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Stereodivergent Allylic Substitutions with Aryl Acetic Acid Esters by Synergistic Iridium and Lewis Base Catalysis

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Abstract

The preparation of all possible stereo-isomers of a given chiral molecule bearing multiple stereocenters by a simple and unified method is a significant challenge in asymmetric catalysis. We report stereodivergent allylic substitutions with aryl acetic acid esters catalyzed synergistically by a metallacyclic iridium complex and benzotetramisole. Through permutations of the enantiomers of the two chiral catalysts, all four stereoisomers of the products bearing two adjacent stereocenters are accessible with high diastereoselectivity and enantioselectivity. The resulting chiral activated ester products can be converted readily to enantioenriched amides, unactivated esters, and carboxylic acids in a one-pot manner.

Transition-metal-catalyzed allylic substitutions are useful methods for the enantioselective construction of carbon–carbon bonds.[1] If both the nucleophiles and electrophiles of the allylation reactions are prochiral, synthetically useful adducts that contain two contiguous stereocenters can be constructed in one step. However, most reported reactions of this type that afford products enantioselectively and diastereoselectively form one out of two possible relative configurations (anti vs syn).[2] Few methods provide stereodivergent access to all four possible stereoisomers of the products with either the anti or syn configuration. Recently, Carreira and co-workers reported the allylation of aldehydes in a stereodivergent fashion by the synergistic reactivity of iridium and amine catalysts under acidic conditions.[3] Zhang and co-workers reported the combination of iridium and zinc catalysts for the related allylation of α-hydroxy phenones.[4] An approach to the stereodivergent allylation of carbonyl compounds in the carboxylic acid oxidation state has not been published.[5]

Mechanistic studies[6] have revealed that metallacyclic iridium complexes[7] developed in our group govern the geometry, facial selectivity, and regioselectivity of the allyl moiety in allylation reactions (Scheme 1, A). Lewis basic chiral tertiary amines are known to react with acyl precursors to form C1-ammonium enolates that have a well-defined geometry and

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Notes

The authors declare no competing financial interest.

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b11692.

Experimental procedures and spectra (PDF)

Crystallographic data for *ent*-**3aj** (CIF)

that react with high facial selectivity (Scheme 1, B).[8] The metallacyclic iridium catalyst for allylic substitution that we discovered[7] operates under basic conditions. Thus, a system with a Lewis basic catalyst displacing an alkoxide or phenoxide anion to generate the enolate would be compatible with our iridium catalysts. We envisioned that the allylation reaction between **A** as an electrophile and **B** as a nucleophile would be highly regio-, diastereo-, and enantioselective. Furthermore, the iridium complex and the Lewis base (LB) could dictate the configurations of the two stereogenic centers of the product arising from the electrophile (marked blue) and the nucleophile (marked red), respectively. Thus, our proposed allylation method could access all four possible stereoisomers of the product by simple permutations of the enantiomers of the two catalysts ($Ir_R + LB_R$, $Ir_S + LB_R$, $Ir_R + LB_S$, $Ir_S + LB_S$).[9]

A critical concern that underlies our proposed transformation is the turnover of the Lewis base catalyst. Regeneration of this catalyst typically requires an intramolecular acyl transfer to a proximal nucleophile on the acylammonium intermediate. In this case, only lactones and lactams are accessible as the products.[8c,d,10] Although external nucleophiles can be employed as acyl acceptors,[11] this external nucleophile can react with intermediate **C** before allylation occurs. In addition, the direct allylation of an external nucleophile can compete or override the allylation of the enolate.

We considered that the “rebound” strategy disclosed recently by Scheidt,[12] Smith,[13] and Snaddon[14] could be followed to regenerate the Lewis base. In this scenario, the electron-deficient phenolate (Scheme 1, OAr^-) substituted by the Lewis base catalyst serves as an acyl acceptor after α-functionalization of the ester. The low concentration and low nucleophilicity of the electron-deficient phenolate would prevent the direct allylation of the phenolate.

