Asymmetric Catalysis

DOI: 10.1002/anie.201406778

Iridium-Catalyzed Regio- and Enantioselective Allylic Substitution of Silyl Dienolates Derived from Dioxinones**

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Abstract: *Reported herein is the iridium-catalyzed regio- and enantioselective allylic substitution reactions of unstabilized silyl dienolates derived from dioxinones. Asymmetric allylic substitution of a variety of allylic trichloroethyl carbonates with these silyl dienolates gave γ-allylated products selectively in 60–84% yield and 90–98% ee.*

The alkylation of 1,3-dicarbonyl compounds (e.g., **A**, Figure 1) is a classic reaction in organic chemistry. Because the α-position contains the most acidic proton, electrophiles add to this site in the presence of a base to give the product **B**. This fundamental reactivity has been translated into one of the most commonly studied reactions of organometallic catalysis for organic synthesis—asymmetric allylic substitution of soft, stabilized, anionic carbon nucleophiles to form products of type **C**.[1,2]

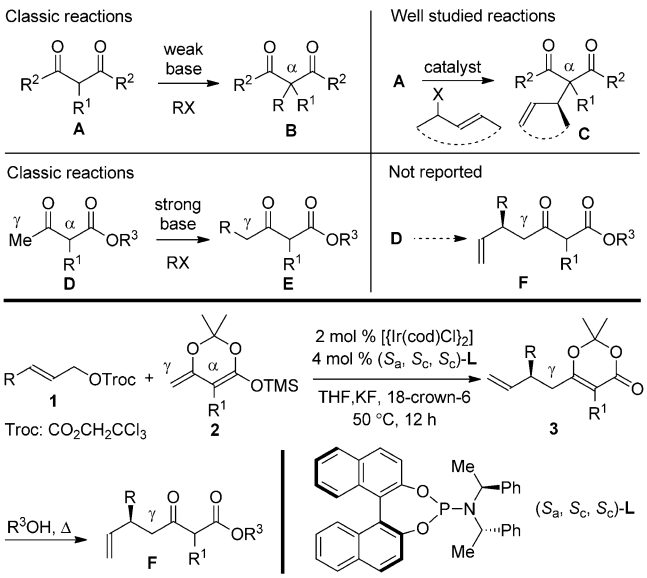

Figure 1. Iridium-catalyzed regio- and enantioselective allylic substitution with silyl dienolates. cod = 1,5-cyclooctadiene, THF = tetrahydrofuran, TMS = trimethylsilyl.

Alkylations of the β-keto esters **D** to form the isomeric γ-alkylated products **E** are also classic reactions in organic chemistry (Figure 1).[3] These reactions occur in the presence of a base which is strong enough to doubly deprotonate the dicarbonyl compounds. Electrophiles then add to the most nucleophilic γ-position with high regioselectivity. Despite the value of the γ-alkylation reaction, catalytic asymmetric allylations of **D** at the γ-position to form products of type **F** have not been reported. The products of such allylations are highly versatile synthetic intermediates[4] because they contain three functional groups: an alkene, an ester, and a ketone carbonyl group.

Silyl dienolates (**2**, Figure 1) are synthetically equivalent to β-keto ester dianions.[5a–c] After the formation of a new carbon–carbon bond at the γ-position, the dioxinone moiety in the product (e.g., **3**) can be induced to extrude acetone to generate an acyl ketene intermediate. This intermediate can then be trapped with alcohols to give β-keto esters. As shown by the groups of Sato, Carreira, and Evans, the silyl dienolates **2** undergo enantioselective aldol reactions with aldehydes to provide γ-addition products with high regioselectivity.[5d–h] However, these reagents have not undergone catalytic enantioselective reactions with alkyl or allyl electrophiles.

Herein, we report iridium-catalyzed enantioselective allylic substitution reactions[6–9] of silyl dienolates (**2**), derived from dioxinones, with trichloroethyl (Troc) allylic carbonates that occur in good yields with high γ-selectivities, enantioselectivities, and branched-to-linear (b/l) selectivities (Figure 1). This reaction sets the stereogenic center at the electrophilic carbon atom and is the equivalent of γ-selective, asymmetric alkylations of β-keto esters. The dioxinone moiety in these products can be transformed into a variety of functional groups while preserving the enantiomeric excess of the product. The key to achieving highly enantioselective and γ-selective alkylations is the combination of a dioxinone as an equivalent of the β-keto ester, a Troc ester of the allylic alcohol as the electrophile, and a chiral, nonracemic phosphoramidite ligand on iridium.

