JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
Communication
pubs.acs.org/JACS

Enantio- and Regioselective Iridium-Catalyzed Allylic Esterification

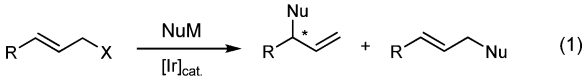
Jianping Qu, Lydia Roßberg, and Günter Helmchen*

Organisch-Chemisches Institut der Ruprecht-Karls-Universität Heidelberg, Im Neuenheimer Feld 270, D-69120 Heidelberg, Germany

Supporting Information

ABSTRACT: A highly enantioselective and regioselective Ir-catalyzed allylic esterification is described, in which branched allylic esters are synthesized directly. Carboxylates were used as nucleophiles and linear allylic phosphates as electrophiles. In some cases the allylic substitution reaction was found to be accompanied by a kinetic resolution process, which causes a change of the enantiomeric excess.

Asymmetric allylic substitution has found numerous applications in organic synthesis.[1] After years of predominance by Pd-catalysis, catalysts based on other metals have been gaining importance, particularly for reactions of monosubstituted allylic substrates to give branched products (eq 1).



(1)

Among these, the iridium-catalyzed asymmetric allylic substitution offers a very broad scope, particularly with respect to the range of possible nucleophiles.[2] As catalysts, (allyl)Ir complexes derived in situ from $[Ir(cod)Cl]_2$ and a phosphoramidite by treatment with base have most often been used (Figure 1). More recently, pure (π-allyl)Ir complexes **C** have become readily available,[3] which are air stable and are now often used as single component catalysts.[2c−e]

Regioselectivity can be low with allylic substrates carrying an sp^3 bound substituent R. In such cases, replacement of cod by dbcot (dbcot = dibenzocyclooctatetraene) generally gives improved results.[4] In addition, reactions catalyzed by dbcot complexes can be run under air, tolerate a wide variety of solvents, and can be run at higher temperatures than reactions catalyzed by cod complexes.

Over the past few years, allylic substitutions with O-nucleophiles have received considerable attention. While good results were obtained for reactions with phenolates and alkoxides,[5] water and carboxylates turned out to be problematic nucleophiles, necessitating the use of water surrogates, such as silanoates.[6] We were able to solve the "water problem" by using bicarbonate as the nucleophile in conjunction with allylic carbonates as electrophiles and catalysts **C2** or **C3** in an aqueous reaction medium.[7] Concerning allylic esterification with Ir catalysts, only kinetic resolutions with branched allylic esters as substrates have been reported (Carreira[8a] and Hartwig's[8b] group). Hartwig et al. observed a remarkably high selectivity factor for kinetic resolutions with branched allylic benzoates.[8b] More but still limited success was obtained with other transition metal catalysts. Onitsuka et al. developed Ru-catalyzed reactions of (*E*)-allylic chlorides; however, high ee was only achieved in the case of arylallyl chlorides.[9] The catalyst requires an elaborate synthesis involving ∼10 linear steps, which is a serious impediment to applications.[10] Overman and Kirsch accomplished asymmetric Pd-catalyzed allylic esterifications with (*Z*)-allylic trichloroacetimidates, albeit with a narrow substrate scope excluding sp^2 bound substituents, i.e., aryl and alkenyl groups.[11]

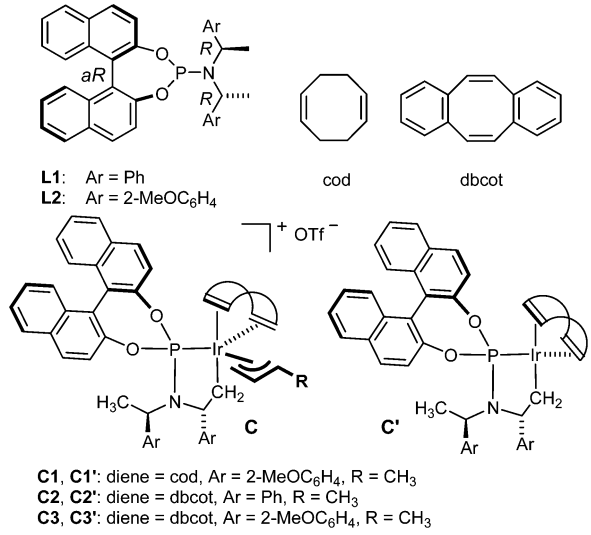


Figure 1. Ligands and (π-allyl)Ir complexes used in this work.

