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A Highly Enantio- and Diastereoselective Molybdenum-Catalyzed Asymmetric Allylic Alkylation of Cyanoesters

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Supporting Information

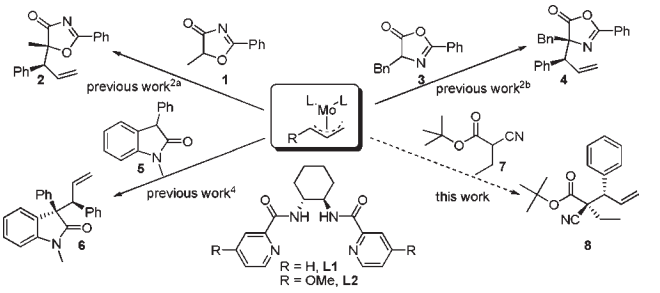
ABSTRACT: An efficient molybdenum-catalyzed asymmetric allylic alkylation (Mo-AAA) of cyanoester nucleophiles is reported. A number of highly functionalized branched cyanoesters containing a quaternary carbon stereocenter with a vicinal tertiary stereocenter are obtained. This method generates a number of functionalized cyanoesters in excellent yield and chemoselectivity in good to excellent diastereoselectivity and enantioselectivity.

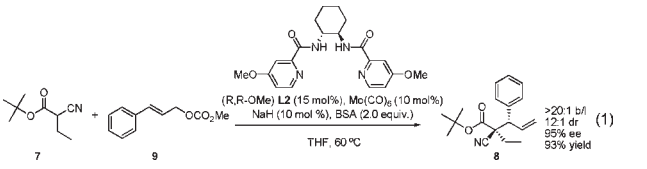
The stereoselective formation of quaternary carbon centers is a significant challenge in asymmetric catalysis; creation of these centers is complicated by nonbonded interactions between the carbon substituents.[1] The problem is further exacerbated when a vicinal tertiary stereocenter is present. Molybdenum catalysis[2,3] is especially well suited for the construction of these highly congested vicinal stereocenters in a single chemical operation. This is exemplified by our recent success accomplishing this challenge in the molybdenum-catalyzed asymmetric allylic alkylation (Mo-AAA) of oxazolones,[2a] azlactones,[2b] and oxindoles[4] (Scheme 1). A critical challenge for these Mo-catalyzed reactions is to broaden the currently very limited scope of suitable prochiral nucleophilic partners.

In looking to expand the scope of the reaction, we asked whether β-cyanoesters could serve as competent nucleophiles for the transformation, on account of the similar acidity of the α-proton relative to that of the malonate. Furthermore, the reaction of β-cyanoesters in the Mo-AAA could allow rapid formation of latent quaternary amino acids bearing a vicinal tertiary stereocenter. This is a complementary process to the addition of azlactone nucleophiles,[2a] which provide a route to α-amino acids, as the product could lead to β-amino acids. Furthermore, the cyanoester is a functional equivalent of a desymmetrized malonate wherein one of the esters has been converted into an ester surrogate. Catalytic asymmetric phase transfer alkylations and Rh−Pd cocatalytic asymmetric simple allylation of cyanoesters in addition to stoichiometric chiral auxiliary alkylations have been noted.[5] However, no example of creating vicinal stereocenters by alkylations of cyanoesters has been reported. *Herein we report our recent success in the Mo-AAA of cyanoester nucleophiles leading exclusively to the branched isomer in good to excellent yield, diastereoselectivity, and enantioselectivity. In addition to providing access to amino acids, the resulting products contain a number of functional handles which could provide access to interesting chiral building blocks.*

We began by investigating the addition of cyanoester **7** to cinnamyl carbonate **9**. Initial studies centered around use of **L1** as a ligand for the Mo-AAA. However, **L1** provided diminished yields (i.e <50%) and low levels of diastereoselectivity (~5:1 dr), albeit with excellent enantioselectivity (>99% ee).[6] After some optimization, it was determined that the reaction between 2.2 equiv of the cyanoester **7** and 1.0 equiv of cinnamyl carbonate **9**[7] occurred in the presence of (*R*,*R*)-**L2**[8] (15 mol %), 10 mol % of $Mo(CO)_6$, 10 mol % NaH, and 2.0 equiv of bis(trimethylsilyl)-acetamide (BSA). These conditions gave rise to the desired branched cyanoester **8** in 93% yield with a 12:1 dr and 99% ee (eq 1).

Scheme 1. Recent Examples of the Mo-AAA Reaction





$Mo(CO)_6$ was employed as the precatalyst owing to its ease of use and commercial availability. In the present instance, it was also found to give more reproducible results than $Mo(CO)_3(C_7H_8)$, which has been previously preferred in many Mo-AAA's.[2,3a,4] The level of regio- and diastereoselectivity achieved was independent of the molybdenum source.