We began our studies on the allylic substitution reaction with **2a** (see Table 1) under the reaction conditions we have developed for the asymmetric allylation with α,β-unsaturated ketones.[9j] Although Mayr and co-workers have determined that the π-nucleophilicity at the α-position of dienolates (**2**) is much weaker than that at the γ-position,[10] there are cases in which the nucleophilic addition occurred at the α-position selectively.[11] Therefore, to identify an appropriate allylic electrophile for the reaction, several cinnamyl alcohol

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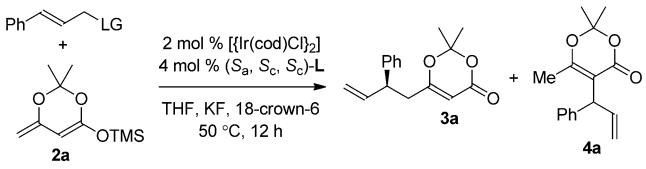
[**] Financial support provided by the National Institutes of Health (GM-58108 and S10-RR027172) is gratefully acknowledged.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201406778.

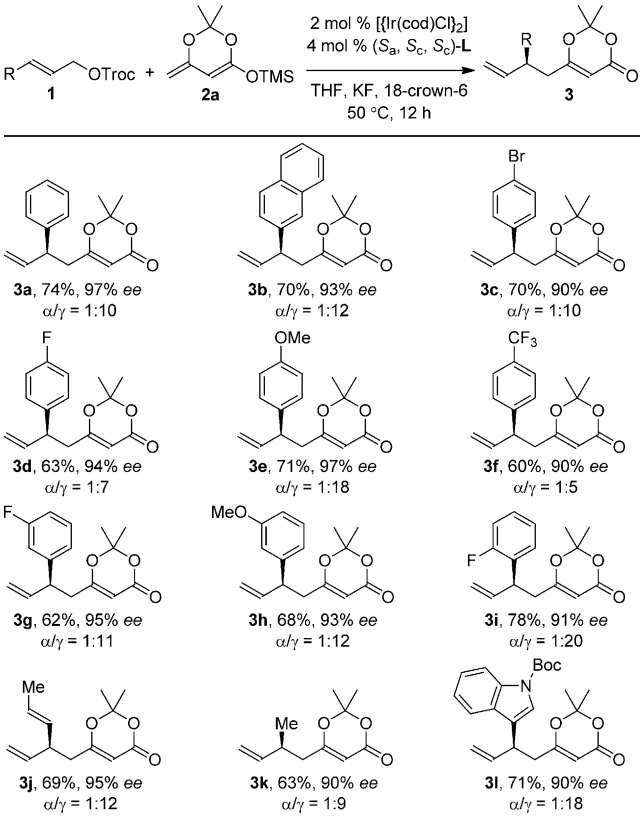
Table 1: Evaluation of the allylic electrophile for the iridium-catalyzed asymmetric allylic substitution with **2a**.[a]



Entry	LG	γ/α (**3a**/**4a**)[b]	**3a** Yield [%][c]	**3a** *ee* [%][d]
1	$OCOMe$[e]	2:1	53	n.d.
2	$OCOPh$[e]	1:1	36	n.d.
3	$OP(O)(OEt)_2$	1:1	38	n.d.
4	OCO_2tBu	1:1	41	n.d.
5	OCO_2Me	6:1	62	96
6	$OCO_2CH_2CCl_3$	10:1	74	97

[a] Reaction conditions: cinnamyl ester (0.2 mmol, 1.0 equiv), **2a** (0.4 mmol, 2.0 equiv), [{Ir(cod)Cl}$_2$] (2 mol%), (S_a,S_c,S_c)-**L** (4 mol%), KF (1.0 equiv), 18-crown-6 (1.0 equiv), THF (0.4 mL), 50°C, 12 h. [b] Ratios of γ- to α-substitution (**3a**/**4a**) were determined by ^{1}H NMR analysis of the crude reaction mixtures. [c] Yield of isolated product. [d] Determined by HPLC analysis using a chiral stationary phase. [e] Reactions were carried out at 50°C for 24 h. n.d. = not determined.