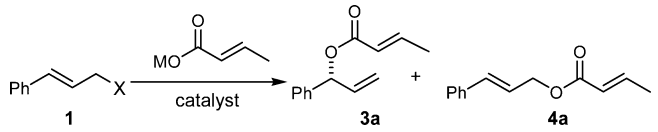
Thus, the development of a generally applicable allylic esterification appeared as a true challenge, which we have accepted. Herein we are pleased to report the first transition-metal-catalyzed asymmetric esterification with linear allylic substrates with broad substrate scope and catalyst loading as low as 0.2 mol %. Exploratory experiments were carried out with carboxylates containing a double bond, e.g., crotonates, in order to ensure synthetic applications via ring closing metathesis.[12]

We initially used cinnamyl derivatives **1a−e** as substrates (Table 1), because it was known that esters of branched arylallylic alcohols can undergo an Ir-catalyzed rearrangement, via (π-allyl)Ir complexes, to the linear esters.[8b] This process could lead to reduced yield and ee of the branched product. (*E*)-Crotonate was employed as the standard nucleophile. Using *ent*-**C1** as catalyst, the phosphate **1d** gave promising results, whereas the carbonate **1a**, the chloride **1b**, and the

Received: November 21, 2013
Published: January 14, 2014

 © 2014 American Chemical Society dx.doi.org/10.1021/ja411869r | J. Am. Chem. Soc. 2014, 136, 1272−1275

Table 1. Optimization of Reaction Variables Using 3-Phenylallylic Substrates[a]

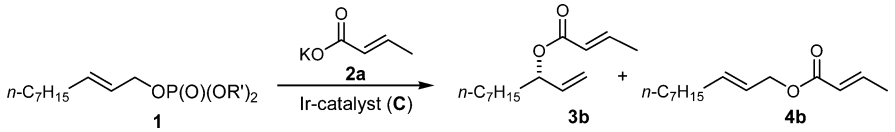


1 3a 4a

entry	X	1	M	1/2	catalyst	temp (°C)	time (h)	*ent*-3a/4a[b]	yield (%)[c]	ee (%)[d]
1	OCO_2Me	**1a**	K	2:1	*ent*-**C1**	45	24	1:5	nd	13
2	Cl	**1b**	K	2:1	*ent*-**C1**	45	2	>20:1	61	43
3	$OCNHCCl_3$	**1c**	K	2:1	*ent*-**C1**	45	24	nd	<10	nd
4	$OP(O)(OEt)_2$	**1d**	K	2:1	*ent*-**C1**	45	2	>10:1	nd	75
5	$OP(O)(OEt)_2$	**1d**	Na	2:1	*ent*-**C1**	rt	24	6:1	40	84
6	$OP(O)(OEt)_2$	**1d**	Li	2:1	*ent*-**C1**	rt	24	6:1	28	88
7	$OP(O)(OEt)_2$	**1d**	K	2:1	*ent*-**C2**	45	2	>10:1	nd	80
8	$OP(O)(OEt)_2$	**1d**	K	2:1	*ent*-**C3**	45	0.5	>20:1	80	88
9	$OP(O)(OEt)_2$	**1d**	Cs	2:1	*ent*-**C3**	rt	1	>10:1	80	92
10	$OP(O)(OEt)_2$	**1d**	K	2:1	*ent*-**C3**	rt	2	>10:1	63	91
11	$OP(O)(OEt)_2$	**1d**	Na	2:1	*ent*-**C3**	rt	5	>10:1	80	91
12	$OP(O)(OEt)_2$	**1d**	Li	2:1	*ent*-**C3**	rt	6	>10:1	68	92
13	$OP(O)(OEt)_2$	**1d**	K	2:1	*ent*-**C3**	0	0.5	>20:1	60	90
14	$OP(O)(OEt)_2$	**1d**	K	1.05:1	*ent*-**C3**	0	1.0	8:1	65	89
15	$OP(O)(OEt)_2$	**1d**	K	1:1.5	*ent*-**C3**	0	1.0	6:1	63	89
16	$OP(O)(OEH)_2$[e]	**1e**	K	1.05:1	*ent*-**C3**	0	4.0	>20:1	60	94