Herein we report stereodivergent allylic substitutions with aryl acetic acid esters catalyzed synergistically by a metallacyclic iridium complex and a chiral Lewis base. By variation of the combination of enantiomers of the two catalysts, all four stereoisomers of the products are formed with high diastereoselectivity and enantioselectivity. The resulting chiral activated esters are readily converted to enantioenriched amides, unactivated esters, and carboxylic acids in a one-pot manner.

To develop a stereodivergent allylation of aryl acetic acid esters, we treated **1a** with **2a** (X = OBoc) in the presence of $^{i}Pr_2NEt$ as the base, iridium catalyst **[Ir]-1**, and a range of Lewis base catalysts (Table S1). These studies revealed that benzotetramisole (BTM)[15] is compatible with our proposed synergistic catalysis (>99% yield, >20:1 dr; see the Supporting Information (SI) for details). Reactions conducted with other Lewis bases, such as tetramisole and quinine, delivered the product in lower yields (<40%) or with lower diastereoselectivity (<4:1). The use of the pentafluorophenyl ester as the nucleophile precursor was critical; reactions conducted with esters derived from other electron-deficient phenols, such as 4-nitrophenol and 2,4,6-tricholorophenol, gave the corresponding products in low yield and dr (Table S2; see the SI for details).

To test the effect of the leaving group on the allyl moiety in this reaction, various cinnamyl alcohol derivatives were subjected to the reaction conditions (Table 1). The reaction

conducted with *tert*-butyl cinnamyl carbonate (**2a**) gave (*S,S*)-**3aa** in the highest yield (97%) with >20:1 dr and >99% ee (entry 7). Only the branched product was observed. A similar result was obtained in the absence of $^{i}Pr_2NEt$, indicating that the *tert*-butoxide generated from oxidative addition of **2a** and subsequent decarboxylation acted as a base to deprotonate the acyl–BTM adduct (entry 8).

Metallacyclic iridium catalysts with different aryl substituents on the phosphoramidite ligands were evaluated. Reactions conducted with **[Ir]-3** and **[Ir]-4** bearing naphthyl substituents on the ligands afforded (*S,S*)-**3aa** quantitatively with excellent diastereoselectivity and enantioselectivity (>20:1 dr, >99% ee; entries 10 and 11). However, the reaction conducted with **[Ir]-2** bearing 2-methoxyphenyl substituents on the ligand gave (*S,S*)-**3aa** in a lower yield of 71% with a lower dr of 11:1 (entry 9).

When the reaction was conducted with (*R*)-BTM as the Lewis base catalyst instead of (*S*)-BTM, the diastereoselectivity was completely reversed; (*R,S*)-**3aa** was obtained instead of (*S,S*)-**3aa** in 97% yield with >20:1 dr and >99% ee (entry 12). A small amount of linear product was observed when the reaction was conducted with the catalyst combination of **[Ir]-1** and (*R*)-BTM. However, employing **[Ir]-4** and (*R*)-BTM as the catalysts suppressed the formation of the linear product while maintaining high dr and ee (entry 15).

To examine the stereodivergence of our allylation method, **1a** and **2a** were treated with four different combinations of the enantiomers of the two catalysts under otherwise identical conditions (Scheme 2). As a result, all four stereoisomers of **3aa** were obtained individually in high yield with excellent diastereo-and enantioselectivity, indicating nearly complete control of the configurations at the allyl electrophile and the enolate nucleophile by the metallacyclic Ir complex and the BTM base, respectively, and the dominance of catalyst control of these configurations over potential substrate control. The absolute configurations of the products are consistent with a stereo-chemical model based on previous mechanistic studies of the Ir[6] and BTM[16] catalysts (Scheme S1), rendering the stereochemical outcome of our allylation method predictable.

The scope of aryl acetic acid esters that underwent the stereodivergent allylic substitutions is summarized in Table 2. Various para-substituted phenyl acetic acid esters were suitable for this transformation. Electron-donating (**3aa**, **3da**, **3ea**), electron-neutral (**3ba**, **3ca**) and electron-withdrawing (**3fa**) functional groups on the phenyl ring of the phenyl acetic acid ester were tolerated in this reaction, furnishing the corresponding products in high yields (≥77%) with high dr (≥11:1) and excellent ee (≥97%). The reaction with 4-(methylsulfonyl)-phenyl acetic acid ester (**1m**), a substrate bearing a readily enolizable position as a result of the strong electron-withdrawing effect of the sulfonyl group, formed the product **3ma** in high yield (88%) but with modest dr (3.8:1). Further investigations showed that the low diastereoselectivity resulted from the competing reaction of **1m** with **2a** occurring without participation of BTM, not from racemization of the product (Table S4).

