Synthetic Methods

International Edition: DOI: 10.1002/anie.201501851
German Edition: DOI: 10.1002/ange.201501851

Iridium-Catalyzed Enantioselective Allylic Alkylation with Functionalized Organozinc Bromides**

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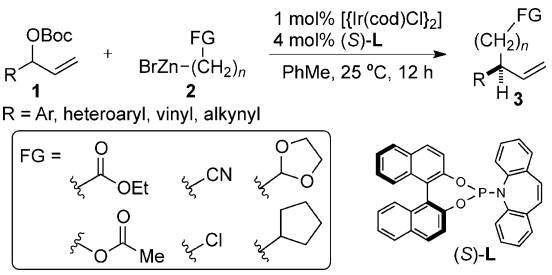
Abstract: *Iridium-catalyzed enantioselective allylic alkylation of branched racemic carbonates with functionalized alkylzinc bromide reagents is described. Enabled by a chiral Ir/(P,olefin) complex, the method described allows allylic substitution with various primary and secondary alkyl nucleophiles with excellent regio- and enantioselectivities. The developed reaction was showcased in a concise, asymmetric synthesis of (−)-preclamol.*

Transition metal-catalyzed asymmetric allylic substitution reactions are among the most powerful transformations currently available for the enantioselective formation of carbon–carbon bonds.[1] Among these, iridium-catalyzed allylic substitution reactions have recently enjoyed much attention, thus resulting in a wide range of reaction partners which can be employed.[2] Despite these significant advances, however, nonstabilized alkyl metal reagents are absent altogether as nucleophiles. The use of nonstabilized alkyl nucleophiles in iridium-catalyzed reactions would considerably expand the scope of such processes by providing new routes to previously inaccessible products, especially when the alkyl reagents incorporate functional groups for further elaboration.[3] Herein, we disclose the development of an enantioselective allylic alkylation reaction involving racemic branched allylic carbonates and functionalized alkylzinc bromide reagents, and it is catalyzed by a chiral iridium/(P,olefin) complex (Scheme 1). The method delivers adducts



Scheme 1. Iridium-catalyzed enantioselective allylic alkylation with RZnBr. cod = 1,5-cyclooctadiene.

including functionality such as esters, nitriles, halides, and acetals with high enantioselectivity (up to >99% *ee*) and complete branched regioselectivity. The synthetic utility of this method is demonstrated in an asymmetric synthesis of (−)-preclamol, a promising drug candidate for the treatment of schizophrenia.

Pioneering studies from the groups of Alexakis, Bäckvall, Feringa, and Hoveyda have led to impressive copper-catalyzed processes for asymmetric alkylations with various nonstabilized alkyl nucleophiles ($pK_a > 25$),[4] including Grignard,[5] organolithium,[6] organoaluminum,[7] and organozinc[8] reagents. Asymmetric allylic substitutions catalyzed by chiral complexes of palladium or iridium represent an alternative approach. Developments in palladium-catalyzed processes, the most extensively studied system in this field, have been hampered by deleterious competing mechanistic pathways such as β-hydride elimination. Thus, only recently Maulide and co-workers have disclosed palladium-catalyzed allylic alkylation using dialkylzinc reagents.[9]

In general, the high reactivity of nonstabilized alkyl nucleophiles has not only limited their utility in catalytic processes but also their compatibility with functional groups. Alkylzinc halides represent a notable exception, and yet they are a particularly attractive class of nonstabilized alkyl nucleophiles as a consequence of their superb functional-group tolerance and the fact that they transfer the sole alkyl group they bear.[10] Importantly, recent advances by Knochel and co-workers have allowed ready access to a wide variety of functionalized organozinc reagents.[11]

Chiral iridium complexes have recently emerged as versatile catalysts for regio- and stereoselective allylic substitution reactions.[2] In this context, we have developed and employed a complex formed from iridium(I) and a chiral phosphoramidite olefin bidentate ligand for a number of highly enantio- and diastereoselective carbon–carbon bond-forming transformations.[12] As part of an ongoing effort to extend the synthetic utility of the allyl iridium intermediates, we were intrigued by the possible use of functionalized alkylzinc bromides to gain access to a class of functionalized, optically pure adducts.[2p] To the best of our knowledge, allylic substitution with nonstabilized alkyl nucleophiles has not been documented with iridium catalysis.