[a]Conditions: argon atmosphere, **1** (2.0 equiv), crotonic acid salt (1.0 equiv), catalyst (4 mol %), THF (10 mL/mmol of **2**). [b]Determined by ^{1}H NMR analysis of the crude product. [c]Isolated yield of branched product; nd = not determined. [d]Determined by HPLC on a chiral column. [e](EH = 2-ethylhexyl).

Table 2. Optimization of Reaction Conditions for 3-Heptyl-allyl Phosphates and the Crotonate 2a as Substrates (EH = 2-Ethylhexyl)[a]



1 3b 4b

entry	X (substrate)	1	catalyst (mol %)	solvent	temp (°C)	time (h)	3/4[b]	yield[c] (conv)[d] (%)	ee (%)[e]
1	$OP(O)(OEt)_2$	**1f**	*ent*-**C3** (4)	THF	0	0.5	20:1	nd (95)	70
2	$OP(O)(OiPr)_2$	**1g**	*ent*-**C3** (4)	THF	0	1	20:1	nd	79
3	$OP(O)(OtBu)_2$	**1h**	*ent*-**C3** (4)	THF	0	1	>20:1	nd	79
4	$OP(O)(OEH)_2$	**1i**	*ent*-**C3** (4)	THF	0	5	>20:1	nd	85
5	$OP(O)(OEH)_2$	**1i**	*ent*-**C3** (4)	THF	−20	8	>20:1	54 (70)	75
6	$OP(O)(OEH)_2$	**1i**	*ent*-**C3** (1)	THF	rt	2	>20:1	77	92.5
7	$OP(O)(OEH)_2$	**1i**	**C3** (1)	*t*-BuOMe	rt	0.5	>20:1	89	93
8	$OP(O)(OEH)_2$	**1i**	**C3** (0.5)	*t*-BuOMe	rt	2	>20:1	80	93
9[f]	$OP(O)(OEH)_2$	**1i**	**C3** (0.5)	*t*-BuOMe	rt	3	>20:1	75	95.5
10[f]	$OP(O)(OEH)_2$	**1i**	**C3** (0.2)	*t*-BuOMe	35	12	20:1>	60	94.5
11[g]	$OP(O)(OEH)_2$	**1i**	**C3** (0.5)	*t*-BuOMe	rt	0.5	>20:1	90	77
12	$OP(O)(OEH)_2$	**1i**	**C3** (0.5)[i]	*t*-BuOMe	rt	3	>20:1	70	98
13[h]	$OP(O)(OEH)_2$	**1i**	**C3** (0.5)[i]	*t*-BuOMe	rt	3	>20:1	70	99
14[j]	$OP(O)(OEH)_2$	**1i**	**C3** (0.5)[i]	*t*-BuOMe	rt	1.5	>20:1	73	96
15[k]	$OP(O)(OEH)_2$	**1i**	**C3** (0.5)[i]	*t*-BuOMe	rt	3.5	>20:1	71	95
16	$OP(O)(OEH)_2$	**1i**	**C3** (0.5)[i,l]	*t*-BuOMe	rt	2.5	>20:1	70	98