Table 2: Scope of the iridium-catalyzed asymmetric allylic substitution of trichloroethyl allylic carbonates (**1**) with **2a**.[a–d]



[a] Reaction conditions: allylic carbonate **1** (0.2 mmol, 1.0 equiv), **2a** (0.4 mmol, 2.0 equiv), [{Ir(cod)Cl}$_2$] (2 mol%), (S_a,S_c,S_c)-**L** (4 mol%), KF (1.0 equiv), 18-crown-6 (1.0 equiv), THF (0.4 mL), 50°C, 12 h. [b] The *ee* value was determined by HPLC analysis using a chiral stationary phase. [c] Ratios of γ- to α-substitution were determined by ^{1}H NMR analysis of the crude reaction mixtures. [d] Yield is that of the isolated product (the average of at least two runs). Boc = *tert*-butoxycarbonyl, OTroc = $OCO_2CH_2CCl_3$.

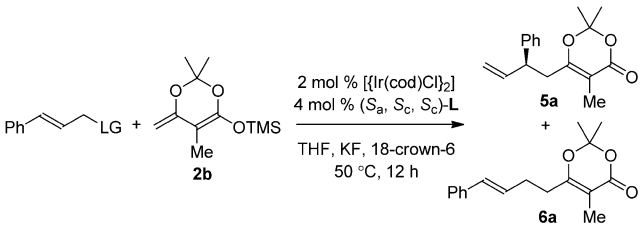
derivatives were synthesized and asymmetric allylic substitution reactions of these derivatives with **2a** were examined.

As shown in Table 1, treatment of the cinnamyl acetate (1 equiv) and **2a** (2 equiv) with 2 mol% [{Ir(cod)Cl}$_2$] and 4 mol% (S_a,S_c,S_c)-**L** (for structure see Figure 1) in the presence of KF (1 equiv) and 18-crown-6 (1 equiv) at 50°C for 24 hours provided a 2:1 mixture of the γ-substituted product **3a** and α-substituted product **4a** in 53 and 28% yield, respectively (entry 1, Table 1). When the cinnamyl acetate was replaced with the cinnamyl benzoate, a 1:1 mixture of **3a** and **4a** was obtained (entry 2). Because prolonged heating (24 h) was required for the full conversion of these cinnamyl esters, further investigation of the reaction was conducted with more reactive cinnamyl phosphates and carbonates as the electrophile. When the ethyl cinnamyl phosphate was employed in the reaction, the consumption of the starting phosphate was complete within 12 hours at 50°C, but no improvement of the regioselectivity was achieved (entry 3). The allylation reaction of the *tert*-butyl cinnamyl carbonate with **2a** also gave a 1:1 mixture of **3a** and **4a** (entry 4). However, when the methyl cinnamyl carbonate was utilized, a 6:1 mixture of **3a** and **4a** was obtained with **3a** as the major isomer in 62% yield and 96% *ee* (entry 5). Finally, allylic substitution of the trichloroethyl cinnamyl carbonate with **2a** provided a 10:1 mixture of **3a** and **4a** (entry 6). The γ-allylated product **3a** was obtained in 74% yield and 97% *ee* after purification.

Table 2 summarizes the scope with respect to the allylic carbonate **1** that undergoes the asymmetric allylation with **2a** under the developed conditions. In general, allylic substitution of a variety of substituted cinnamyl carbonates with **2a** gave the allylation products **3a**–**i** in good yields with high enantioselectivities and γ-selectivities, although in the cases of **3d** and **3f**, moderate γ/α-selectivities were observed. Alkenyl- and alkyl-substituted allylic carbonates also reacted to provide the allylated products **3j** and **3k** in 69 and 63% yield, respectively, with corresponding 12:1 and 9:1 γ-selectivities. Allylation of the allylic carbonate containing a heterocyclic indolyl group gave the product **3l** in 71% yield with excellent γ-selectivity. In all cases, the allylated products were obtained with greater than or equal to 90% *ee* and greater than 20:1 b/l selectivity.