Next we demonstrated that a variety of substituted allylic carbonates were tolerated under the reaction conditions (Table 1). Allyl methyl carbonate reacted efficiently, in excellent yield, with both *tert*-butyl 2-cyanopropanoate (99% yield, 99% ee) and *tert*-butyl 2-cyanobutanoate (96% yield, 98% ee). The absolute stereochemistry of **9** was determined by comparison to the known chiral cyanoester reported by Itoh.[5a,b] This stereochemistry could be extrapolated to the cyanoester chiral center for the remaining substrates. Cinnamyl carbonates bearing an

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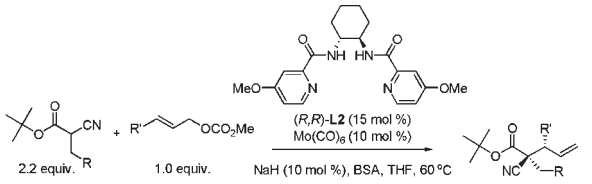
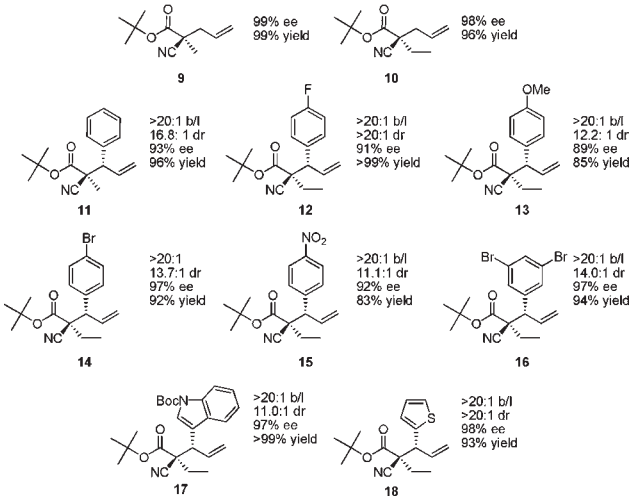
Table 1. Survey of Substituted Allylic Carbonates in the Mo-AAA of Cyanoester Nucleophiles





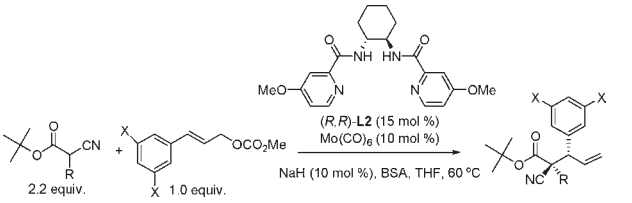
[a] Reactions were carried out at 60 °C at 0.10 M (with respect to the allylic carbonate) under argon for 17 h after activation of the catalyst with 0.10 mmol of allyl carbonate and 0.22 mmol of cyanoester. Branched/linear (b/l) ratio and the diastereomeric ratio (dr) were determined by crude ^{1}H NMR. All yields listed are isolated yields from a single run. Enantioselectivity was determined by chiral HPLC utilizing either an AD-H or OD-H column (details in Supporting Information). [b] BSA = *N,O*-bis(trimethylsilyl)acetamide.

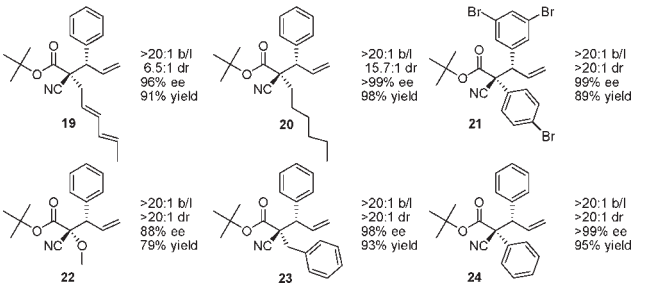
electron-donating group or an electron-withdrawing group in the *para* position were tolerated under the reaction conditions, generating **13** and **15** respectively. Carbonates bearing halogens as in *p*-fluoro **12**, *p*-bromo **14**, and 3,5-dibromo **16** provided similar levels of selectivity to that of cinnamyl carbonate. Additionally, heteroaryl substituted carbonates also showed similar impressive reactivity and selectivity as in the case of 3-indoyl and 2-thienyl yielding **17** and **18** respectively.

The scope of some of the cyanoester nucleophiles tolerated under the reaction conditions are illustrated in Table 2. Derivatives with longer chain alkyl **20**, aryl **24**, substituted aryl **21**, and benzylic substitution (**23**) provided the highest diastereomeric ratios. Olefin substitution (**19**) on the cyanoester led to some loss of dr; however it still furnished the product with reasonable dr and in excellent yield and enantioselectivity. Additionally, heteroatom substitution was also tolerated under the reaction conditions furnishing **22** in >20:1 dr, 88% ee, and 79% yield.

