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Communication

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Enantio- and Regioselective Iridium-Catalyzed Allylic Esterification

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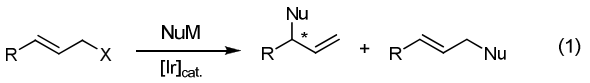
Abstract: A highly enantioselective and regioselective Ir-catalyzed allylic esterification is described, in which branched allylic esters are synthesized directly. Carboxylates were used as nucleophiles and linear allylic phosphates as electrophiles. In some cases the allylic substitution reaction was 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).

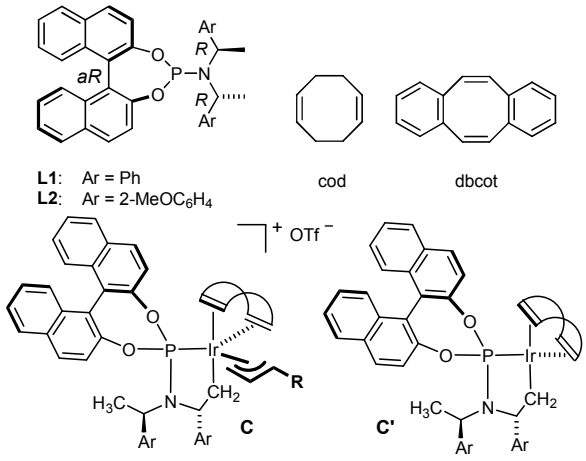


Among these, the iridium-catalyzed asymmetric allylic substitution offers a very broad scope, particularly with respect to the range of possible nucleophiles.[2] As catalysts, (allyl)Ir-complexes derived in situ from $[Ir(cod)Cl]_2$ and a phosphoramidite by treatment with base have most often been used (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 last 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 approximately 10 linear steps, which is a serious impediment to applications.[10] Overman, Kirsch et al. 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]

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, for example crotonates, in order to ensure synthetic applications via ring closing metathesis.[12]

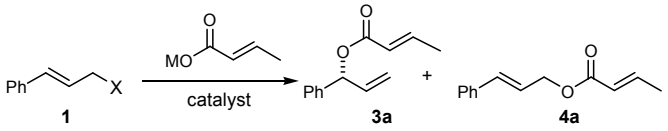


C1, **C1'**: diene = cod, Ar = 2-$MeOC_6H_4$, R = CH_3
C2, **C2'**: diene = dbcot, Ar = Ph, R = CH_3
C3: **C3'**: diene = dbcot, Ar = 2-$MeOC_6H_4$, R = CH_3

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

We initially used cinnamyl derivatives **1a**-**1e** as substrates (Table 1), because it was known that esters of branched *aryl*allylic 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 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)**

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



1 **3a** **4a**

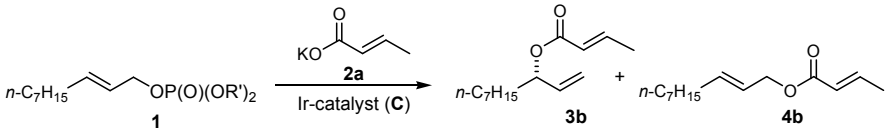
entry	X	**1**	M	**1**/**2**	catalyst	temp (°C)	time (h)	*ent*-**3a**/**4a**[b]	yield (%)[c]	ee (%)[d]
1	OCO_2Me	**1a**	K	2:1	*ent*-**C1**	45	24	1:5	n.d.	13
2	Cl	**1b**	K	2:1	*ent*-**C1**	45	2	>20:1	61	43
3	$OCNHCCl_3$	**1c**	K	2:1	*ent*-**C1**	45	24	n.d.	<10	n.d.
4	$OP(O)(OEt)_2$	**1d**	K	2:1	*ent*-**C1**	45	2	>10:1	n.d.	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	n.d.	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; n.d. = not determined. [d] Determined by HPLC on a chiral column. [e] (EH = 2-ethylhexyl).

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 in the range 0-30°C. However, selectivity and rate are fairly sensitive to the counter ion 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). Commercial dry grade *t*-

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	n.d. (95)	70
2	$OP(O)(OiPr)_2$	**1g**	*ent*-**C3** (4)	THF	0	1	20:1	n.d.	79
3	$OP(O)(OtBu)_2$	**1h**	*ent*-**C3** (4)	THF	0	1	>20:1	n.d.	79
4	$OP(O)(OEH)_2$	**1i**	*ent*-**C3** (4)	THF	0	5	>20:1	n.d.	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] The reaction mixture was subjected to freeze-pump-thaw degassing. [g] 2.8 equiv of water were added. [h] MS 4Å 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.