In the initial screening studies, we examined the substitution reaction of the 2-naphthyl vinyl carbinol derivative **1** with the bis(homoenolate) reagent **2a**, prepared in THF, in the presence of a complex formed in situ from a phosphoramidite olefin ligand (*S*)-**L** and [{Ir(cod)Cl}$_2$] (Table 1). By employing the benzoyl ester of **1** in 1,4-dioxane (entry 1), the product **3a** was obtained in 90% *ee*, albeit in only 20% yield. A survey of different derivatives of **1** revealed the corre-

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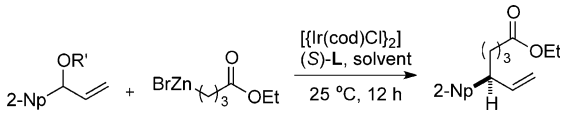
[**] We are grateful to the ETH Zürich and the Swiss National Science Foundation (200020_152898) for financial support.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201501851.

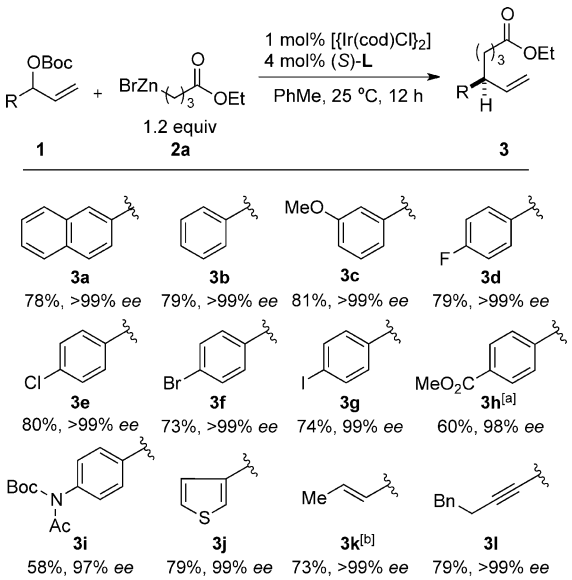
Table 1: Reaction development of enantioselective allylic alkylation.[a]



1 **2a** **3a**

Entry	Cat. [mol%]	R′	Equiv **2a** in THF	Solvent	Yield [%][b]	*ee* [%][c]
Variation of leaving group						
1	4	Bz	1.5 (0.5 M)	1,4-dioxane	20	90
2	4	TFA	1.5 (0.5 M)	1,4-dioxane	23	93
3	4	CO_2Me	1.5 (0.5 M)	1,4-dioxane	46	96
4	4	Boc	1.5 (0.5 M)	1,4-dioxane	61	89
Variation of organozinc concentration						
5	4	Boc	1.5 (1.0 M)	1,4-dioxane	73	96
6	4	Boc	1.5 (2.0 M)	1,4-dioxane	79	98
Optimization of catalyst loading, organozinc stoichiometry, and solvent						
7	1	Boc	1.5 (2.0 M)	1,4-dioxane	79	98
8	1	Boc	1.2 (2.0 M)	1,4-dioxane	78	>99
9	*1*	*Boc*	*1.2 (2.0 M)*	*PhMe*	*85*	*>99*

[a] Reaction conditions: [{Ir(cod)Cl}$_2$], [Ir]/(*S*)-**L** = 1:2, **1** (0.125 mmol, 1.0 equiv), **2a** (solution in THF), solvent (0.25 mL), 25 °C, 12 h. [b] Determined by ^{1}H NMR spectroscopy by using an internal standard (1,4-dinitrobezene). [c] Determined by supercritical fluid chromatography (SFC) on chiral stationary phase. Absolute configuration assigned by comparison with known compounds. Boc = *tert*-butoxycarbonyl, Bz = benzoyl, 2-Np = 2-naphthyl, TFA = trifluoroacetyl.



Scheme 2. Substrate scope of enantioselective allylic alkylation. Unless otherwise noted, all reactions performed on 0.25 mmol scale under the standard reaction conditions (see Table 1, entry 9). Yield of the isolated product after purification by chromatography on silica gel. Enantiomeric excess determined by SFC on chiral stationary phase. [a] 24 h reaction. [b] Obtained as a mixture of two branched regioisomers (15:1 = SN2/SN2′). Ac = acetyl, Bn = benzyl.

