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Enantioselective γ-Alkylation of α,β-Unsaturated Malonates and Ketoesters by a Sequential Ir-Catalyzed Asymmetric Allylic Alkylation/Cope Rearrangement

Wen-Bo Liu,[†] Noriko Okamoto,[†] Eric J. Alexy, Allen Y. Hong, Kristy Tran, and Brian M. Stoltz*

Warren and Katharine Schlinger Laboratory for Chemistry and Chemical Engineering, Division of Chemistry and Chemical Engineering, California Institute of Technology, Pasadena, California 91125, United States

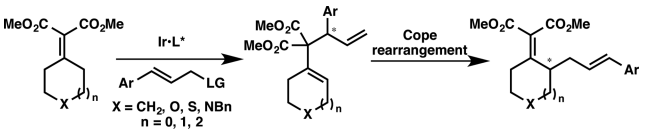
Supporting Information

ABSTRACT: A catalytic, enantioselective γ-alkylation of α,β-unsaturated malonates and ketoesters is reported. This strategy entails a highly regio- and enantioselective iridium-catalyzed α-alkylation of an extended enolate, and a subsequent translocation of chirality to the γ-position via a Cope rearrangement.

Enantioenriched unsaturated carbonyl compounds are valuable synthetic intermediates owing to their multiple reactive sites poised for further manipulation to synthesize complex molecules with contiguous stereocenters.[1] Direct asymmetric functionalization at the γ-position of α,β-unsaturated carbonyl derivatives would be a straightforward way to access such motifs. However, this transformation has proven challenging, likely due to the absence of proximal functionality to interact with a catalyst in order to induce facial selectivity. Furthermore, issues arise with regard to regioselectivity (α- vs γ-functionalization) and chemoselectivity (C- vs O-alkylation). To date, this transformation has only been achieved in a handful of examples.[2,3] In particular, work from the Tunge group demonstrated the ability of α,β-unsaturated carbonyls to undergo palladium-catalyzed decarboxylative allylation/Cope rearrangement, but only one asymmetric example with an alkylidene malononitrile was provided with poor enantiocontrol.[2b] Recently, the Jørgensen group reported an asymmetric γ-allylation of α,β-unsaturated aldehydes via organocatalysis combined with either iridium or palladium catalysis, providing branched or linear products, respectively.[3g] Alternatively, a Birch−Cope sequence has been developed by the Malachowski group as an efficient method to access γ-alkylated α,β-unsaturated ketoesters, although stoichiometric alkali metals and chiral auxiliaries were required.[4] Despite these reports, a general strategy to selectively produce γ-functionalized unsaturated carbonyl derivatives has remained elusive.

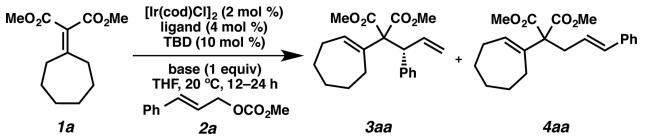
Since the initial report in 1997, iridium-catalyzed allylic alkylation has emerged as a successful strategy for the assembly of chiral chemical architectures.[5,6] Numerous studies have been performed in this field elucidating a wide range of suitable nucleophiles.[5,7] However, the use of α,β-unsaturated carbonyls as nucleophiles has seen little attention.[3g] We hypothesized that α-alkylation of extended enolates derived from such compounds could provide chiral 1,5-dienes poised to undergo a [3,3]-sigmatropic rearrangement, producing γ-alkylation products (Scheme 1).[8] A similar approach was utilized by Arseniyadis and Cossy to produce γ-substituted 2(5*H*)-furanones.[9]

Scheme 1. Sequential Asymmetic Allylic Alkylation/Cope Rearrangement



We began our studies with the seven-membered cyclic alkylidene malonate **1a** and cinnamyl carbonate **2a** as the model substrates (Table 1). A variety of conditions including different bases, solvents, and substrate ratios were examined with iridacycle catalysts[10] generated in situ by the treatment of $[Ir(cod)Cl]_2$ and phosphoramidites (Figure 1) with 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD).[11,12] Using *N*-aryl