Substitutions at the ortho (**3ga**, **3ha**) or meta (**3ia**) position of the phenyl ring of the phenyl acetic acid ester had little effect on the allylation reaction; the corresponding products were all obtained in ≥89% yield with ≥11:1 dr and ≥98% ee. The allylation also occurred with

heteroaryl acetic acid esters. For example, **1l**, which is derived from the nonsteroidal anti-inflammatory drug indomethacin, was allylated in 92% yield with >20:1 dr and >99% ee. In the cases of **3ga** and **3la**, addition of 1.1 equiv of $^{i}Pr_2NEt$ was necessary to reach full conversion of the starting allylic carbonates within 9 h, presumably by accelerating the enolization of the acyl–BTM intermediate.

The scope of allylic carbonates that underwent the stereo-divergent allylic substitutions with aryl acetic acid esters is summarized in Table 3.[17] Various substituents on the phenyl ring of the cinnamyl carbonate were tolerated, giving the corresponding products in ≥90% yield with ≥17:1 dr and ≥98% ee (**3aa–ah**). The allylic substitutions also occurred with allylic carbonates containing heteroaryl and alkenyl substituents. Allylic carbonates bearing a thiazole ring (**2j**) or a pyrimidine ring (**2k**) reacted to form the products **3aj** and **3ak**, respectively, with high diastereoselectivity and enantioselectivity (>20:1 dr, >99% ee). The reaction with *tert*-butyl sorbyl carbonate proceeded smoothly, furnishing **3al** in 90% yield with 17:1 dr and >99% ee.

To demonstrate the stereodivergence of this allylation reaction further, the reactions in Table 4 were conducted. In these reactions, the same enantiomer of the iridium catalyst was used with the two enantiomers of the Lewis basic catalyst BTM. Both diastereomers of **3ca**, **3ea**, **3ja**, **3ac**, **3ad**, and **3ak** were isolated in high yield with high regio-, diastereo-, and enantioselectivity.

The pentafluorophenyl ester products generated from this allylation are readily elaborated under mild conditions (Scheme 3). Addition of benzylamine and $^{i}Pr_2NEt$ to the reaction mixture at the end of the allylation reaction generated amide **4aa** in a one-pot manner (98% yield with >20:1 dr and 98% ee). Similarly, one-pot syntheses of methyl ester **5aa** and carboxylic acid **6aa** were realized with 4-dimethylaminopyridine (DMAP) as the catalyst for methanolysis and hydrolysis of **3aa**. Finally, primary alcohol **7aa** was obtained through reduction of **3aa** in 98% yield with >20:1 dr and >99% ee.