Allylic substitution reactions with silyl dienolate **2b** were examined next (Table 3). With a methyl substituent at the α-position in **2b**, we anticipated that the asymmetric allylation of allylic esters with **2b** should proceed with high γ-selectivity. Indeed, when the reaction was performed with cinnamyl acetate and **2b** under standard reaction conditions, the γ-substituted product **5a** was obtained in 60% yield with greater than 20:1 γ-selectivity. However, a significant amount of linear product **6a** (21%) was also isolated (entry 1). Because high b/l selectivities (>20:1) were observed in the allylic substitution reactions with **2a** (Tables 1 and 2), we expected that reactions with **2b** should proceed with comparable b/l selectivities. The unexpected low b/l selectivity

Table 3: Evaluation of the allylic electrophile for the iridium-catalyzed asymmetric allylic substitution with **2b**.[a]



Entry	LG	b/l (**5a**/**6a**)[b]	**5a** Yield [%][c]	**5a** *ee* [%][d]
1	$OCOMe$[e]	2.5:1	60	n.d.
2	$OCOPh$[e]	2:1	54	n.d.
3	$OP(O)(OEt)_2$	1:1	41	n.d.
4	OCO_2tBu	2.5:1	56	n.d.
5	OCO_2Me	4:1	67	n.d.
6	$OCO_2CH_2CCl_3$	15:1	81	90

[a] Reaction conditions: cinnamyl ester (0.2 mmol, 1.0 equiv), **2b** (0.4 mmol, 2.0 equiv), [{Ir(cod)Cl}$_2$] (2 mol%), (S_a,S_c,S_c)-**L** (4 mol%), KF (1.0 equiv), 18-crown-6 (1.0 equiv), THF (0.4 mL), 50°C, 12 h. [b] The b/l (**5a**/**6a**) were determined by ^{1}H NMR analysis of the crude reaction mixtures. [c] Yield of isolated product. [d] Determined by HPLC analysis using a chiral stationary phase. [e] Reactions were carried out at 50°C for 24 h.

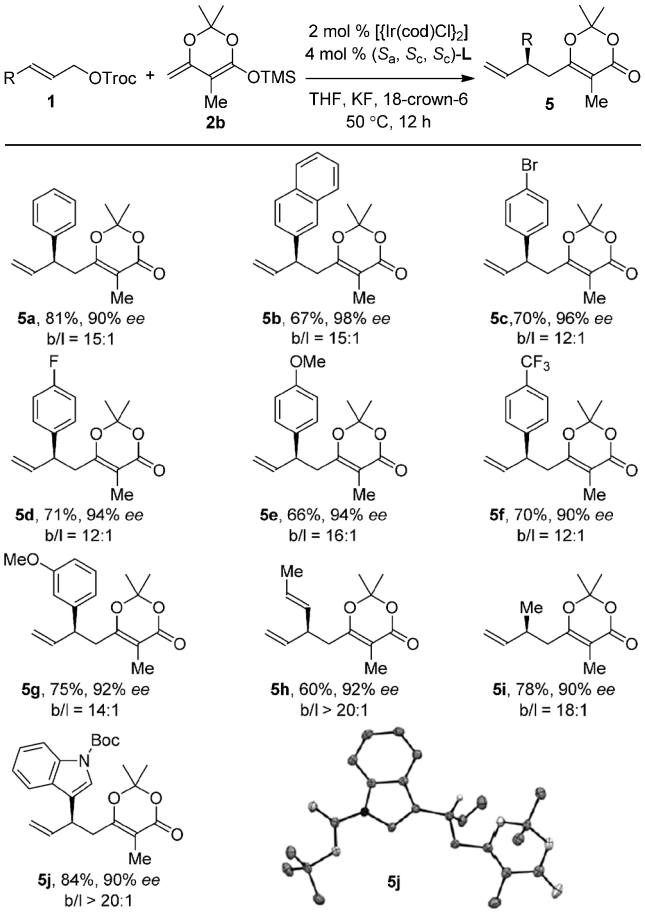
presumably resulted from steric interactions because **2b** is more sterically hindered than **2a**.

To improve b/l selectivity with dienolate **2b**, allylation reactions of **2b** with a variety of cinnamyl alcohol derivatives were explored (Table 3). The reaction of the cinnamyl benzoate with **2b** only gave a 2:1 mixture of **5a** and **6a** (entry 2). The b/l selectivity decreased to 1:1 in the reaction of the cinnamyl phosphate with **2b** (entry 3). The reaction of the *tert*-butyl cinnamyl carbonate with **2b** provided a 2.5:1 mixture of **5a** and **6a** (entry 4). The b/l selectivity was improved to 4:1 when methyl cinnamyl carbonate was utilized (entry 5). Finally, when the trichloroethyl cinnamyl carbonate was used, again, as the electrophile, the allylic substitution with **2b** provided **5a** in 81% yield, 90% *ee*, and a 15:1 b/l selectivity (entry 6).