Table 1. Optimization of Ir-Catalyzed Allylic Alkylation Reactions.[a]



entry	ligand	base	conv (%)[b,c]	3aa/4aa[b]	ee of 3aa (%)[d]
1	**L1**	KO*t*-Bu	>95 (57)	3:1	>99
2	**L2**	KO*t*-Bu	<10[e]	-	-
3	**L3**	KO*t*-Bu	>95[e]	>20:1	> 99
4	(±)-**L4**	KO*t*-Bu	>95	1:1	-
5	**L5**	KO*t*-Bu	52	2:1	40
6	**L6**	KO*t*-Bu	>95 (69)	>20:1	>99
7[f]	**L6**	KO*t*-Bu	89 (84)	>20:1	>99
8[f]	**L6**	LiO*t*-Bu[g]	92 (90)	>20:1	>99
9[h]	**L6**	LiO*t*-Bu[g]	>95 (93)	>20:1	>99

[a]Reactions performed with 0.1 mmol of **2a**, 0.2 mmol of **1a**, 0.1 mmol of base in 1 mL of THF at 20 °C for 12−24 h. [b]Regioselectivity determined by ^{1}H NMR analysis of the crude reaction mixture. [c]Yields of isolated product **3aa** given in parentheses. [d]Determined by SFC. [e]Complex mixture. [f]With 0.1 mmol of **1a** and 0.15 mmol of **2a**. [g]1.2 equiv. [h]With 0.1 mmol of **1a** and 0.2 mmol of **2a**.

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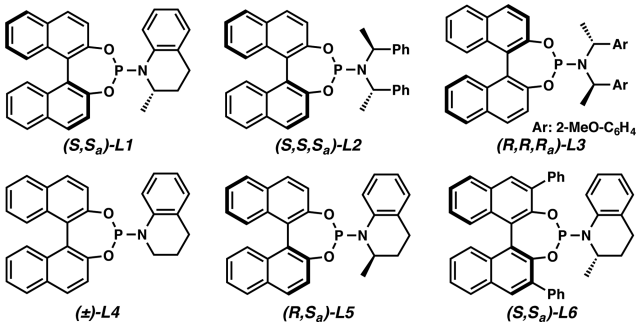
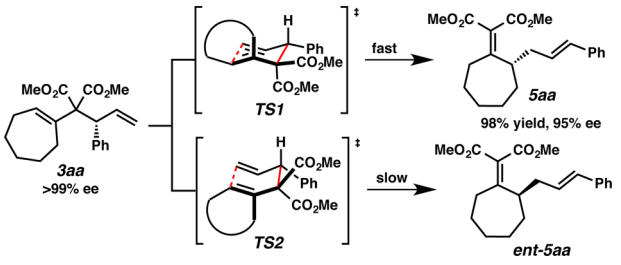


Figure 1. Representative phosphoramidite ligands.

phosphoramidite ligand **L1**, developed by the You group,[12,13] α-alkylation product **3aa** is furnished in perfect enantioselectivity and moderate regioselectivity (entry 1). The investigation of solvents revealed that THF affords optimal reactivity and selectivity (see SI for details). The use of Feringa-type ligands[14] **L2** and **L3** resulted in either a lack of reactivity or formation of a complex mixture of side products (entries 2 and 3). Moreover, ligands **L4** and **L5** led to diminished regio- and enantioselectivity, respectively (entries 4 and 5). The use of the more sterically congested 3,3′-diphenyl-substituted phosphoramidite **L6**[15] resulted in a dramatic improvement in regioselectivity and a modest improvement in yield (entry 6). After a careful analysis of the crude reaction mixture, we found that the moderate yield is due to hydrolysis of the carbonate under the reaction conditions. Thus, by increasing the quantity of the carbonate (1.5−2 equiv) and switching the base (LiO*t*-Bu), we were able to obtain the desired product **3aa** in 93% yield, >99% ee, and >20:1 regioselectivity (entries 8 and 9). The absolute configuration of α-alkylated product (*R*)-**3aa** was determined by X-ray crystallography.[16]