The absolute stereochemistry of the cyanoester stereogenic center was established by comparison to the compound prepared by Itoh[5a,b] which determined the configuration to be *S*. A strategy for determining the chirality at the vicinal tertiary center arose from the study of iodolactone **26** derived from cyanoester **11**

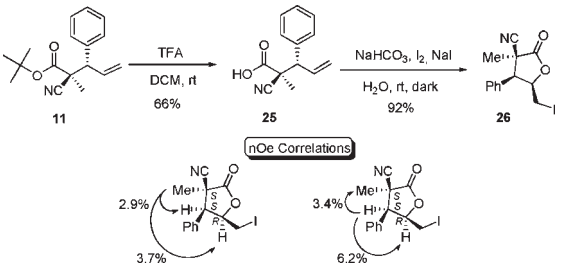
Table 2. Survey of Substitution on the Cyanoester Nucleophile





[a] Reactions were carried out at 60 °C at 0.10 M (with respect to the allylic carbonate) under argon for 17 h after activation of the catalyst with 0.10 mmol of carbonate and 0.22 mmol of cyanoester. Branched/linear (b/l) ratio and the diastereomeric ratio (dr) were determined by crude ^{1}H NMR. All yields listed are isolated yields from a single run. Enantiomeric excess (ee) was determined by chiral HPLC utilizing either an AD-H or OD-H column (details in Supporting Information). [b] BSA = *N,O*-bis(trimethylsilyl)acetamide.

Scheme 2. Determination of Relative Stereochemistry



(Scheme 2). Saponification of cyanoester **11** with trifluoroacetic acid gave the carboxylic acid **25** in 66% yield. Iodolactonization[9] of the acid with I_2 and $NaHCO_3$ gave the iodolactone **26** as a single diastereomer in 92% yield. The relative configuration of the stereocenters was determined by irradiation of the methyl and benzylic protons. The methyl group, benzylic proton, and lactone proton were all found to be on the same face. This established the tertiary center configuration as *S*.

Previous analysis of the Mo-AAA diastereomeric transition state structures demonstrated that molybdenum enolates benefit from minimization of steric strain (Figure 1). Given that the only detectable product by ^{1}H NMR is the branched regioisomer we believe that the *O*-bound enolate[10] structure is favored (**TS1**). The more substituted allylic terminus bound to the sp^2 carbon of the enolate to provide the branched[10] product via a favored "Claisen-like" transition state. **TS2** contains two unfavorable

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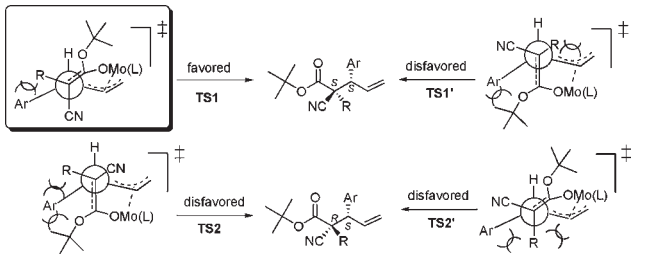

Figure 1. Molybdenum enolate structures.

nonbonded interactions. The first lies between the R group of the cyanoester nucleophile and aryl group of the molybdenum π-allyl complex. Additionally, the bulky *tert*-butyl ester also has an unfavorable interaction with the aryl group of the π-allyl complex. Alternatively, the enolate in which the nitrile and *tert*-butyl ester are syn can be considered as in **TS1′** and **TS2′**. However, these two transition states each contain two unfavorable interactions as in **TS2**. The larger the R group of the cyanoester, the greater the discrimination between the two possible diastereomeric transition state structures. Indeed this is what was observed experimentally from cyanoester **19** which has slightly diminished diastereoselectivity. Furthermore, it has been previously demonstrated[4b,d,8,11] that a more electron-rich molybdenum center should disfavor reductive elimination and promote equilibration between the two isomers, moving toward a Curtin−Hammett situation. Indeed the utilization of bis-methoxy ligand **L2** rather than **L1** supports this conclusion. Finally, the enantioselectivity observed in the reaction speaks to the utility of **L2**[8,11] as a catalyst for π-allyl molybdenum catalysis.

In summary, we have developed a catalytic Mo-AAA of cyanoesters that proceeds in high regio-, diastereo-, and enantioselectivity. The products of the transformation provide a fully functionalized quaternary stereocenter which contain a vicinal tertiary stereocenter that is otherwise difficult to access. The substituted cyanoester products are interesting from the standpoint that they contain a number of functional handles with orthogonal reactivity that can allow for further elaboration. Also interesting is the high selectivity for the branched product in all cases even though in some cases the cyanoester nucleophile is extremely sterically demanding. The versatility of this mode of reactivity with molybdenum in the Mo-AAA reaction is ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information. Complete experimental details and characterization of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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