[a]Conditions: argon atmosphere, phosphate **1** (1.05 equiv), nucleophile **2a** (1.0 equiv), catalyst *ent*-**C3** or **C3** (4−0.2 mol %), dry solvent (10 mL/mmol of **2a**). [b]Regioselectivity was determined by ^{1}H NMR analysis of the crude product. [c]Isolated yield of branched product. [d]Conversion of **1** was determined by ^{1}H NMR of the crude product. [e]Determined by GC on a chiral column. [f]Reaction mixture was subjected to freeze−pump−thaw degassing. [g]2.8 equiv of water was added. [h]MS 4 Å was added (200 mg/mmol). [i]A mixture of **C3** and **2a** was kept under oil pump vacuum for 10 min, then argon was introduced and further components were added. [j]c = 0.2 M. [k]c = 0.5 M. [l]Reaction in air.

trichloroacetimidate **1c** were found to be unsuitable substrates (Table 1, entries 1−6). Significant improvement of enantio- as well as regioselectivity and rate were obtained with the dbcot complexes *ent*-**C2** and *ent*-**C3** as catalysts (entries 7, 8). The branched/linear (b/l) ratio (*ent*-**3**/**4**) was high, when the allylic component **1** was used in excess (cf. entries 13−15); we used a 5% excess of **1** in all further reactions. Under these conditions an allyl complex **C** is expected to be the resting state[3] of the reaction (see below). Further investigation of the reaction conditions revealed that the reaction selectivity is insensitive to temperature

dx.doi.org/10.1021/ja411869r | J. Am. Chem. Soc. 2014, 136, 1272−1275

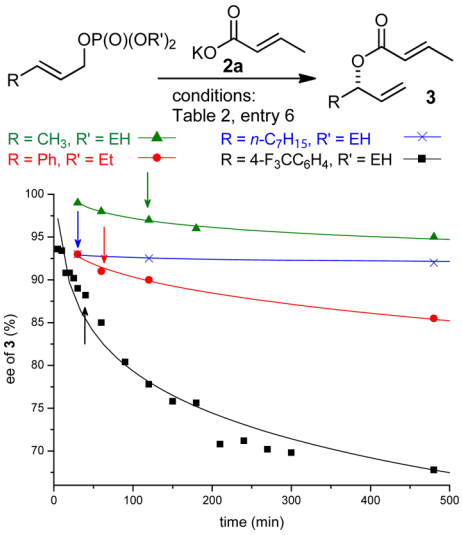
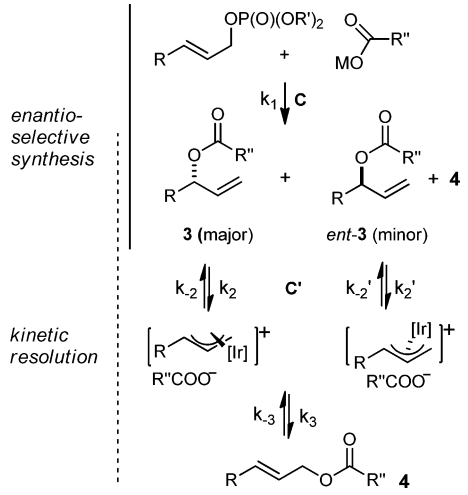


Figure 2. Dependence of enantioselectivity on time for allylic esterifications of arylallyl and alkylallyl substrates. The arrows mark workup of the substitution reactions (EH = 2-ethylhexyl).

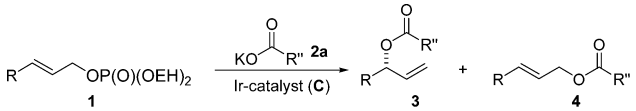
Scheme 1. Mechanistic Rationale of a Combined Allylic Substitution/Kinetic Resolution