Table 4 summarizes the results of the asymmetric allylation of **2b** with the allylic carbonates **1**. A wide range of allylic Troc esters readily participated in the reaction to give allylated products in good yields with high enantioselectivities and b/l selectivities. Allylation of **2b** with substituted cinnamyl carbonates afforded the products **5a**–**g** in 66–81% yield with 90–98% *ee* and b/l ratios ranging from 12:1 to 16:1. Reactions of alkenyl- and alkyl-substituted allylic carbonates gave the products **5h** and **5i** in 60 and 78% yield, respectively, and the corresponding 92 and 90% *ee* and 20:1 and 18:1 b/l selectivities. The allylic carbonate with an indolyl group also reacted to provide product **5j** in 84% yield with 90% *ee* and an excellent branched selectivity. In all cases, detectable amounts of α-allylated products were not formed from these reactions. The absolute configuration of allylation product **5j** was determined by single-crystal X-ray diffraction.

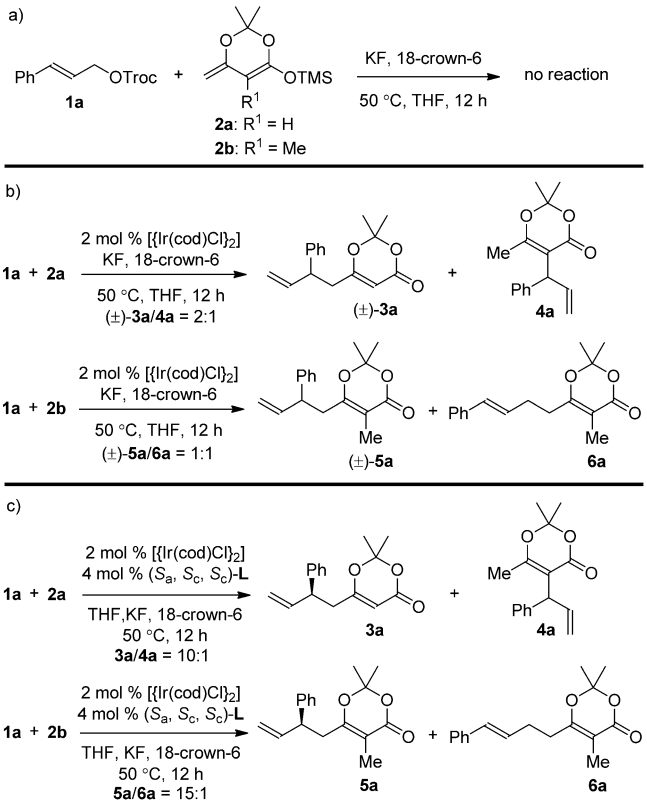
A series of experiments evaluating the influence of the ligand and leaving group on the regioselectivity of the

Table 4: Scope of the iridium-catalyzed asymmetric allylic substitution of trichloroethyl allylic carbonates (**1**) with **2b**.[a–d]



[a] Reaction conditions: allylic carbonate **1** (0.2 mmol, 1.0 equiv), **2b** (0.4 mmol, 2.0 equiv), [[Ir(cod)Cl}$_2$] (2 mol%), (S_a,S_c,S_c)-**L** (4 mol%), KF (1.0 equiv), 18-crown-6 (1.0 equiv), THF (0.4 mL), 50°C, 12 h. [b] The *ee* value was determined by HPLC analysis using a chiral stationary phase. [c] The b/l ratios were determined by ^{1}H NMR analysis of the crude reaction mixtures. [d] Yield is that of the isolated product (the average of at least two runs).[14]