In summary, we have shown that the combination of a metallacyclic iridium complex and a chiral Lewis base catalyzes stereodivergent allylic substitutions with aryl acetic acid esters. All four possible stereoisomers of the resulting products containing two contiguous stereocenters are accessible by simple permutations of the enantiomers of the two catalysts. The activated pentafluorophenyl esters as nucleophile precursors in this reaction allowed regeneration of the Lewis base catalyst through a “rebound” strategy while simultaneously allowing the resulting allylation products to be converted readily to enantioenriched amides, unactivated esters, and carboxylic acids. Studies to expand the scope with respect to general aliphatic carboxylic acid derivatives are underway.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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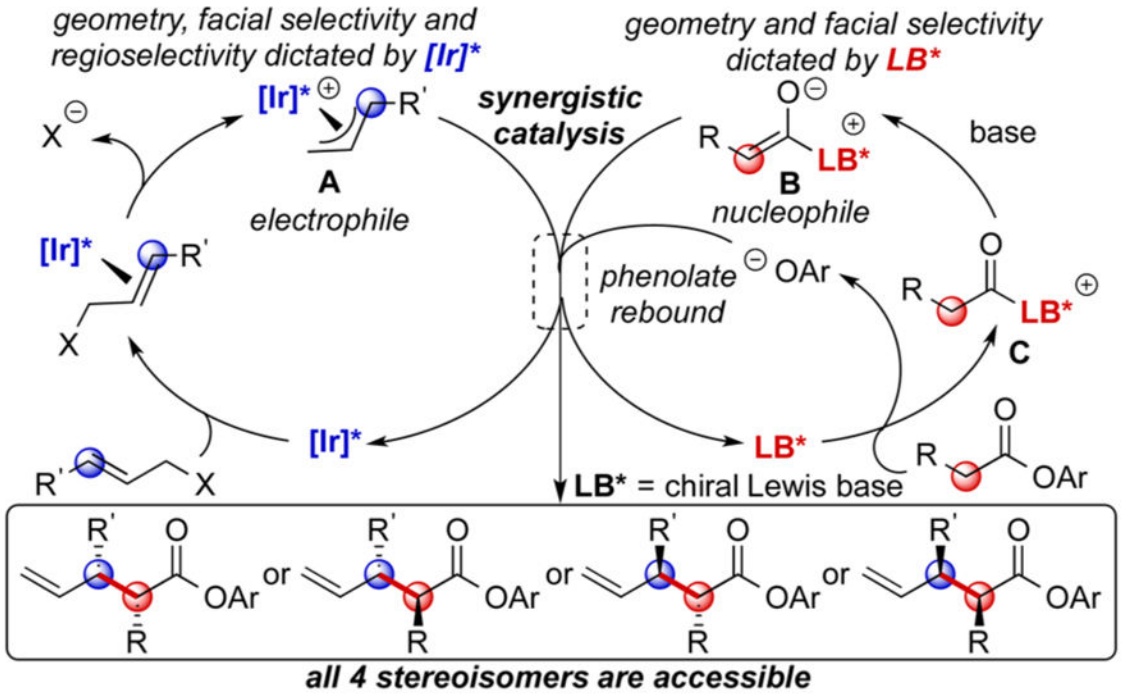
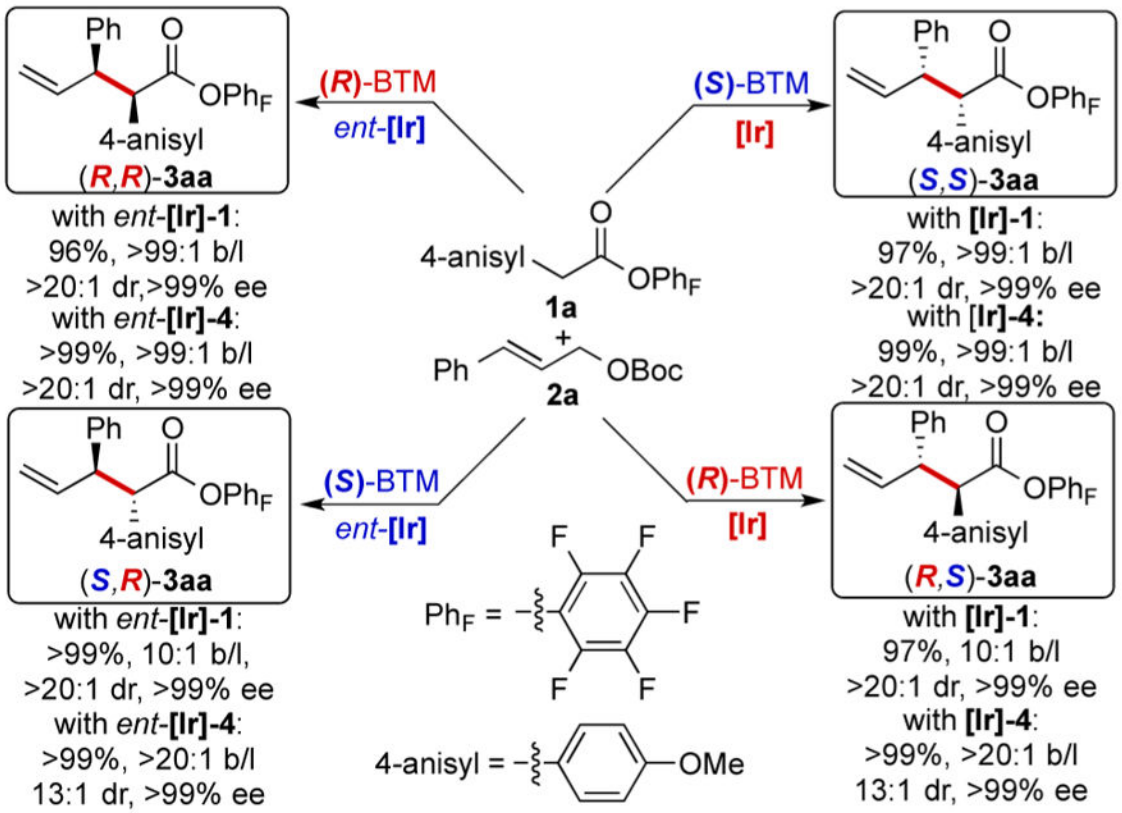
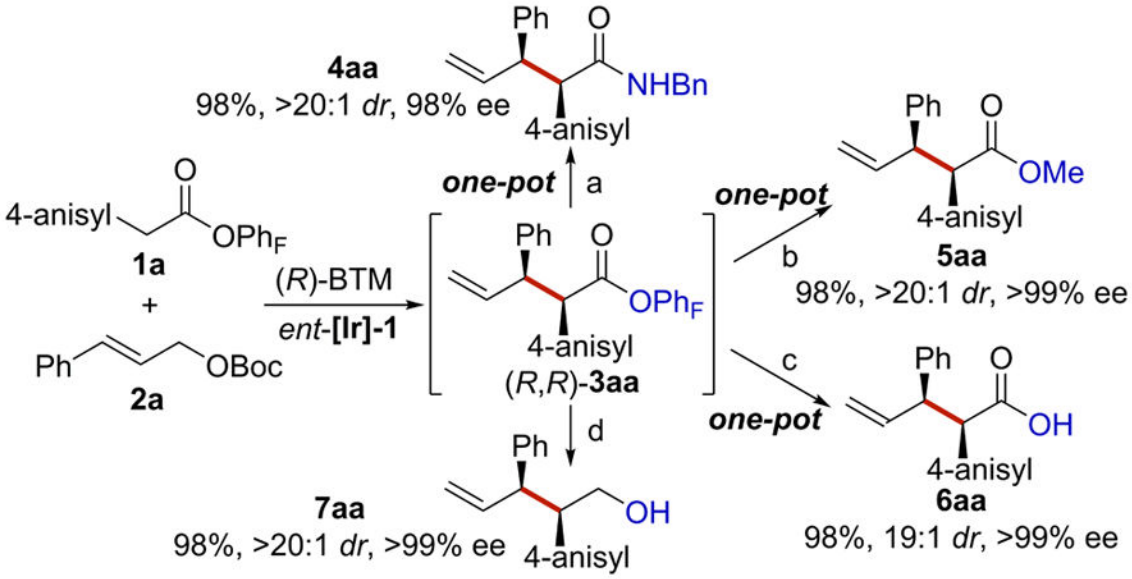
17. In the isolated products, a small amount of (*R*,*R*)-**3aa** impurity derived from the catalyst *ent*-**[Ir]-1** was observed by GC.



