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Experimental and theoretical investigation of the scope of enantioselective ketone allylations employing Nakamura's allylzinc–bisoxazoline reagent

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ABSTRACT

The scope of enantioselective allylations employing Nakamura's allylzinc–bisoxazoline reagent was examined by performing allylations of a selection of readily available ketones. Low-to-moderate ee's were observed, and a computational study was conducted to rationalize the results. Examination of transition structures of previously performed allylations that proceeded with high ee revealed the importance of both local and global control elements in these successful reactions. The ability of density functional theory methods to estimate the enantioselectivity of these asymmetric ketone allylations was established. All allylations that were studied computationally exhibited low (<5 kcal/mol) activation barriers, a result that is consistent with the highly reactive nature of Nakamura's reagent.

Chiral homoallylic alcohols are versatile intermediates for the construction of many natural products and medicinal agents.[1] A straightforward means of preparing enantiopure tertiary homoallylic alcohols involves the asymmetric allylation of a prochiral ketone.[2] Although this is more challenging than the corresponding allylations of aldehydes, a variety of useful enantioselective ketone allylation protocols have recently been developed.[3,4] In the course of a synthetic effort targeting the hasubanan alkaloids, we examined the enantioselective allylation of masked *ortho*-benzoquinones of type **1** (Fig. 1). Interestingly, we discovered that Nakamura's chiral allylzinc–bisoxazoline reagent **2**[4f] was uniquely effective in this case.[5] In a separate yet related endeavor, we employed **2** in the reagent-controlled diastereoselective allylation of a chiral ketone substrate. This highly selective transformation (93:7 dr) enabled the enantioselective total synthesis of (−)-acutumine.[6] The masked *ortho*-benzoquinones that we employed in both of these endeavors differ significantly in structure from the alkynyl ketones for which the Nakamura reagent was initially designed.[4f] Accordingly, we became curious as to the scope and limitations of enantioselective ketone allylations mediated by **2**. Herein, we disclose the results of an experimental investigation into the utility of this transformation along with a computational study that explains both the sense and degree of enantioselectivity in allylations of achiral ketones.

To determine if the scope of the Nakamura reagent extended beyond allylations of alkynyl ketones and masked *ortho*-benzoquinones, we examined the allylations of a variety of simple ketones with **2**. Our results are collected in Table 1.[7] Aryl methyl ketones **4a–e** afforded good yields of the corresponding homoallylic alcohols **5a–e** (entries 1–5). Unfortunately, the allylation of acetophenone (**4a**) exhibited only moderate (54%) ee, while slightly better results (60–71% ee) were obtained from allylations of *p*-substituted acetophenone derivatives **4b**, **4d**, and **4e**. The *o*-substituted ketone **4c** afforded poor (10%) ee. The aliphatic substrate methyl phenethyl ketone (**4f**) underwent the asymmetric allylation with low yield and ee (entry 6). Interestingly, the results with its α,β-unsaturated congener (*E*)-**4g** were significantly better (entry 7). Methyl β-naphthyl ketone (**4h**) was a poor substrate for this reaction (entry 8), but α-tetralone (**4i**) performed similarly to the aryl methyl ketones (entry 9). The allylation of cyclohexenone (**4j**) afforded numerous uncharacterized byproducts, and the desired homoal-

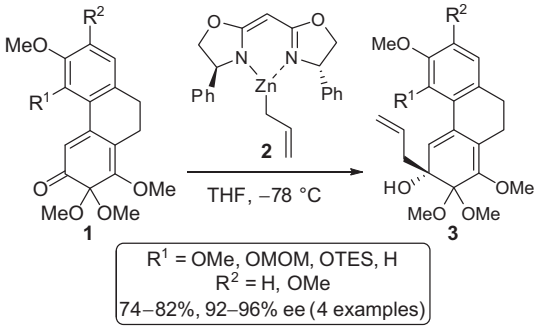

Figure 1. Enantioselective allylation of masked *ortho*-benzoquinones with allylzinc–bisoxazoline reagent **2**.