With optimized conditions for the α-alkylation procedure established, we next examined the possibility of intramolecular chirality transfer by a Cope rearrangement. To our delight, 1,5-diene **3aa** was converted to the rearranged γ-alkylated product **5aa**[17] in 98% yield and 95% ee after heating in toluene (Scheme 2). The high degree of chirality transfer (96%)[18] can be

Scheme 2. Cope Rearrangement of 3aa[a]

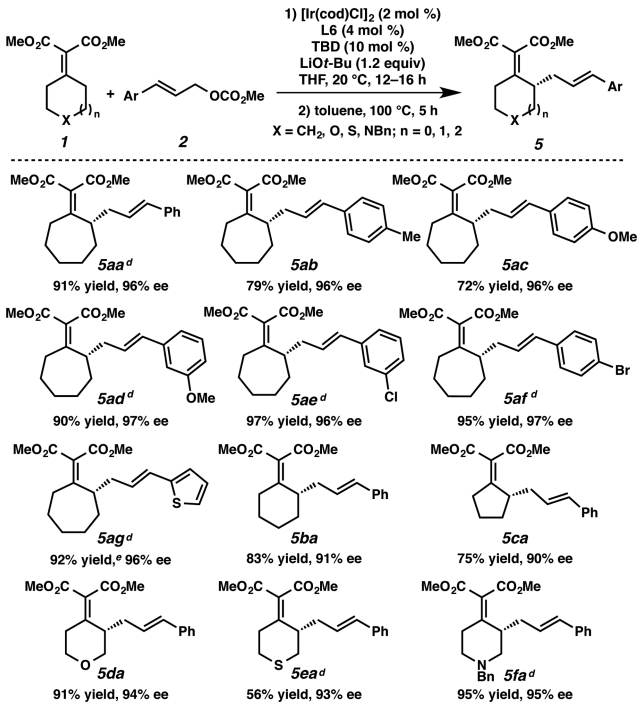


[a]Reaction conditions: 0.1 mmol of **3aa** in toluene at 100 °C for 5 h.

rationalized by the preferential rearrangement of the diene **3aa** through a chairlike transition state (**TS1**), over the corresponding boatlike transition state (**TS2**). A one-pot procedure for the allylic alkylation/Cope rearrangement is also possible, providing the product **5aa** in 91% overall yield and 96% ee (Scheme 3).

We next explored the impact of functional groups and ring size on this sequential protocol (Scheme 3).[19] A variety of cinnamyl carbonates containing either electron-rich or electron-deficient substituents are well tolerated, and the corresponding γ-

Scheme 3. Substrate Scope of Sequential (One-Pot) Ir-Catalyzed Allylic Alkylation/Cope Rearrangement[a,b,c]



[a]Reactions performed on a 0.2 mmol scale in 2 mL of THF at 20 °C for 12−16 h, followed by stirring in toluene at 100 °C for 5 h, see SI for details. [b]Regioselectivity of the allylic alkylation determined by ^{1}H NMR analysis of the crude mixture (>20:1 b:l for all cases), and ee determined by SFC. [c]Yields of isolated product. [d]One-pot procedure employed. [e]Inseparable mixture with carbonate **2g**, NMR yield.

alkylation products (**5ab**−**5af**) were obtained in high yield and excellent enantioselectivity. Moreover, a thienyl-substituted allylic carbonate is also compatible in this reaction, delivering product **5ag** in good yield and enantioselectivity. Five- and six-membered unsaturated malonates provide the desired products (**5ca** and **5ba**), albeit in slightly decreased yield (75% and 83%) and enantioselectivity (90% ee and 91% ee), respectively. Notably, oxygen, sulfur, and nitrogen containing heterocycles were compatible, providing the corresponding products (**5da**−**5fa**) in excellent ee and yield, except for **5ea**, which was obtained in moderate yield.