Scheme 1.
Proposed Mechanism for Synergistic Catalysis



Scheme 2.
Synthesis of All Four Stereoisomers of 3aa

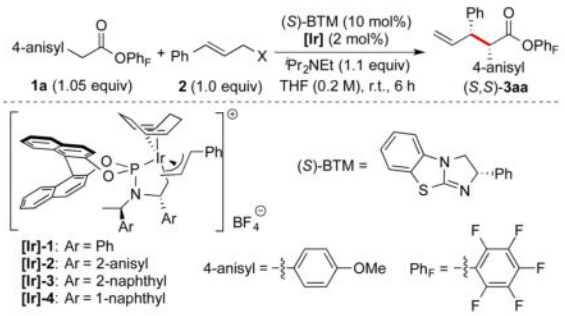


Scheme 3. Derivatizations of (*R*,*R*)-3aa[a]

[a]Conditions: (a) $^{i}Pr_2NEt$ (1.5 equiv), $BnNH_2$ (1.3 equiv), r.t., 12 h; (b) DMAP (0.2 equiv), Et_3N (5.0 equiv), MeOH/THF, 65 °C, 12 h; (c) DMAP (0.2 equiv), Et_3N (5.0 equiv), H_2O/THF, 65 °C, 12 h; (d) $LiAlH_4$ (1.5 equiv), THF, r.t., 12 h.

