, 1206.

The authors declare no competing financial interest.