Concurrent with these studies, we investigated the reactivity of a endocyclic α,β-unsaturated β-ketoesters, a more challenging class of nucleophiles. It is widely appreciated that iridium-catalyzed allylic alkylation of prochiral nucleophiles can be problematic due to a lack of diastereocontrol during the formation of vicinal stereocenters.[5] Until recently, success has been limited to only a few examples.[13,20,21] Subjecting α,β-unsaturated β-ketoester **6a** to a slightly modified version of our optimized conditions, the branched product **7aa** was formed exclusively, but as a 1:1 mixture of diastereomers (entry 1, Table 2). When ligand **L1** was used, a slight increase in diastereo- and enantioselectivity was obtained (entry 2). Lowering the reaction temperature gave modest improvement in diastereoselectivity; however, the reaction required days to reach a satisfactory conversion (entry 3).

Unfortunately, despite extensive attempts to further enhance the diastereoselectivity, no improved conditions were identified. We therefore decided to move forward with this moderate

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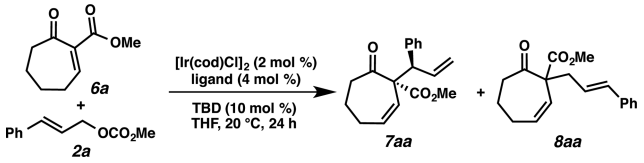
Table 2. Ir-Catalyzed Allylic Alkylation of Cyclic α,β-unsaturated Ketoester 6a[a]

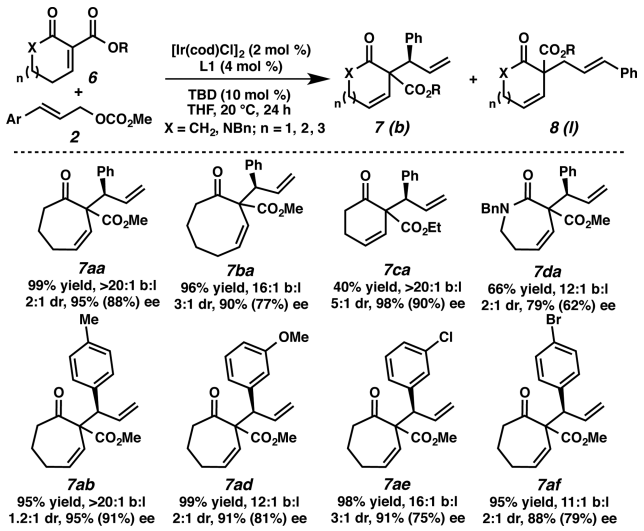


entry	ligand	conv (%)[b]	7aa/8aa[b]	dr of 7aa[b]	ee of 7aa (%)[c]
1	L6	>95	>20:1	1:1	89 (70)
2	L1	>95 (99)[d]	>20:1	2:1	95 (88)
3[e]	L1	>95	>20:1	5:1	98 (89)

[a]Reactions performed with 0.4 mmol of **6a** and 0.2 mmol of **2a** in 2 mL of THF. [b]Determined by ^{1}H NMR analysis. [c]Determined by SFC. [d]Combined yields of isolated diastereomers. [e]At 0 °C for 7 d.

diastereoselectivity and evaluate the substrate scope of the reaction with regard to both reaction partners (Scheme 4). It is

Scheme 4. Substrate Scope of Ir-Catalyzed Allylic Alkylation of Cyclic α,β-unsaturated β-Ketoester[a,b,c,d]