Table 1

Evaluation of the Reaction Conditions for the Allylation of 1a[a]



entry	[Ir]	X	b/l[b]	dr[b]	ee/%[c]	yield/%[d]
1	**[Ir]-1**	OAc	n.d.	n.d.	n.d.	13
2		OBz	>99:1	>20:1	n.d.	59
3		OPiv	n.d.	n.d.	n.d.	8
4		OPO(OEt)$_2$	n.d.	6:1	n.d.	38
5		OCOOMe	>99:1	5:1	n.d.	43
6		OTroc	>99:1	9:1	n.d.	90
7		OBoc	>99:1	>20:1	>99	>99 (97)
8[e]	**[Ir]-1**	OBoc	>99:1	>20:1	>99	99 (97)
9[e]	**[Ir]-2**		>99:1	11:1	n.d.	71
10[e]	**[Ir]-3**		>99:1	>20:1	>99	>99 (>99)
11[e]	**[Ir]-4**		>99:1	>20:1	>99	99 (99)
12[e,f]	**[Ir]-1**		10:1	<1:20	>99	98 (97)
13[e,f]	**[Ir]-2**		>20:1	1:13	n.d.	57
14[e,f]	**[Ir]-3**		10:1	<1:20	>99	99 (>99)
15[e,f]	**[Ir]-4**		>20:1	1:13	>99	99 (>99)

[a]The absolute configuration of (*S*,*S*)-**3aa** was assigned by analogy.

[b] Determined by ^{1}H NMR analysis of the crude reaction mixtures.

[c] Determined by chiral supercritical fluid chromatography of the major isomers.

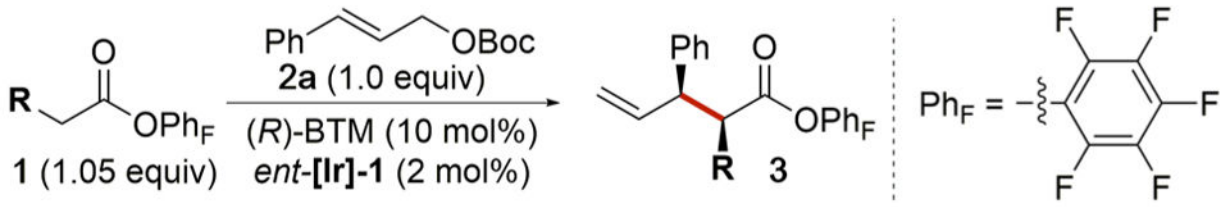
[d] Combined yields of the two diastereomers of the branched product and the linear product, determined by ^{1}H NMR analysis with mesitylene as an internal standard. Yields in parentheses are for all isomers isolated.

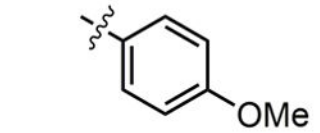
[e] Without iPr$_2$NEt.

[f] (*R*)-BTM was used instead of (*S*)-BTM.