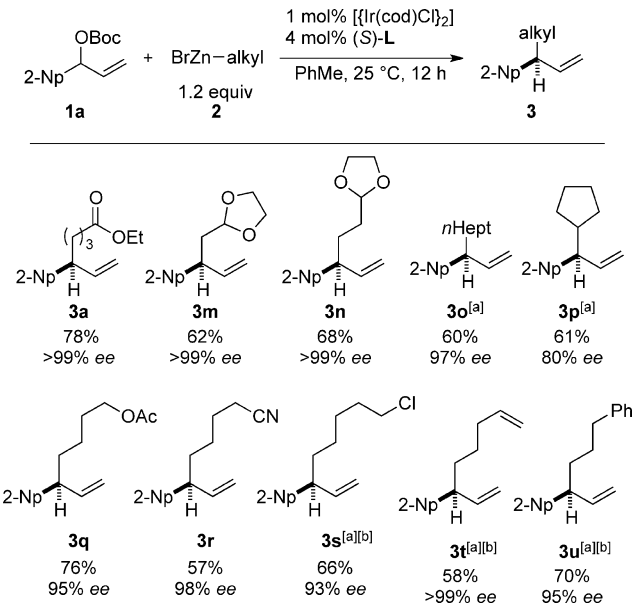
sponding *tert*-butyl carbonate as optimal, with **3a** formed in 61% yield and 89% *ee* (entries 2–4). The lower yield observed for the methylcarbonate derivative was traced back to the formation of the corresponding methyl ether byproduct (entry 3). Following the identification of the *tert*-butyl carbonate as optimal, we then turned our attention to the evaluation of reaction parameters (see Tables S1–S6 in the Supporting Information for full details).

Although **2a** was prepared as a 0.5 M solution in THF following the protocol of Knochel, we found that increasing the concentration of **2a** to 2.0 M by partial evaporation of THF under reduced pressure was advantageous to the reaction outcome (Table 1, entries 5 and 6). Thus, the use of **2a** (2.0 M in THF) furnished **3a** in 79% yield and 98% *ee* (entry 6). The use of only 1 mol% [{Ir(cod)Cl}$_2$] and 1.2 equivalents of **2a** led to comparable product yield and greater than 99% *ee* (entry 8). With toluene as optimal solvent, the coupled product was obtained in 85% yield and greater than 99% *ee* (entry 9). Finally, we note that formation of the undesired, achiral linear alkylation adduct was not detected throughout this study.[13]

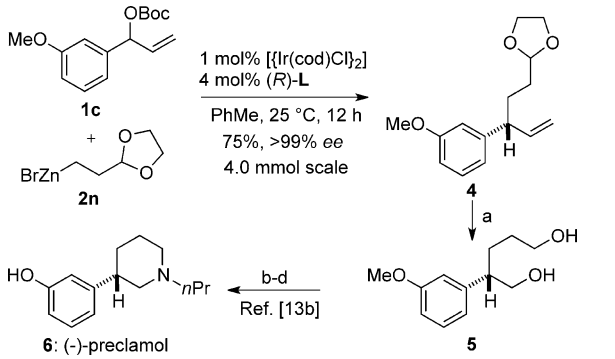
Having identified optimized reaction conditions for enantioselective alkylation, we explored the substrate scope of this reaction with **2a** as a standard nucleophile as summarized in Scheme 2. Unsubstituted (**3b**) as well as alkoxy-substituted (**3c**) phenyl substrates gave the corresponding adducts in 79 and 81% yield, respectively and greater than 99% *ee*. Substrates incorporating halogenated arenes (**3d**–**g**) were also compatible with the process. Although the substrate possessing an electron-withdrawing ester substituent resulted in a diminished yield (60%) because of lower conversion, the adduct **3h** was produced in 98% *ee*. Additionally, aromatics with appended protected amines (**3i**) and heteroaromatic (**3j**) allyl carbonates underwent the asymmetric allylic alkylation successfully. Gratifyingly, 1,4-diene **3k** and 1,4-enyne **3l** furnished adducts in high yields with greater than 99% *ee*.[5g] Aliphatic allylic carbonates did not undergo the described allylic alkylation.