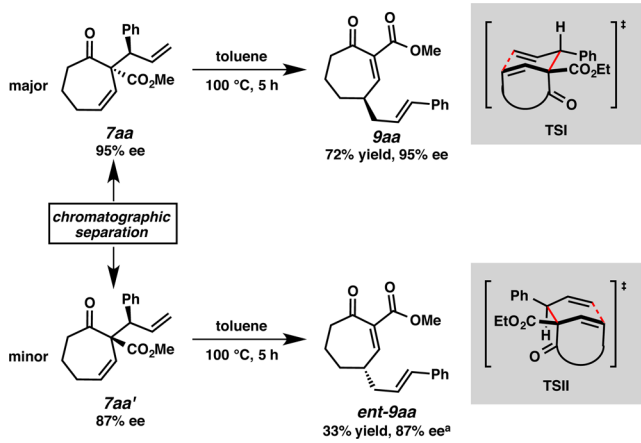


[a]Reactions performed with 0.4 mmol of **6** and 0.2 mmol of **2** in 2 mL of THF. [b]Regioselectivity (b:l) was determined by ^{1}H NMR analysis of the crude mixture and ee was determined by SFC. [c]Combined yields of isolated diastereomers. [d]ee of the minor diastereomer given in parentheses.

worth noting that in each case, both diastereomers were isolated and characterized (see SI for details). The reaction with an eight-membered unsaturated β-ketoester gave desired product **7ba** with high branched selectivity and moderate diastereoselectivity. Six-membered substrate afforded the corresponding alkylation product **7ca**[22] with an increased diastereo- and regioselectivity, but in only moderate yield due to the decomposition of the β-ketoester **6c** during the reaction. Lactam derivative **7da** was also accessed, although with diminished enantioselectivities for both diastereomers. Finally, several carbonates bearing various electronically differentiated substituents were found to be well tolerated, and the corresponding products **7ad**–**7af** were furnished in good yield, with high enantioselectivity and moderate diastereoselectivity.

Having investigated the allylic alkylation, we next turned to the Cope rearrangement (Scheme 5). The major isomer (**7aa**) undergoes the rearrangement more readily than the minor

Scheme 5. Cope Rearrangement of Diastereomeric 1,5-Dienes 7



[a]Unreacted **7aa′** was recovered in 61% yield and 86% ee.

isomer **7aa′**. Again, this is likely due to geometrical differences of a chairlike transition state of the major isomer (**TSI**) in contrast to a boat like transition state of the minor isomer (**TSII**). The rigidity of the transition state plays a key role in enabling the chirality transfer (>99%).[4b] It is worth noting that the rearranged γ-alkylation products from the major isomer **7aa** and the minor isomer **7aa′** have opposite absolute configurations (Scheme 5). Since the diastereomers **7aa** and **7aa′** have identical tertiary chiral centers, the outcome of the rearrangement is controlled solely by the quaternary center.

In summary, we have developed a sequential iridium-catalyzed allylic alkylation/Cope rearrangement to synthesize enantioenriched γ-substituted α,β-unsaturated malonates and β-ketoesters. The initial alkylation reaction provides efficient access to chiral 1,5-dienes with high regio- and enantioselectivities, with *N*-aryl phosphoramidite ligands being crucial. Selective translocation of the newly established chirality to the γ-position was realized by a subsequent thermal Cope rearrangement. Further studies toward the application of this useful method in natural product synthesis are currently ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b02153.

Experimental procedures and characterization data (PDF)
^{1}H NMR and ^{13}C NMR spectra (PDF)
Single crystal X-ray analysis (CIF)
Single crystal X-ray analysis (CIF)

■ AUTHOR INFORMATION

Corresponding Author

*stoltz@caltech.edu

Author Contributions

†These authors contributed equally to this work.

Notes

The authors declare no competing financial interest.

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(16) See Supporting Information for details.

(17) The absolute structure of **5aa** was assigned by X-ray analysis of its derivative, see Supporting Information for details.

(18) Chirality transfer = $(ee_{product}/ee_{substrate}) \times 100\%$.

(19) Certain γ-alkylation products and starting materials were inseparable, thus a two-step procedure was required, see Supporting Information.

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(22) See SI for the assignment of the absolute structure of **7ca**.

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