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Arynes and Cyclic Alkynes as Synthetic Building Blocks for Stereodefined Quaternary Centers

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Abstract

We report a facile method to synthesize stereodefined quaternary centers from reactions of arynes and related strained intermediates using β -ketoester-derived substrates. The conversion of β -ketoesters to chiral enamines is followed by reaction with in situ generated strained arynes or cyclic alkynes. Hydrolytic workup provides the arylated or alkenylated products in enantiomeric excesses as high as 96%. We also describe the one-pot conversion of a β -ketoester substrate to the corresponding enantioenriched α -arylated product. Computations show how chirality is transferred from the *N*-bound chiral auxiliary to the final products. These are the first theoretical studies of aryne trapping by chiral nucleophiles to set new stereocenters. Our approach provides a solution to the challenging problem of stereoselective β -ketoester arylation/alkenylation, with formation of a quaternary center.

Graphical Abstract

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Notes

The authors declare no competing financial interest.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: [10.1021/jacs.8b02875](https://doi.org/10.1021/jacs.8b02875).

Detailed experimental procedures, compound characterization data, and computational analysis (PDF)

Data for C₂₁H₂₅NOS (CIF)

INTRODUCTION

Arynes have historically been avoided as synthetic intermediates as a result of their high reactivity.^{1,2} However, recent studies have demonstrated that arynes can be generated under mild reaction conditions,³ trapped regioselectively using predictive models,⁴ and employed in a host of synthetic applications. The utility of arynes is evident, as they have now been used to synthesize natural products, ligands, materials, agrochemicals, and pharmaceutical agents (e.g., **1–3**, Figure 1a).^{1,5}

The majority of reported synthetic applications of arynes are intermolecular reactions that lead to achiral or racemic products.^{5d,e,6} We questioned if arynes and related strained intermediates could instead serve as building blocks to generate enantioenriched products bearing quaternary centers. Only two methodologies leading to intermolecular, stereoselective aryne trappings have been reported and are limited to the synthesis of tertiary stereocenters.^{7,8}

We considered the reaction manifold in which β -ketoesters **4**⁹ would be trapped with strained alkynes **5**, to give their corresponding α -arylated products **6** with formation of a quaternary stereocenter (Figure 1b).¹⁰ As prior efforts to achieve this direct functionalization in a racemic sense were accompanied by an undesired C–C bond fragmentation,¹¹ we considered a two-step, alternative approach. First, β -ketoesters **4** would be treated with amines **7** to afford the corresponding enamines **8**.¹² Trapping of the enamines **8** with in situ-generated arynes (or strained cyclic alkynes) would give the α -arylated or alkenylated products **6** after hydrolysis in the same pot.¹³ The use of a chiral amine (i.e., **7**) in this process would ultimately give rise to enantioenriched products **6** bearing quaternary stereocenters.^{10,14} It should be noted that the enantioselective α -arylation of β -ketoesters has remained a challenging synthetic problem.¹⁵ Promising developments include the use of hypervalent iodine reagents (racemic or modest enantioenrichment),¹⁶ the Cu-catalyzed, enantioselective coupling of 2-methyl acetates with 2-iodotrifluoroacetanilides,¹⁷ and the Pd-catalyzed α -arylation of malonates and cyanoacetates (racemic).¹⁸ A general method for the stereo-controlled α -arylation or -alkenylation of β -ketoesters has not been disclosed.

We report the development of the synthetic sequence shown in Figure 1b, which provides a facile method to achieve the stereoselective α -arylation/alkenylation of β -ketoesters.⁹ In addition to providing access to adducts bearing stereodefined quaternary centers, this methodology demonstrates that highly reactive arynes and related intermediates can serve as building blocks to access enantioenriched products by intermolecular trapping. In addition, the origins of stereoselectivity have been revealed by a computational investigation of these reactions.

RESULTS AND DISCUSSION

Development of a Racemic and Stereospecific Reaction to Generate Quaternary Centers.