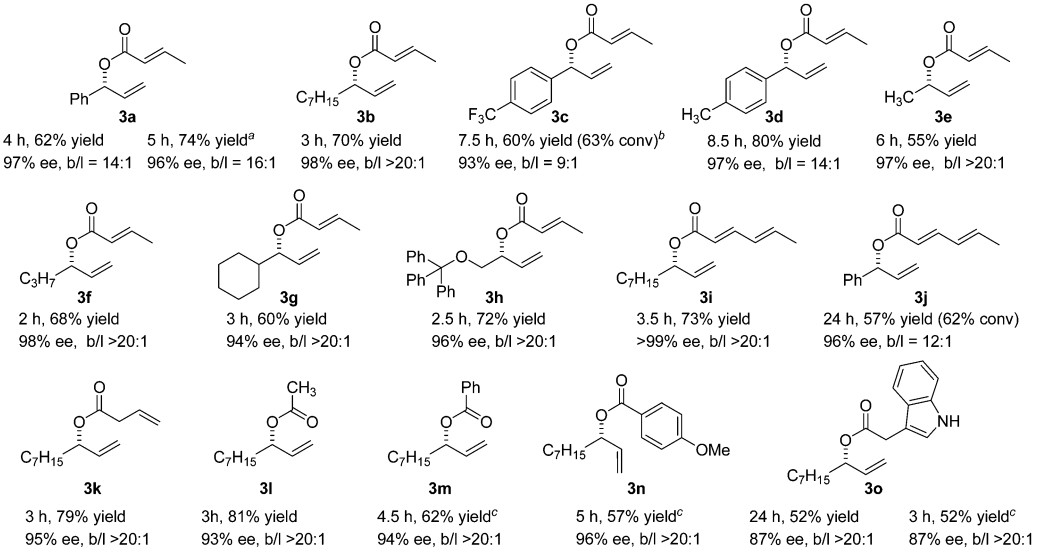


in the range 0−30 °C. However, selectivity and rate are fairly sensitive to the counterion of the carboxylate; faster reactions were obtained with Cs^+ and K^+ than Na^+ and Li^+ (entries 4−6 and 9−12). Potassium salts were henceforth used.

Substrates with aryl substituents often give rise to particularly high selectivities. Initial experiments with substrate **1f**, R = *n*-heptyl, and potassium crotonate were disappointing; while regioselectivity was high, the ee was low (Table 2, entry 1). The b/l ratio and ee were improved by increasing the size of the leaving group (entries 1−4). The readily available di-(2-ethylhexyl)-phosphates showed high reactivity (entry 6), gave optimal selectivity, and were henceforth generally employed.[13] An improvement was also found for the corresponding cinnamyl derivative (Table 1, entry 16). Solvent tests demonstrated that toluene and ethers give rise to high ees, while polar solvents give rise to low ees (see Supporting Information, SI). Commercial dry grade *t*-BuOMe was chosen as a standard solvent (entry 7). Rearrangement of the branched to the linear product, even with an excess of the nucleophile, was not observed with substrate **1f**. The catalyst loading could be reduced to 0.2 mol % without substantial decrease in yield or ee (entries 8−10). In view of previous results with aqueous reaction media,[7a,14] it was a surprise that water as an additive led to a marked decrease of the enantiomeric excess (entry 11). As a consequence, catalyst **C3** and salt **2a** were dried prior to the reaction; this led to a distinct increase of enantioselectivity (entry 12). Addition of MS 4 Å further improved the ee to 99% (entry 13). In order to get a value of the reaction time not biased by low solubility of

Table 3. Branched Allylic Esters Prepared by Ir-Catalyzed Allylic Substitution Using Conditions According to Table 2, Entry 12[d]





[a]Diethyl phosphate **1d** was used instead of **1e**. [b]1 mol % of **C3**. [c]2 mol % of **C3**. [d]For definition of substrates and linear esters see the SI.

dx.doi.org/10.1021/ja411869r | J. Am. Chem. Soc. 2014, 136, 1272−1275

the salt **2a**, a rather low standard concentration of 0.1 M was chosen. However, the reaction could be run at higher concentration, with a small accompanied decrease of the ee (entries 14, 15). Finally, it was possible to carry out reactions in air (entry 16).

As mentioned above, the rearrangement of the branched to the linear isomers is potentially accompanied by a decrease of the ee. Therefore, time dependence of the ee was investigated in detail with representative substrates using THF as the solvent (Figure 2). A marked decrease in ee was found for arylallyl substrates and a crotyl derivative (R = CH_3), while the ee was constant for another alkylallyl compound (R = *n*-heptyl). Generally, the effect is small during the reaction time.