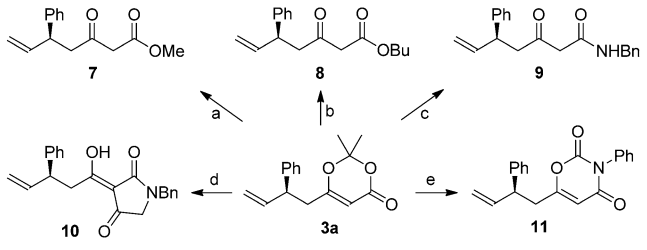
reaction is shown in Scheme 1. No allylation reaction of **1a** with either **2a** or **2b** was observed in the absence of [{Ir(cod)Cl}$_2$] and (S_a,S_c,S_c)-**L** (Scheme 1a). However, [{Ir(cod)Cl}$_2$] does catalyze the allylic substitution of **1a** with either **2a** or **2b** without the added phosphoramidite ligand. As shown in Scheme 1b, the allylation of **1a** with **2a** at 50°C for 12 hours gave a 2:1 mixture of (±)-**3a** and **4a** in 55% combined yield in the presence of 2 mol% [{Ir(cod)Cl}$_2$], KF (1 equiv), and 18-crown-6 (1 equiv). Under the identical reaction conditions, the reaction of **1a** with **2b** gave a 1:1 mixture of (±)-**5a** and **6a**. However, the same reactions conducted with the catalyst generated from [{Ir(cod)Cl}$_2$] and the phosphoramidite ligand (S_a,S_c,S_c)-**L** occurred with much higher regioselectivity (in the case of **2a**) and b/l selectivity (in the case of **2b**; Scheme 1c). These data show that the identity of the leaving group of the allylic electrophile alone does not control the site selectivities of these reactions. Instead, the combination of the phosphoramidite ligand (S_a,S_c,S_c)-**L** and



Scheme 1. Comparison of the results of control experiments.

the leaving group of the allylic electrophile is crucial to obtaining high regioselectivity at the nucleophiles and high b/l selectivity at the electrophile.

The dioxinone moiety is a useful precursor to a variety of functional groups.[12] To demonstrate the synthetic utility of our asymmetric allylations of dioxinones, a number of transformations of **3a** were conducted. As illustrated in Scheme 2,



Scheme 2. Derivatization of **3a**: a) K_2CO_3, MeOH, RT, 95%. b) BuOH, toluene, 120°C, 2 h, 78%. c) $BnNH_2$, toluene, 120°C, 2 h, 76%. d) 1. *N*-Benzyl-glycine ethyl ester, toluene, 130°C; 2. KO*t*Bu, THF, RT, 71% over two steps. e) Phenyl isocyanate, 130°C, 4 h, 78%.

treatment of **3a** with K_2CO_3 and MeOH at ambient temperature gave the β-keto ester **7** in 95% yield. The reaction of **3a** with butanol at 120°C for 2 hours gave the butyl ester **8** in 78% yield. Likewise, treatment of **3a** with benzylamine under the same reaction conditions produced the β-keto amide **9** in 76% yield.

In addition to serving as a masked β-keto ester, the dioxinone moiety in **3a** can be utilized for the synthesis of heterocycles, such as tetramic acids. These heterocyclic compounds are important pharmacophores in agrochemicals as well as pharmaceutical agents.[13] Treatment of **3a** with *N*-benzyl-glycine ethyl ester at 130°C for 2 hours provided the corresponding amide, which underwent subsequent Dieckmann cyclization under basic conditions to give the tetramic acid **10** in 71% yield (two steps; Scheme 2). The reaction of compound **3a** with phenyl isocyanate at 130°C afforded 1,3-oxazin-2,4-dione **11** in 78% yield.

In conclusion, we have developed an iridium-catalyzed γ-selective asymmetric allylation of silyl dienolates derived from dioxinones. By utilizing the silyl dienolate as the synthetic equivalent of the β-keto ester dianion, the inherent α-selectivity of β-keto esters was inverted to the γ-selectivity. Under the developed reaction conditions, asymmetric allylic substitution of a variety of allylic trichloroethyl carbonates with silyl dienolates gave γ-allylated products in 60–84% yield and 90–98% *ee* with high γ-selectivity and b/l selectivity. The control experiments revealed that the nature of the leaving group on the allylic electrophiles, in combination with the added chiral phosphoramidite ligand, is key to the high regioselectivity and b/l selectivity of the reaction. Further studies of silyl dienolates are currently underway in this laboratory.

Received: July 1, 2014
Published online: September 15, 2014

Keywords: alkylation · allylic compounds · asymmetric catalysis · enantioselectivity · iridium

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[14] CCDC 1023607 (**5j**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