To commence our studies, we selected β -ketoester **9** as an initial substrate for the two-step arylation procedure (Figure 2). As the use of enamines and arynes to construct quaternary stereocenters was unknown, we first pursued a racemic transformation. Benzylamine was

condensed with ketoester **9** to yield enamine **10** quantitatively. Next, enamine **10** was used to trap benzyne, which was generated in situ from silyl triflate **11** (1.5 equiv) in DME at 30 °C (6 h). After quenching with 1 M HCl_(aq), we were delighted to obtain the desired α -arylated product **12** in 92% yield with introduction of a quaternary center.¹⁹ Furthermore, we surveyed several other highly reactive intermediates to gauge the possibility of utilizing substituted benzyne and cyclic alkynes. The use of fused arynes 2,3-naphthalene and *N*-Boc-4,5-indolyne²⁰ provided arylated products **13** and **14**, respectively.²¹ In addition, trapping with known heterocyclic alkynes²² delivered tetrahydropyridine **15** and dihydropyran **16** in 67% and 74% yields, respectively. Regioselectivities for the formation of **14–16** were in accord with the distortion/interaction model.^{20,22} These results represent a facile means to install aryl and vinyl moieties onto a cyclic β -ketoester with quaternary center formation.

Having developed the racemic arylation/alkenylation reaction, we turned our attention to the discovery of a diastereoselective variant to access enantioenriched products (Table 1).²³ Thus, a series of enantioenriched chiral amines, readily prepared using Ellman auxiliary chemistry (i.e., **18–24**),^{24,25} were condensed with ketoester **9** to access enamines **17**. Subsequent arylation under the conditions depicted in Figure 2 furnished **12** in enantioenriched form. Utilization of phenyl derivative **18** resulted in the formation of **12** in good yield and 74% enantiomeric excess (ee) (entry 1). Employing amine **19**, bearing a cyclohexyl moiety, gave the desired product in a lower ee of 30% (entry 2). Recognizing the importance of the aryl fragment, we examined 1- and 2-naphthyl derived amines **20** and **21**, which provided **12** in 80% and 56% ee (entries 3 and 4, respectively). With improved results in the case of **20**, we examined anthracenyl amines **22–24** (entries 5–7). As the use of ethyl derivative **23** furnished **12** with the best combination of yield and ee (entry 6), **23** was selected for subsequent studies. It should be noted that the Ellman-approach provides both enantiomers of **23**, which, in turn, permits access to each enantiomer of the products depicted subsequently.^{26,27}

Scope of Methodology.

With a suitable chiral amine identified, we evaluated several cyclic alkynes in the stereoselective arylation/alkenylation reaction to form quaternary stereocenters (Figure 3). The reaction was tolerant of substituted benzyne intermediates and extended aryl units, giving rise to arylated products **28** and **13**, respectively.²⁸ Moreover, trapping of an indolyne intermediate delivered heterocycle-containing product **14**. When applied to non-aromatic, strained alkynes, the methodology provided alkenylated products in good yields and stereoselectivities. For example, trapping of cyclohexyne²⁹ provided cyclohexene derivative **29** in good yield and 86% ee. Additionally, by employing heterocyclic alkynes, products **15** and **16** were obtained in excellent yields and comparable stereoselectivities. As shown in Figure 4, the methodology is also tolerant of variation in the nucleophilic component. For example, replacement of the ethyl ester with a benzyl ester in the parent substrate gave rise to arylated product **32** in 71% yield and 86% ee. Furthermore, piperidinone and tetrahydropyranone derivatives could be employed to access heterocyclic products (i.e., **33–35**). Enamines derived from 7-membered ring β -ketoesters could also be utilized, as shown by the formation of arylated products **36** and **37** with excellent stereoselectivity.

Lastly, the formation of ketoester **38** demonstrates the viability of utilizing this methodology for the α -arylation of acyclic β -ketoesters.

One-Pot, Stereoselective Arylation.

As one final application of this methodology, we developed a one-pot variant of the methodology to convert ketoester substrate **39** to α -arylated product **36**, with recovery of the chiral auxiliary (Figure 5). β -Ketoester **39** was reacted with amine **23** to generate enamine **40** in situ. Addition of CsF and silyl triflate **11**, followed by stirring at 30 °C for 6 h, and subsequent acid-mediated hydrolysis yielded the desired α -arylated product **36**. When performed on mmol scale, the reaction gave **36** in 68% yield and 92% ee, in addition to 67% recovered amine **23**. This protocol provides a promising means to achieve the direct, asymmetric α -arylation of β -ketoesters.

Computational Analysis of Chirality Transfer.