A rationale for the decrease of the ee over time is represented in Scheme 1. The allylic substitution promoted by catalysts of type **C** via the standard catalytic cycle[3] (see SI) yields the ester **3** as the major and *ent*-**3** as the minor branched product and the linear isomer **4**. As already observed by Hartwig et al.,[8b] branched allylic esters can undergo kinetic resolution with a high selectivity factor.[15] In the present case, kinetic resolution involves reaction of the branched isomer **3** with the 16 e^- complex **C′** (Figure 1). **C′** is formed in the catalytic cycle, at a rate $k_2 < k_1$ but $k_2 > k_2'$ to give the linear isomer **4** in a practically irreversible step because $k_{-3} \ll k_1$. As the major branched product is both formed faster and removed more rapidly than the minor one, the mixture is depleted of the major enantiomer, and the ee slowly decreases.[16]

The scope of the esterification reaction was explored using the optimal conditions (Table 2, entry 12) in conjunction with catalyst **C3**. The results presented in Table 3 demonstrate that even with substrates containing an sp^2 substituent (R) the ee is generally high, if the reaction is stopped at 62−85% conversion in order to prevent further rearrangement. We also reexamined the phosphate leaving group. For the formation of **3a**, diethyl phosphate **1d** was as well suited as the more complicated phosphate **1e**.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

g.helmchen@oci.uni-heidelberg.de

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the Deutsche Forschungsgemeinschaft (SFB 623) and the Fonds der Chemischen Industrie. J.Q. thanks the Alexander von Humboldt foundation for a scholarship. We thank Mascha Jäkel for samples of the catalysts and Prof. K. Ditrich (BASF SE) for enantiomerically pure 1-arylethylamines, and Dr. S. C. E. Stieber for linguistic polishing of the manuscript.

■ REFERENCES

(1) Reviews covering the whole field of allylic substitutions: (a) Trost, B. M.; Lee, C. In *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley-VCH: New York, 2010, pp 593−649. (b) Lu, Z.; Ma, S. *Angew. Chem., Int. Ed.* **2008**, *47*, 258. (c) Helmchen, G.; Kazmaier, U.; Förster, S. In *Catalytic Asymmetric Synthesis*, 3rd ed.; Ojima, I., Ed.; Wiley-VCH: New York, 2010, pp 497−461.

(2) (a) Helmchen, G.; Dahnz, A.; Dübon, P.; Schelwies, M.; Weihofen, R. *Chem. Commun.* **2007**, 675. (b) Helmchen, G. In *Iridium Complexes in Organic Synthesis*; Oro, L. A., Claver, C., Eds.; Wiley-VCH: Weinheim, 2009, pp 211−250. (c) Hartwig, J. F.; Stanley, L. M. *Acc. Chem. Res.* **2010**, *43*, 1461. (d) Liu, W.-B.; Xia, J.-B.; You, S.-L. *Top. Organomet. Chem.* **2012**, *38*, 155. (e) Tosatti, P.; Nelson, A.; Marsden, S. P. *Org. Biomol. Chem.* **2012**, *10*, 3147.

(3) (a) Spiess, S.; Raskatov, J. A.; Gnamm, C.; Brödner, K.; Helmchen, G. *Chem.—Eur. J.* **2009**, *15*, 11087. (b) Raskatov, J. A.; Spiess, S.; Gnamm, C.; Brödner, K.; Rominger, F.; Helmchen, G. *Chem.—Eur. J.* **2010**, *16*, 6601. (c) For an alternative preparation: Madrahimov, S. T.; Markovic, D.; Hartwig, J. F. *J. Am. Chem. Soc.* **2009**, *131*, 7228.

(4) (a) Spiess, S.; Welter, C.; Franck, G.; Taquet, J.-P.; Helmchen, G. *Angew. Chem., Int. Ed.* **2008**, *47*, 7652. (b) Raskatov, J. A.; Jäkel, M.; Straub, B. F.; Rominger, F.; Helmchen, G. *Chem.—Eur. J.* **2012**, *18*, 14314.