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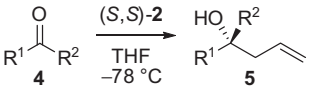
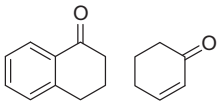
Table 1
Enantioselective allylation of ketones with **2**



4a, R^1 = Ph, R^2 = CH_3
4b, R_1 = 4-MePh, R_2 = CH_3
4c, R^1 = 2-MePh, R^2 = CH_3
4d, R^1 = 4-NO_2Ph, R^2 = CH_3
4e, R^1 = 4-MeOPh, R^2 = CH_3
4f, R^1 = $PhCH_2CH_2$, R^2 = CH_3
4g, R^1 = PhCH=CH, R^2 = CH_3
4h, R^1 = 2-naphthyl, R^2 = CH_3



4i **4j**

Entry	Ketone	Product	Yield[a] (%)	ee[b] (%)
1	**4a**	**5a**	91	54
2	**4b**	**5b**	78	60[c]
3	**4c**	**5c**	75	10
4	**4d**	**5d**	99	68[c]
5	**4e**	**5e**	72	71
6	**4f**	**5f**	30	26
7	**4g**	**5g**	83	42
8	**4h**	**5h**	19	36
9	**4i**	**5i**	89	39
10	**4j**	**5j**	20	3

[a] Isolated yield.
[b] Determined by chiral HPLC (Chiralcel OD-H, 99:1 hexanes/*i*-PrOH, 0.8 ml/min) unless otherwise noted.
[c] Determined by ^{31}P NMR of the adducts formed by reaction of the alcohol with the chiral derivatizing agent of Alexakis.[4c,9]

lylic alcohol **5j** was isolated in low yield and negligible ee (entry 10). Each of the allylations summarized in Table 1 requires stoichiometric quantities of (*S*,*S*)-**2**, and in practice a slight excess (1.3 equiv) was employed to ensure complete consumption of ketones **4**. Fortunately, the bisoxazoline ligand can be isolated as a Zn complex after chromatography. The complex can be hydrolyzed according to Nakamura's protocol,[8] allowing efficient recycling of the purified ligand.

The results of this investigation were disappointing and indicated that **2** is not a useful reagent for the enantioselective allylation of several common types of ketones. However, effective catalysts or reagents already exist for many of these ketones.[3,4] The successful allylations conducted by Nakamura with alkynyl ketones[4f] and by us with masked *ortho*-benzoquinones[5] suggested that **2** exhibits a pattern of reactivity and selectivity that is complementary to other methods.

To understand the high enantioselectivity for reactions of **2** with ketones **1** and the lower enantioselectivity with ketones **4**, we have employed B3LYP[10] and M06-2X[11] density functional theory (DFT) methods to examine transition structures that lead to the favored and disfavored allylation products. B3LYP/6-31G(d,p) optimizations were performed using GAUSSIAN 03.[12] M06-2X energy calculations were carried out using Jaguar 7.7[13] with the LACV3P++** basis set. These DFT methods were previously used to successfully model the enantioselectivity of alkene hydroboration.[14]

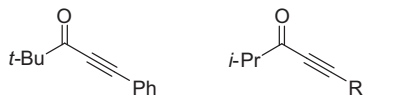
Nakamura and co-workers proposed a single chair like transition state to account for the highly enantioselective allylations of propargyl ketones by **2**.[4f] Based on this transition state, they suggested that the alkynyl group occupies an axial position due to its smaller size relative to the other group attached to the ketone. This was termed 'local' control. However, the alkyne group is long enough to be recognized by the BOX ligand phenyl moieties, a condition that was referred to as 'global' control. In allylations of alkynyl ketones by **2**, these local and global factors were believed to cooperate, affording the homoallylic alcohol products in high enantioselectivity.

To begin our study, we tested the ability of B3LYP and M06-2X methods to estimate the observed enantioselectivity for reaction of **2** with alkynyl ketones **6**–**9**[4f] (Fig. 2). For each enantiomeric product, two possible pseudo-chair transition states were located. In addition, the BOX ligand is slightly flexible, resulting in additional transition state structures for each pseudo-chair conformation. We did not consider boat transition structures, which are known to be significantly higher in energy than chair transition structures in allylation reactions.[15]

Because multiple transition states lead to both the favored and disfavored enantiomers, we considered modeling the enantioselectivity by an approximate ensemble method.[14] However, in these cases an ensemble set of transition states gave results of comparable accuracy to the selectivity computed by using only the lowest-energy favored and lowest-energy disfavored transition structures. For example, an ensemble approximation of the allylation of ketone **8** based on B3LYP energies predicted 88% ee, while consideration of only the lowest-energy transition states predicted 67% ee, which is in exact agreement with experiment. M06-2X gave a lower selectivity of 53% ee. For allylations of ketone **9**, B3LYP predicted an elevated selectivity of 79% ee, whereas M06-2X predicted a lower selectivity of 49% ee. In general, B3LYP predicted higher selectivity than M06-2X.