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 4Å further improved the ee to 99 % (entry 13). In order to get a value of the reaction time not biased by low solubility of 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 (Fig. 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 Supporting Information) 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 $k_{-3} << k_1$. 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]

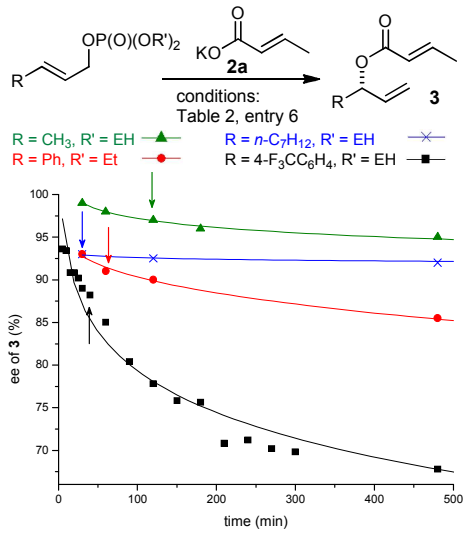
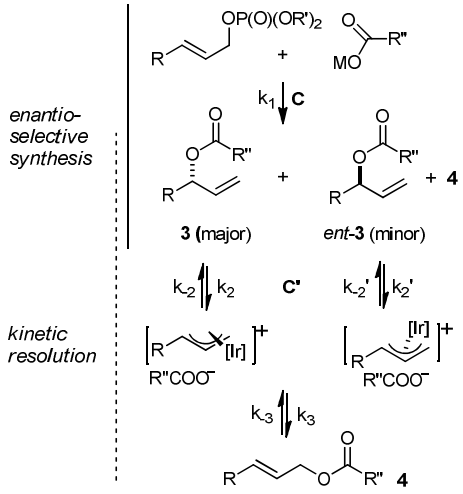


Figure 2. Dependence of enantioselectivity on time for allylic esterifications of arylallyl and alkylallyl substrates. The arrows mark work-up of the substitution reactions (EH = 2-ethylhexyl).

Scheme 1. Mechanistic rationale of a combined allylic substitution/ kinetic resolution.



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**.

Absolute configurations of the products with known configuration were as expected on the basis of a general rule, which was found to be valid for all allylic substitutions catalyzed by cyclometallated Ir-complexes.[2a]

In summary, we have developed the first direct Ir-catalyzed enantioselective allylic esterification, which allows for synthetically valuable branched allylic esters to be generated. A wide variety of solvents and reaction conditions as well as air are tolerated. Excellent regioselectivities and enantioselectivities have been achieved with a representative set of substrates.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures, results of catalyst screening experiments, characterization of compounds, determination of regio- and enantioselectivities. 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.

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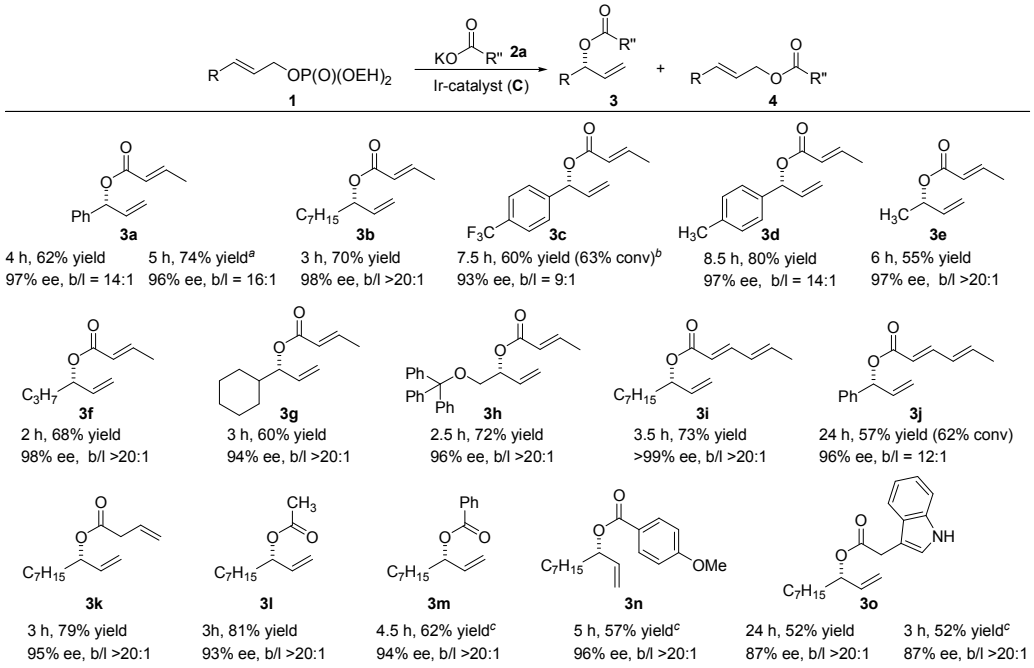
Table 3. Branched Allylic Esters Prepared by Ir-Catalyzed Allylic Substitution (Conditions According to Table 2, Entry 12). For Definition of Substrates and Linear Esters See the Supporting Information



[a] Diethyl phosphate **1d** was used instead of **1e**. [b] 1 mol% of **C3**. [c] 2 mol% of **C3**.

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(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 Supporting Information). 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 Supporting Information.

Graphical Abstract