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Enantioselective Ir-Catalyzed Allylic Alkylation of Racemic Allylic Alcohols with Malonates

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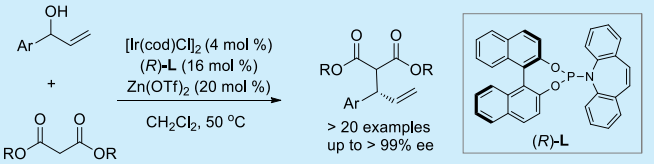
Supporting Information

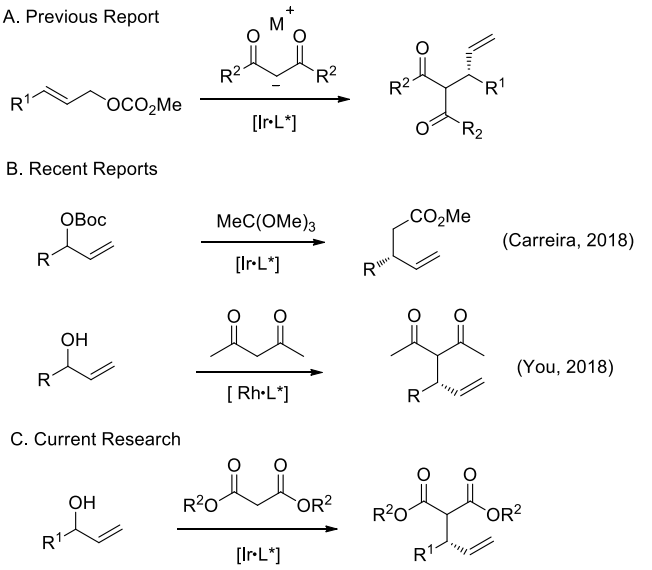
ABSTRACT: Ir-catalyzed enantioselective allylic alkylation of branched racemic allylic alcohols with malonates is described. Enabled by Carreira's chiral Ir/(P, olefin) complex, the method described allows allylic substitution with various aromatic alcohols and malonates with excellent enantioselectivity. The malonates could be used directly as efficient nucleophiles without the need of preactivation.



Transition-metal-catalyzed allylic substitution is a cornerstone of organometallic and synthetic chemistry. Enantioselective allylation has been developed with catalysts derived from a number of transition metals such as palladium, molybdenum, nickel, ruthenium, rhodium, copper, and iridium.[1] Among these metals, the palladium- and iridium-catalyzed versions are particularly useful in organic synthesis due to the wide scope of the nucleophile and functional group compatibility. However, in contrast to palladium, the iridium-catalyzed allylic substitutions are more regioselective, providing branched, chiral products.[2] Over the last two decades, two types of allylic electrophiles have emerged in iridium-catalyzed allylic substitution. In the first type, introduced by Takeuchi and Helmchen in 1997, linear allylic esters are frequently employed as substrates under basic reaction conditions.[3] In the second type, introduced by Carreira in 2007, environmentally friendly branched allylic alcohols, occasionally derivatives of branched alcohols, can be used under acidic conditions.[4]

Inspired by the original and systematic studies of the Carreira group,[5] we recently carried out a series of total syntheses of natural alkaloids based on the strategical applications of the Ir-catalyzed allylic substitution.[6] During the exertion of total synthesis, we found an interesting phenomenon in the literature. Although many papers reporting the use of malonates, stabilized enolates, or active methylene compounds as the nucleophile in the iridium-catalyzed allylation have been documented in the literature,[7] none of them concerns malonate as a nucleophile and branched alcohol as an electrophile (Scheme 1). In this context, we proposed that a new Ir-catalyzed asymmetric allylation of racemic secondary alcohol with malonate could be realized under the appropriate conditions. Notably, during our studies, Carreira reported an elegant methodology for the Ir-catalyzed allylation of branched allylic carbonates, in which the trimethyl orthoacetate acts as an enolate surrogate (Scheme 1).[8] Meanwhile, You et al. disclosed an asymmetric Rh-catalyzed allylic alkylation of branched alcohols with 1,3-diketones.[9] Here we wish to report our own results.

Scheme 1. Ir- or Rh-Catalyzed Asymmetric Allylic Alkylation



The initial prospecting reactions were carried out with methyl malonate (**2a**) and phenyl vinyl carbinol (**1a**). With $Zn(OTf)_2$ as a promoter in combination with $[Ir(cod)Cl]_2$ and Carreira ligand (*R*)-**L** as the catalyst and DCE as the solvent, product **3a** was obtained in 68% yield, with 99% ee (Table 1, entry 1). Prolonging the reaction time from 3 to 6 h can improve the yield but can also erode the enantioselectivity (entry 2). When the reaction was promoted by $Yb(OTf)_3$, the product was obtained in higher yields than those of $Zn(OTf)_2$ but with slightly lower enantioselectivity (entries 3 and 4). Subsequent experimentation revealed that other promoters