The lowest-energy favored (**TS-6R**) and lowest-energy disfavored (**TS-6S**) transition states for the reaction of **2** with ketone **6** are shown in Figure 3. Based on these transition structures, $\Delta\Delta E$ = 2.9 kcal/mol (M06-2X), which predicts 98% ee. In **TS-6R** it is clear that the long alkynyl group fits in a position where the left-hand BOX phenyl group is oriented up. The *t*-Bu group is not long enough to interact substantially with the right-hand BOX phenyl group that is oriented down. In **TS-6S** the phenyl alkyne group clearly interacts with the right-hand BOX phenyl group, leading to destabilization. Interestingly, **TS-6R** and **TS-6S** do not have the same pseudo-chair structure. The allyl moiety in **TS-6S** is positioned so that the alkynyl group is closer to the BOX phenyl group than in the opposite pseudo-chair structure. However, **TS-6S** is favored over alternative chair structures by more than 1 kcal/mol because the *t*-Bu group is in the equatorial position, allowing a stabilizing interaction between a C–H bond located on the axial alkynyl phenyl group and the π system of the BOX phenyl group. These transition structures confirm Nakamura's proposal of 'global' (i.e., substrate–ligand interactions) and 'local' (i.e., axial versus equatorial positions) control of selectivity.[4f] In addition, these allylation reactions for ketones **6**–**9** proceed with very low activation barriers, typically less than 5 kcal/mol compared to the complexes between **2** and the ketone substrates.

In our earlier study, the absolute configurations of alcohols **3** were not assigned due to our inability to complete the total syntheses of the hasubanan alkaloids.[5] By applying Nakamura's transition state model to ketones **1**, we posited that the bulky dimethyl ketal moiety would occupy an equatorial position in the transition state, and the planar aryl group would reside in an axial position. This analysis predicts that the (*S*)-enantiomers of **3** will predomi-



6 (96% ee)
7, R = Me (88% ee)
8, R = Ph (67% ee)
9, R = $SiMe_3$ (65% ee)

Figure 2. Enantiomeric excesses reported by Nakamura for allylations of ketones **6**–**9** by **2**.[4f]

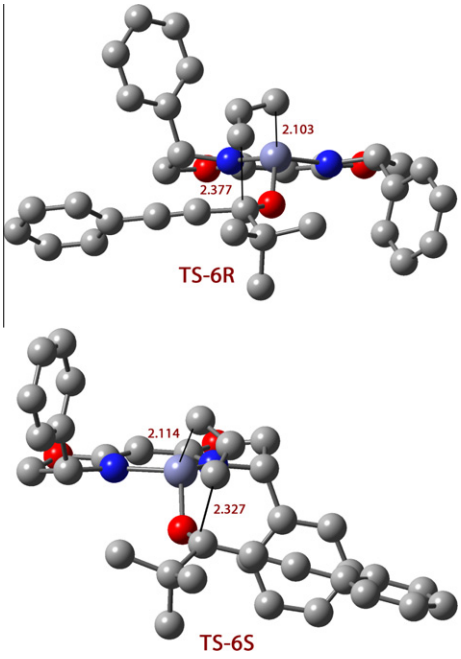


Figure 3. Lowest energy favored (**TS-6R**) and lowest energy disfavored (**TS-6S**) transition states for the reaction of **2** with ketone **6**. Hydrogen atoms have been removed for clarity.

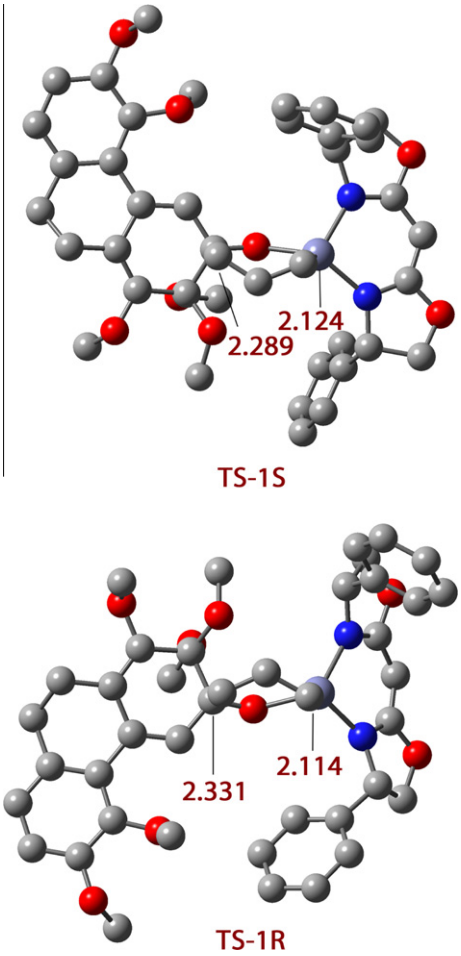


Figure 4. Transition structures for allylation of ketone **1** (R^1 = OMe, R^2 = H) with **2**. Hydrogen atoms have been removed for clarity.