Density functional theory (DFT) calculations were performed to understand how stereochemical information is transferred from the chiral auxiliary to the newly formed quaternary stereocenter. Our laboratories have studied reactions of arynes in nucleophilic additions using computations,⁴ but no theoretical studies of aryne trapping by chiral nucleophiles to set new stereocenters have been reported. All calculations described here utilize the M06-2X³⁰/def2-TZVPP-SMD³¹ (diethyl ether)/B3LYP³²/6-31+G(d,p) level of theory (see the SI for a discussion of the computational methods and results with other density functionals).

We first calculated the stereocontrolling transition structures for the reaction of benzyne and enamine (*S*)-**41**, which possesses the 1-naphthyl group at the chiral center. The stereochemistry-controlling transition structures are shown in Figure 6. Each pathway has a low barrier ($G^\ddagger = 9.6$ and 11.6 kcal/mol, respectively). TS1 leads to the experimentally preferred stereoisomer, (*S*)-**12**, whereas TS2 yields the minor enantiomer, (*R*)-**12**.³³ The difference in free energy of activation ($G^\ddagger$) is 2.0 kcal/mol, within error of the experimentally observed selectivity of 80% ee ($G^\ddagger = 1.3$ kcal/mol). In both TS1 and TS2, an intramolecular hydrogen bond between the NH and ester carbonyl is present. Axial-attack by benzyne occurs in both cases, as expected from the preference the forming bond to be staggered with respect to the allylic CH bonds (known previously as the Fürst-Plattner rule).³⁴ Though attack is axial in both cases, and the chiral group is in its favored conformation, the interaction of the CH at the stereogenic center is unfavorable in the minor TS.

In TS2, there is a close-contact H–H interaction of 2.1 Å between the chiral center of the enamine and methylene of the six-membered ring. This contact is alleviated in TS1, with an H–H interaction distance of 2.4 Å. Our laboratory has previously examined the transmission of chirality in the reaction of a similar chiral enamine with acrylonitrile, which similarly revealed the importance of torsional interactions between forming bonds and allylic bonds.³⁴ In that case, the same conformations and their energies were found for the chiral enamine with a phenyl ring instead of naphthyl. Torsional strain³⁵ controls the stereoselectivity of this reaction, where the enamine conformations remain the same for both stereoisomeric transition states.

One might expect that the stereoselectivity cannot be modulated by the size of the substituent, but as found here, enamine **25** has improved enantioselectivity with the larger 9-anthracenyl substituent. We calculated the stereochemistry-controlling transition structures for the reaction of chiral enamine **25** and benzyne using methyl groups in place of ethyl groups to simplify computations.³⁶ The two lowest-energy transition structures leading to the major and minor stereoisomers are shown in Figure 7. **TS3** leads to the experimentally preferred stereoisomer, (*S*)-**12**, whereas **TS4** yields the minor enantiomer. The difference in free energy of activation ($\Delta G^\ddagger$) is 2.5 kcal/mol, within error of the experimentally observed selectivity of 84% ee ($\Delta G^\ddagger = 1.5$ kcal/mol) and 0.5 kcal/mol higher than observed with **20**. Axial-attack by benzyne again occurs for the two half-chair conformers of the cyclohexene. However, here the conformation of the enamine stereogenic group differs between the stereoisomeric transition structures. Whereas the conformation of **TS3** is analogous to that in **TS1**, the enamine in **TS4** is in a higher-energy conformation because the face being blocked to form the (*R*)-isomer is obstructed by the anthracene group. This conformation yields a higher-energy penalty than the torsional strain found in **TS2**, which enables an increase in enantiospecificity.

CONCLUSIONS

We have developed the first methodology that allows for arynes and related strained intermediates to be trapped intermolecularly for the formation of stereodefined quaternary centers. The strategy relies on the facile conversion of β -ketoesters to chiral enamines, which undergo nucleophilic trapping of in situ generated strained arynes or cyclic alkynes. Hydrolysis in the same pot provides the arylated products in good to excellent enantiomeric excesses (up to 96% ee). This strategy circumvents a previously known undesired C–C bond fragmentation, while providing a general solution to the challenging problem of stereoselective β -ketoester arylation/alkenylation, with formation of a quaternary center. In addition, a one-pot procedure for the conversion of a β -ketoester substrate to the corresponding enantioenriched α -arylated product was developed. Finally, computations show how chirality transfer is achieved from the chiral auxiliary to the final products, a type of conformational transmission operating in the trapping of arynes by chiral nucleophiles. We expect these studies will enable further developments of intermolecular, stereoselective reactions of highly reactive aryne and cyclic alkyne intermediates.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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a) Utility of arynes

1
Tubingensin B
(Natural product)

2
XPhos
(Ligand)

3
Isopyrazam
(Agrochemical)

b) Present study

Arynes to generate stereodefined quaternary centers

Figure 1.