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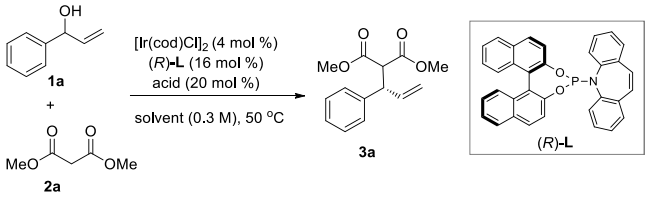
Table 1. Optimization of the Reaction Conditions[a]



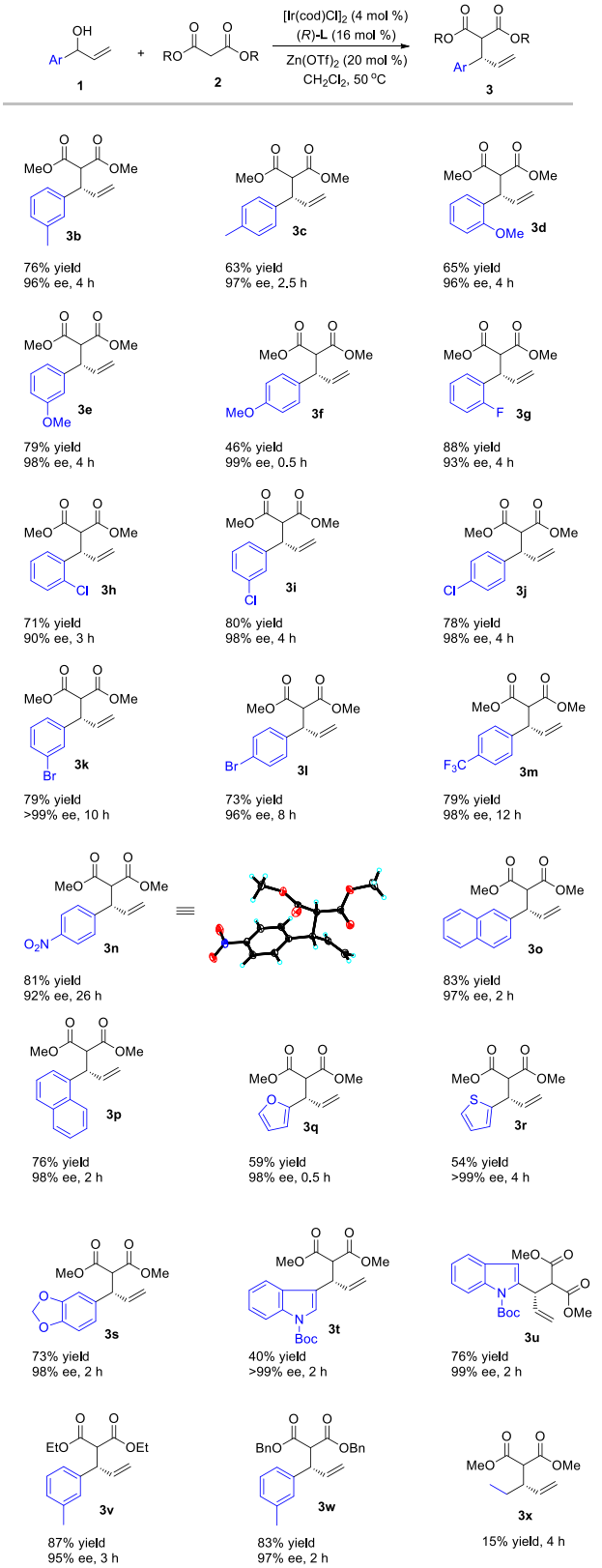
entry	acid	solvent	time (h)	yield[b] (%)	ee[c] (%)
1	$Zn(OTf)_2$	DCE	3	68	99
2	$Zn(OTf)_2$	DCE	6	78	96
3	$Yb(OTf)_3$	DCE	4	77	93
4	$Yb(OTf)_3$	DCE	6	88	89
5	$Sc(OTf)_3$	DCE	3	28	97
6	$Bi(OTf)_3$	DCE	2	0	n.d.
7	$In(OTf)_3$	DCE	6	0	n.d.
8	TFA	DCE	5	0	n.d.
9	$BF_3{\cdot}Et_2O$	DCE	5	0	n.d.
10	$Zn(OTf)_2$	toluene	6	72	91
11	$Zn(OTf)_2$	THF	5	88	90
12	$Zn(OTf)_2$	DCM	5	90	96
13	$Zn(OTf)_2$	1,4-dioxane	5	76	90
14[d]	$Zn(OTf)_2$	DCM	2	92	>99

[a]Reaction conditions: **1a** (0.1 mmol, 1.0 equiv), **2a** (0.3 mmol, 3.0 equiv), $[Ir(cod)Cl]_2$ (4 mol %), (*R*)-**L** (16 mol %), acidic promoter (20 mol %), solvent (0.3 mL, 0.3 M), 50 °C, 2−6 h. [b]Isolated yield. [c]Determined by HPLC. n.d. = not determined. [d]Reaction conducted on a 5.0 mmol scale.

such as $Sc(OTf)_3$, $Bi(OTf)_3$, $In(OTf)_3$, $BF_3{\cdot}Et_2O$, and TFA afforded the product in very low yield or no product at all (entries 5−9). After change of the solvents, dichloromethane was identified as superior to toluene, THF, or 1,4-dioxane and optimal as the solvent for this allylic substitution reaction (entries 10−13). To test the utility of this methodology, the reaction was performed on a 5.0 mmol scale, and the outcome was excellent (entry 14).