nate. However, modeling of the transition states for the reaction of **1** (R^1 = OMe, R^2 = H) with **2** shows that the transition structure leading to the (*R*)-alcohol (**TS-1R**, Fig. 4) is 2.3 kcal/mol (M06-2X) lower in energy than the transition structure that leads to the (*S*)-alcohol (**TS-1S**). According to these calculations, the large, planar aryl group prefers to reside in an equatorial position, placing the dimethyl ketal in an axial orientation. The computed M06-2X enantiomeric excess is 97%, while B3LYP gives a slightly lower value of 89%. Both of these methods agree that there is high enantioselectivity and predict the same absolute configuration for alcohol **3**.

To understand the origin of the high enantioselectivity for the (*R*)-isomer, we have also computed the transition structures for allylations of ketones **10**–**12**, which are truncated versions of **1** (Fig. 5). The M06-2X-predicted selectivity for **10** is only 53% ee ($\Delta\Delta E$ = 0.7 kcal/mol), indicating that the origin of selectivity in the allylation of **1** lies in the methoxy groups attached to the aromatic ring of the substrate. The calculated $\Delta\Delta E$ between transition states for allylation of ketone **11** drops to 0.5 kcal/mol. For ketone **12**, the M06-2X transition state energies show that the selectivity switches to favor the (*S*)-isomer with high ee. In con-

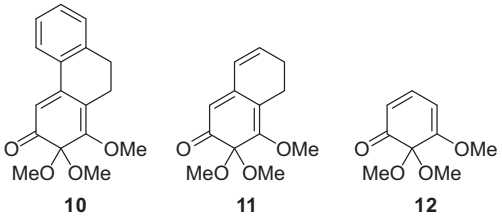


Figure 5. Ketones **10**–**12**.

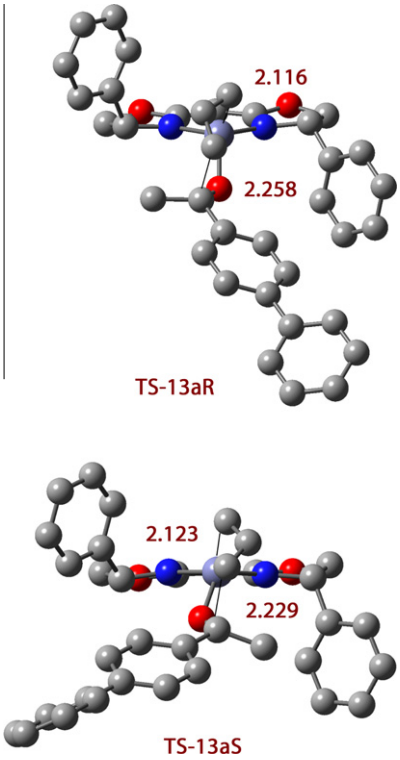
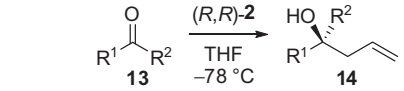
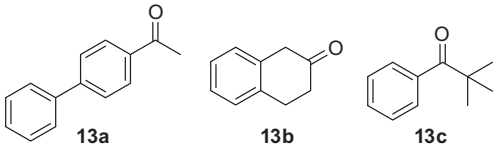


Figure 6. Transition structures for reaction of ketone **13a** with **2**. Hydrogen atoms have been removed for clarity.

Table 2
Enantioselective allylation of ketones **13** with **2**[a]





Entry	Ketone	Product	Yield[b] (%)	Computed ee range[c] (%)	Observed ee[d] (%)
1	**13a**	**14a**	83	~50–80	71
2	**13b**	**14b**	90	~30–40	10
3	**13c**	**14c**	31	Not determined	18

[a] The (*R*,*R*)-enantiomer of **2** was used in this portion of the study due to its availability in our laboratory at the time the experiments were conducted.
[b] Isolated yield.
[c] Range determined by B3LYP enthalpies and free energies.
[d] Determined by ^{31}P NMR of the adducts formed by reaction of the alcohol with the chiral derivatizing agent of Alexakis.[4c,9]

trast, B3LYP predicts only a slight favoring of the transition structure leading to the (*S*)-isomer.