As shown in Scheme 3, we then examined a variety of alkylzinc bromides under the optimal reaction conditions, using **1a** as a standard reaction partner. Alkylzinc reagents of the protected aldehydes **2m** and **2n** underwent the reaction with good yields (62–68%) and greater than 99% enantiocontrol. Simple primary (**2o**) as well as secondary (**2p**) alkylzinc bromides could be employed with the latter forming the adduct with diminished enantioselectivity (80% *ee*). Functional groups such as acetoxy (**2q**), cyano (**2r**), and chloro (**2s**) groups, which may be incompatible with other main group organometallic reagents, were well tolerated. Alkylzinc bromides incorporating an alkene (**2t**) and an arene (**2u**) also engaged in allylic alkylation reactions with 58–70% yield and greater than 99 and 95% *ee*, respectively.

As a means of highlighting the synthetic utility of the method, we examined an enantioselective synthesis of (−)-preclamol,[14] a potent dopaminergic drug candidate with antipsychotic therapeutic effects for the treatment of schizophrenia.[15] As illustrated in Scheme 4, exposure of the allylic carbonate **1c** to the alkylzinc bromide reagent **2n** under optimized reaction conditions afforded **4** in 75% yield and greater than 99% *ee*. Reaction of **4** with ozone followed by reductive work up gave the diol **5**, which was then subjected to a three-step sequence[14b] of reactions to deliver (−)-precla-



Scheme 3. The scope of alkylzinc bromide in enantioselective allylic alkylation. Unless otherwise noted, all reactions performed on 0.25 mmol scale under the standard conditions (see Table 1, entry 9). Yield of the isolated product after purification by chromatography on silica gel. Enantiomeric excess determined by SFC on chiral stationary phase. [a] Reaction conducted in ethylacetate as solvent. [b] Reaction conducted with 2 mol% [{Ir(cod)Cl}$_2$] and 8 mol% (*S*)-**L**.



Scheme 4. Enantioselective synthesis of (−)-preclamol. Reagents and conditions: a) O_3, CH_2Cl_2, −78 °C, then LAH, 25 °C, 70%, >99% *ee*; b) MsCl, Et_3N, 25 °C; c) propylamine, neat, 25 °C; d) aqueous HBr, 120 °C. LAH = lithium aluminum hydride, MsCl = methanesulfonyl chloride.

mol (**6**). The robustness of the substitution reaction was demonstrated by the ability to conduct the asymmetric allylic alkylation on a larger scale (1.1 g, 4.0 mmol).

In summary, we have disclosed an iridium-catalyzed asymmetric alkylation involving branched racemic carbonates and functionalized alkylzinc bromide reagents. The method provides products with high regio- and stereoselectivity. The high functional group compatibility of alkylzinc bromides enables access to enantioenriched polyfunctional scaffolds. In addition to aromatic and heteroaromatic carbonates, 1,4-diene and 1,4-enyne substrates underwent the reaction successfully with superb selectivity. The practicality of this transformation has been further demonstrated with a gram-scale reaction. Finally, the synthetic utility of this methodology has been showcased in a concise catalytic enantioselective synthesis of (−)-preclamol.

Experimental Section

General procedure: [{Ir(cod)Cl}$_2$] (1.7 mg, 2.5 μmol, 1 mol%) and the phosphoramidite ligand (*S*)-**L** (5.1 mg, 10.0 μmol, 4 mol%) were dissolved in toluene (0.5 mL) and vigorously stirred for 15 min under an atmosphere of N_2. To the resulting dark red solution, allylic carbonate **1** (0.25 mmol, 1.0 equiv) and alkylzinc bromide **2** (0.15 mL, 0.30 mmol, 1.2 equiv) were sequentially added. The orange reaction mixture was stirred under N_2 at 25 °C for 12 h. Upon complete consumption of the starting material, one drop of methanol was added to the mixture, which was then directly subjected to flash chromatography to afford the product.

Keywords: alkylation · allylic compounds · enantioselectivity · iridium · zinc

How to cite: *Angew. Chem. Int. Ed.* **2015**, *54*, 7644–7647
Angew. Chem. **2015**, *127*, 7754–7757

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Received: February 26, 2015
Published online: May 12, 2015