Synthetic applications of arynes and strategy for the stereoselective arylation of β -ketoesters.

Figure 2.

Discovery of methodology for the arylation/vinylation of β -ketoesters in racemic fashion. Conditions for enamine formation: ketoester **9** (1.0 equiv), benzylamine (1.5 equiv), Na_2SO_4 (5:1 by wt.), benzene (0.7 M), 80°C , 16 h. Conditions for arylation/alkenylation unless otherwise stated: (i) enamine **10** (1.0 equiv), silyl triflate (1.5 equiv), CsF (7.5 equiv), DME (0.1 M), 30°C , 6 h; (ii) $1\text{ M HCl}_{(\text{aq})}$, 23°C , 30 min. Yields reflect the average of two isolation experiments. ^aAryne trapping performed for 3 h.

Figure 3.

Variation of the electrophile. Conditions unless otherwise stated: (i) enamine **25** (1.0 equiv), silyl triflate **26** (1.5 equiv), CsF (7.5 equiv), DME (0.1 M), 30 °C, 6 h; (ii) 1 M HCl_(aq), 23 °C, 30 min. Yields reflect the average of two isolation experiments. ^aAryne or cyclic alkyne trapping performed for 3 h.

Figure 4.

Variation of the nucleophilic component **30** in the trapping with **11**. Conditions unless otherwise stated: (i) enamine **30** (1.0 equiv), silyl triflate **11** (1.5 equiv), CsF (7.5 equiv), DME (0.1 M), 30 °C, 3 h; (ii) 1 M HCl_(aq), 23 °C, 30 min. Yields reflect the average of two isolation experiments. ^aAryne trapping performed for 6 h.

Figure 5.

One-pot, mmol-scale arylation reaction to furnish **36**. Conditions for enamine formation: ketoester **39** (1.0 equiv), amine **23** (1.0 equiv), benzene (0.7 M), 80°C , 16 h, followed by evaporation of benzene solvent. Conditions for arylation: (i) silyl triflate **11** (1.5 equiv), CsF (7.5 equiv), DME (0.1 M), 30°C , 6 h; (ii) 1 M $\text{HCl}_{(\text{aq})}$, 23°C , 12 h.

Figure 6.

Lowest-energy transition structures **TS1** and **TS2** for the addition of benzyne and the chiral enamine derived from amine 20 (M06-2X/def2-TZVPP-SMD (diethyl ether)//B3LYP/6-31+G(d,p)). Free energy activation barriers ($G^\ddagger$) are compared to separated intermediates. The difference in free energies of activation ($G^\ddagger$), relative to **TS1**, is reported in kcal/mol.

Figure 7. Lowest-energy transition structures **TS3** and **TS4** for the addition of benzyne and chiral enamine **25** (M06–2X/def2-TZVPP– SMD (diethyl ether)//B3LYP/6–31+G(d,p)). Free energy activation barriers ($G^\ddagger$) are compared to separated intermediates. The difference in free energies of activation ($G^\ddagger$), relative to **TS3**, is reported in kcal/mol.

Table 1.

Survey of Chiral Auxiliaries To Give Optically Enriched Ketone 12^a

Entry	X_c-NH_2	Yield	ee	Entry	X_c-NH_2	Yield	ee
1	 18	87%	74%	5	 22	71%	94%
2	 19	64%	30%	6	 23	96%	84%
3	 20	72%	80%	7	 24	100%	66%
4	 21	79%	56%				

^aReaction conditions: (i) enamine 17 (1.0 equiv), silyl triflate 11 (1.5 equiv), CsF (7.5 equiv), DME (0.1 M), 30 °C, 6 h; (ii) 1 M HCl(aq), 23 °C, 30 min.