Similar to ketone **12**, transition structures for the reaction of **4i** with **2** predict a 41% ee leading to the *S* alcohol product. This low computed selectivity is in accord with experiment (see entry 9, Table 1) and indicates that there is neither a substantial spatial recognition between the aliphatic side and the aromatic side of ketone **4i** by the BOX ligand nor is there a large preference in chair structure. This is also true for the other ketones tested in Table 1 that exhibit low enantioselectivity.

In an effort to determine the predictive value of our model, we selected a few ketones to be first computed and then tested experimentally in the enantioselective allylation reaction. Computed estimates of selectivity for the allylation of 1-([1,1′-biphenyl]-4-yl)ethanone (**13a**) ranged from ca. 50%–80% ee, depending on whether enthalpies or free energies were used. In selecting ketone **13a** as a test substrate, we hoped to obtain improved ee values due to increased levels of local control when compared to simple acetophenones **4a–e**. However, consideration of the transition structures shown in Figure 6 indicates that the large size of the biphenyl group in **13a** does not increase the level of local control. The allylation of **13a** with **2** gave a result (71% ee, Table 2) that was consistent with our prediction. Apparently, the selectivity due to local control in the allylations of acetophenones with **2** reaches a maximum at ca. 70% ee. Our calculations suggest that efforts to further improve the selectivity with these aryl alkyl ketone substrates should focus on improving global control by lengthening the alkyl group, thereby improving recognition of the substrate by the BOX chiral ligand.

We expected that readily available β-tetralone (**13b**) would exhibit a lower ee than α-tetralone (**4i**, 39%, Table 1) due to decreased levels of local control. In this case, the experimental ee value was lower than the calculated ee range (10% vs ca. 30%–40%, entry 2, Table 2). Finally, in an effort to improve global control with aryl ketones, *tert*-butyl phenyl ketone (**13c**) was subjected to the enantioselective allylation. A poor yield and low ee were observed (Table 2, entry 3), suggesting that the bulky *tert*-butyl group substantially erodes local control without a useful enhancement of global control.

In conclusion, a survey of common, readily available ketones in the enantioselective allylation protocol developed by Nakamura and later exploited by us resulted in generally good yields and moderate ee values. A computational study provided a rationale for these results and established the importance of choosing substrates for which high levels of local (i.e., size of axial vs equatorial group in transition structure) and global (i.e., ability of BOX ligand to recognize axial group) control are operative. The ee values of allylation reactions with **2** could be predicted with reasonable accuracy, although entropic factors combined with the fact that small energy differences are involved limit the precision of this technique. Nonetheless, we expect the predictive value of DFT methods to result in their increased adoption by the synthetic community to study enantioselective transformations. Perhaps the most useful aspect of chiral allylating agent **2** is its high reactivity, which is consistent with the low (<5 kcal/mol) computed activation barriers. Indeed, ketones **1** were unreactive with the vast majority of chiral catalysts and reagents examined in our prior study.[5] Therefore, **2** should prove to be a useful tool for enantioselective allylations of less reactive (e.g., bulky) ketones that would be expected to exhibit good levels of both local and global control.

Acknowledgments

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Supplementary data

Supplementary data (characterization data for new compounds **14a** and **14c** along with Cartesian coordinates and absolute energies for computed transition structures) associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2010.11.121.

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7. *General procedure*: A solution of bis((*S*)-4-phenyl-4,5-dihydrooxazol-2-yl)methane (1.3 equiv) and 2,2′-dipyridyl (1 crystal) in anhydrous THF (0.45 M) at 0 °C under Ar was treated dropwise with *n*-BuLi (1.6 M in hexanes) until the mixture turned a reddish-brown color. The solution was warmed to rt and stirred for 1 h, then treated dropwise with allylzinc bromide (2.0 M solution in anhydrous THF, 1.4 equiv) and cooled to −78 °C. A solution of ketone **4** in anhydrous THF (0.7 M) was added dropwise, and the resultant mixture was stirred at −78 °C under Ar for 1 h. The reaction was quenched by the addition of 1:1 MeOH/H_2O, and the mixture was extracted with Et_2O. The combined organic layers were washed with 0.5 N NaOH, dried (Na_2SO_4), and concentrated in vacuo. Flash chromatography (SiO_2, Et_2O/hexanes elution) afforded homoallylic alcohol **5**.
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