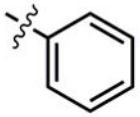
Table 2

Scope of Esters for the Allylation[a]

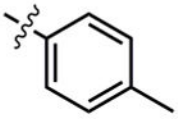




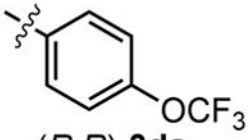
(*R*,*R*)-**3aa**
96%, >20:1 dr, >99% ee



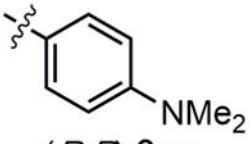
(*R*,*R*)-**3ba**
97%, 18:1 dr, 99% ee



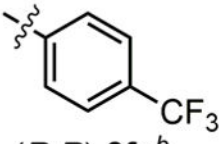
(*R*,*R*)-**3ca**
>99%, >20:1 dr, >99% ee



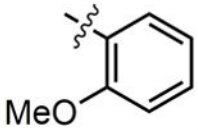
(*R*,*R*)-**3da**
98%, 16:1 dr, 97% ee



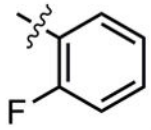
(*R*,*R*)-**3ea**
77%, >20:1 dr, >99% ee



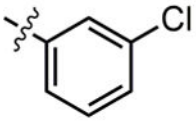
(*R*,*R*)-**3fa**[b]
90%, 11:1 dr, 98% ee



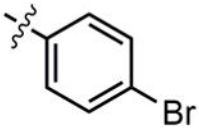
(*R*,*R*)-**3ga**[c,d]
96%, 11:1 dr, >99% ee



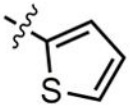
(*R*,*R*)-**3ha**[b]
89%, 12:1 dr, 98% ee



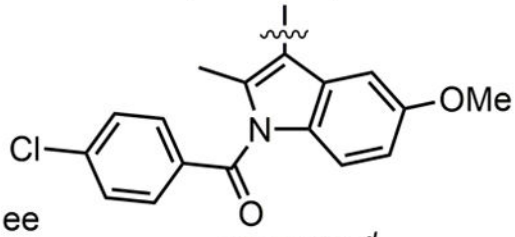
(*R*,*R*)-**3ia**[b]
94%, >20:1 dr, >99% ee



(*R*,*R*)-**3ja**
>99%, 18:1 dr, >99% ee



(*S*,*R*)-**3ka**[b]
98%, 17:1 dr, >99% ee



(*R*,*R*)-**3la**[d]
92%, >20:1 dr, >99% ee

[a]Combined yields of the two isolated diastereomers are reported. The branched products were obtained exclusively.

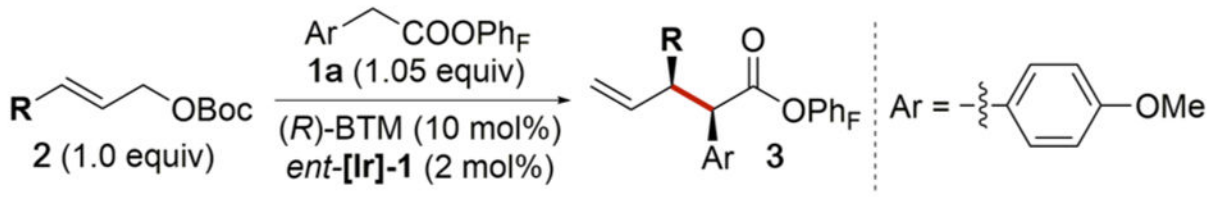
[b]20 mol % (*R*)-BTM was used.

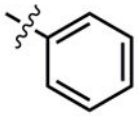
[c]The reaction time was extended to 9 h.

[d] 1.1 equiv of $^{i}Pr_2NEt$ was added.

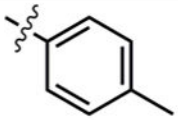
Table 3

Scope of Allylic Carbonates for the Allylation[a]

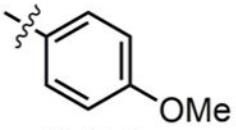




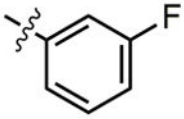
(*R*,*R*)-**3aa**
96%, >20:1 dr, >99% ee



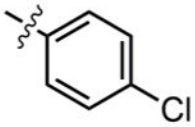
(*R*,*R*)-**3ab**
98%, >20:1 dr, 98% ee



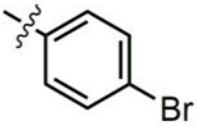
(*R*,*R*)-**3ac**
99%, >20:1 dr, >99% ee



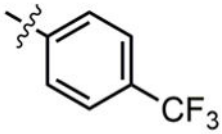
(*R*,*R*)-**3ad**
>99%, 17:1 dr, >99% ee