Having established optimal conditions, we next set out to explore the substrate scope and generality of this allylic substitution reaction by using methyl malonate (**2a**), as summarized in Scheme 2. Thus, a number of methyl-substituted (**3b** and **3c**) and methoxyl-substituted (**3d** and **3e**) aromatics all furnished vinylated products in good yields and excellent enantioselectivities. Although a noticeable decrease in yield was observed in the case of the *p*-MeO-substituted aryl allylic alcohol (**3f**) and its cause is unclear, a very high ee value still was obtained. Other halogenated substrates (**3g**−**3l**) are tolerated, and all provided the desired products with great efficiency. The tolerance of this reaction toward a more electronically demanding substrate is demonstrated in the successful conversion of the *p*-CF_3- or *p*-NO_2-substituted aryl alcohols (**3m** and **3n**). Furthermore, other aromatic and heteroaromatic systems could be employed, as showcased by the example of naphthalene, furan, thiophene, benzodioxole, and indole (**3o**−**3u**). These substrates gave rise to the product in moderate to good yields and high enantioselectivities. In addition, other malonates gave excellent results (**3v** and **3w**). From all of the surveyed substrates, **3n** is a crystalline compound whose absolute stereochemical configuration was verified by the X-ray crystallographic analysis using Cu Kα radiation. The absolute configurations of all products in Scheme 2 were assigned by

Scheme 2. Substrate Scope of the Aromatic Racemic Allylic Alcohols[a,b,c]



[a]Unless otherwise noted, all reactions were performed on a 0.1 mmol scale under the standard conditions. [b]Isolated yields. [c]Enantiomeric excess values were determined by HPLC on a chiral stationary phase.

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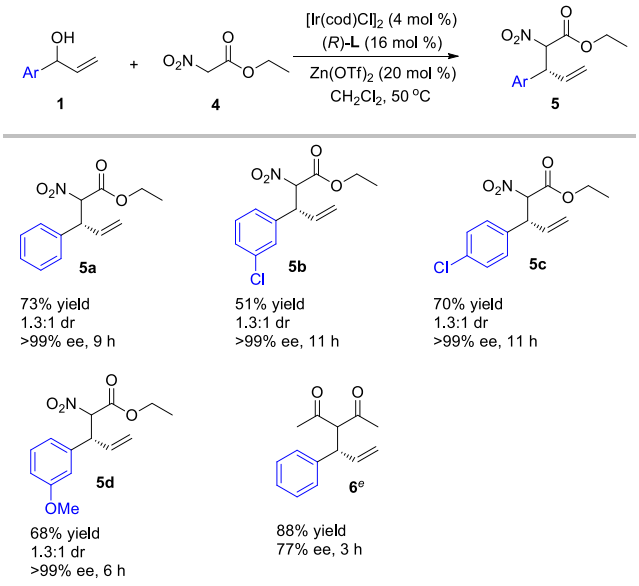
analogy. Currently, one limitation of the reaction is that it is not applicable to the aliphatic allylic alcohol because of the very low yield (**3x**).

As shown in Scheme 3, we also briefly examined ethyl nitroacetate and acetylacetone as nucleophiles. For the former,

Scheme 3. Allylation with Ethyl Nitroacetate[a,b,c,d]



[a]Reactions run on a 0.1 mmol scale under the standard conditions. [b]Isolated yields. [c]ee determined by HPLC on a chiral stationary phase. [d]dr determined by ^{1}H NMR analysis of crude reaction mixture. [e]Acetylacetone used instead of ethyl nitroacetate.

in the presence or absence of substitutes on the phenyl ring, either of an electron-withdrawing group (**5b** and **5c**) or an electron-donating group (**5d**), the reactions took place smoothly, albeit with poor diastereocontrol (dr 1.3:1). Corresponding products were obtained in good yields and excellent enantioselectivities. In the case of acetylacetone (**6**), decreased enantioselectivity was observed.[10]

In conclusion, we have disclosed an iridium-catalyzed asymmetric allylation of malonates with racemic secondary allylic alcohols. The methodology affords the products with excellent enantioselectivity and high functional group tolerance. The use of readily available, branched allylic alcohols and malonates which do not have to be activated beforehand is a salient feature. The application of this methodology to total synthesis is ongoing.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b04143.

Full characterization, analysis of enantioselectivity, spectral data, and experimental procedures (PDF)

Accession Codes

CCDC 1882503 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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