(5) (a) Lopez, F.; Ohmura, T.; Hartwig, J. F. *J. Am. Chem. Soc.* **2003**, *125*, 3426. (b) Welter, C.; Dahnz, A.; Brunner, B.; Streiff, S.; Dübon, P.; Helmchen, G. *Org. Lett.* **2005**, *7*, 1239. (c) Leitner, A.; Shu, C.; Hartwig, J. F. *Org. Lett.* **2005**, *7*, 1093.

(6) Lyothier, I.; Defieber, C.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2006**, *45*, 6204.

(7) (a) Gärtner, M.; Mader, S.; Seehafer, K.; Helmchen, G. *J. Am. Chem. Soc.* **2011**, *133*, 2072. (b) Slightly later the allylic hydroxylation was successfully accomplished with a Ru-catalyst: Kanbayashi, N.; Onitsuka, K. *Angew. Chem., Int. Ed.* **2011**, *50*, 5197.

(8) (a) Fischer, C.; Defieber, C.; Suzuki, T.; Carreira, E. M. *J. Am. Chem. Soc.* **2004**, *126*, 1628. (b) Stanley, L. M.; Bai, C.; Ueda, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2010**, *132*, 8918.

(9) Kanbayashi, N.; Onitsuka, K. *J. Am. Chem. Soc.* **2010**, *132*, 1206.

(10) Synthesis of the Ru catalyst: (a) Hatanaka, M.; Himeda, Y.; Ueda, I. *J. Chem. Soc., Perkin Trans. 1* **1993**, *19*, 2269. (b) Komatsuzaki, N.; Uno, M.; Kikuchi, H.; Takahashi, S. *Chem. Lett.* **1996**, *8*, 677. (c) Dodo, N.; Matsushima, Y.; Uno, M.; Onitsuka, K.; Takahashi, S. *J. Chem. Soc., Dalton Trans.* **2000**, 35. (d) Matsushima, Y.; Komatsuzaki, N.; Ajioka, Y.; Yamamoto, M.; Kikuchi, H.; Takata, Y.; Dodo, N.; Onitsuka, K.; Uno, M.; Takahashi, S. *Bull. Chem. Soc. Jpn.* **2001**, *73*, 527. (e) A simplified version of the Onitsuka catalyst and a few examples of esterification with arylallyl substrates, which gave 88−93% ee, were recently reported: Trost, B. M.; Rao, M.; Dieskau, A. P. *J. Am. Chem. Soc.* **2013**, *135*, 18697.

(11) (a) Kirsch, S. F.; Overman, L. E. *J. Am. Chem. Soc.* **2005**, *127*, 2866. (b) Cannon, J. S.; Kirsch, S. F.; Overman, L. E. *J. Am. Chem. Soc.* **2010**, *132*, 15185.

(12) (a) Kirsch, S. F.; Klahn, P.; Menz, H. *Synthesis* **2011**, 3592. (b) Takii, K.; Kanbayashi, N.; Onitsuka, K. *Chem. Commun.* **2012**, *48*, 3872.

(13) Phosphates are routinely used as substrates for allylic substitutions. However, allylic di-(2-ethylhexyl) phosphates have only once been employed to the best of our knowledge: Zhong, C.; Kunii, S.; Kosaka, Y.; Sawamura, M.; Ito, H. *J. Am. Chem. Soc.* **2010**, *133*, 11441.

(14) Ueda, M.; Hartwig, J. F. *Org. Lett.* **2010**, *12*, 92.

(15) We have determined the selectivity factor of the kinetic resolution of racemic **3c** (cf. Table 3) with potassium crotonate (**2a**) as $s = 42$ (see SI). The determination was carried out according to a method described in Kagan, H. G; Fiaud, J. C. *Topics in Stereochemistry*; Wiley: New York, 1988; Vol. *18*, p 249.

(16) This effect can be used for improvement of the ee of the branched reaction product by subjecting it to a kinetic resolution using the enantiomer of the catalyst that was employed in its preparation. For an example see the SI.