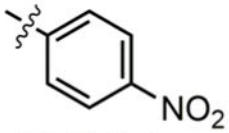
(*R*,*R*)-**3ae**
97%, >20:1 dr, >99% ee



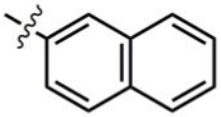
(*R*,*R*)-**3af**
>99%, >20:1 dr, >99% ee



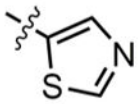
(*R*,*R*)-**3ag**
95%, 20:1 dr, 99% ee



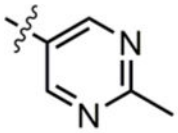
(*R*,*R*)-**3ah**
90%, >20:1 dr, >99% ee



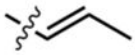
(*R*,*R*)-**3ai**
93%, >20:1 dr, >99% ee



(*R*,*R*)-**3aj**
81%, >20:1 dr, >99% ee



(*R*,*R*)-**3ak**
95%, >20:1 dr, >99% ee

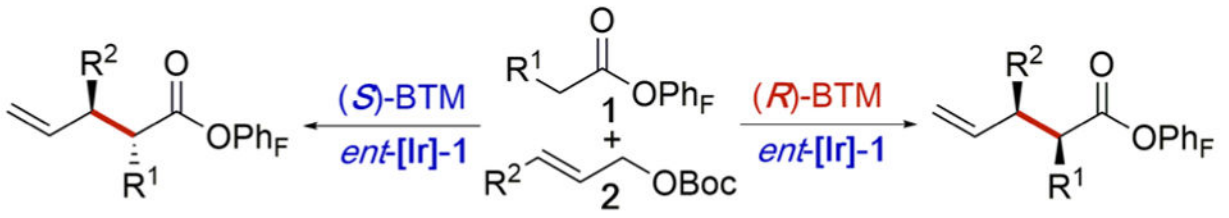


(*R*,*R*)-**3al**
90%, 17:1 dr, >99% ee

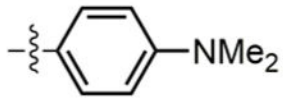
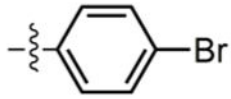
[a]Combined yields of the two isolated diastereomers are reported. The branched products were obtained exclusively.

Table 4

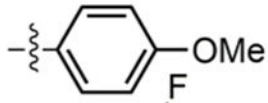
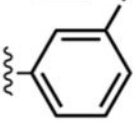
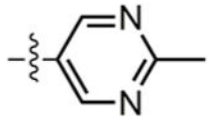
Examples of Stereodivergence[a]



with R^2 = Ph:

(*S*,*R*)-**3ca**, >99% 8:1 b/l, 19:1 dr, >99% ee	R^1 = 	(*R*,*R*)-**3ca**, >99% >99:1 b/l, >20:1 dr, >99% ee
(*S*,*R*)-**3ea**, >99% 13:1 b/l, 16:1 dr, 99% ee	R^1 = 	(*R*,*R*)-**3ea**, 77% >99:1 b/l, >20:1 dr, >99% ee
(*S*,*R*)-**3ja**, >99% 8:1 b/l, 16:1 dr, >99% ee	R^1 = 	(*R*,*R*)-**3ja**, >99% >99:1 b/l, 18:1 dr, >99% ee

with R^1 = 4-anisyl:

(*S*,*R*)-**3ac**, 97% >20:1 b/l, >20:1 dr, 98% ee	R^2 = 	(*R*,*R*)-**3ac**, 99% >99:1 b/l, >20:1 dr, >99% ee
(*S*,*R*)-**3ad**, 99% 6:1 b/l, 12:1 dr, 95% ee	R^2 = 	(*R*,*R*)-**3ad**, >99% >99:1 b/l, 17:1 dr, >99% ee
(*S*,*R*)-**3ak**, 74% >20:1 b/l, 9:1 dr, >99% ee	R^2 = 	(*R*,*R*)-**3ak**, 95% >99:1 b/l, >20:1 dr, >99% ee

[a]See the SI for experimental details.