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Application of a C–C Bond-Forming Conjugate Addition Reaction in Asymmetric Dearomatization of β-Naphthols**

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Abstract: *A C–C bond-forming conjugate reaction was successfully applied to the enantioselective dearomatization of β-naphthols. A C(sp2)–C(sp3) bond is formed by using propargylic ketones as reactive partners. Good to excellent Z/E ratios and ee values were obtained by employing an in situ generated magnesium catalyst. Further transformations of the Z-configured C–C double bond in the products were achieved under mild reaction conditions. Moreover, the stereocontrolling element of this magnesium-catalyzed dearomatization reaction was explored by computational chemistry.*

Recently, the catalytic asymmetric dearomatization reactions[1] of phenols have received much attention because the dearomatization product, containing a cyclic ketone framework, could be used for further transformations to provide various molecules and natural products.[2] Catalytic asymmetric dearomatization of phenols under non-oxidative conditions are highly desirable because of their atom economy. However, there is limited progress in this area compared to the corresponding studies for the oxidative dearomatization of phenols.[3] To date, only a few examples of direct dearomatization of phenols under non-oxidative conditions have been reported, specifically for intermolecular pathways.[4] In 2013, Toste and co-workers reported a direct catalytic asymmetric fluorination of phenols by employing a phase-transfer chiral-anion catalyst.[5] Almost simultaneously, the group of You reported a palladium-catalyzed intermolecular asymmetric allylic dearomatization of β-naphthols with good results.[6] Recently, we described a highly enantioselective dearomatization reaction of β-naphthols with *meso*-aziridines by identifying a novel in situ generated magnesium catalyst.[7,8] However, surprisingly, to date, there are almost no reports on catalytic asymmetric dearomatization of phenols by using of common conjugate addition reactions. Very recently, the breakthrough work utilizing C–N bond-forming conjugate additions in direct asymmetric dearomatization of β-naphthols was realized by the groups of You and Luan independently, although they employed different catalytic systems (Figure 1a).[9,10] Nevertheless, the application of other conjugate addition reactions in direct enantioselective dearomatization of β-naphthols is still unrealized, yet highly desirable. Herein, we report an enantioselective dearomatization reaction of β-naphthols by a C–C bond-forming conjugate addition employing propargylic ketones as reactive partners (Figure 1b).[11,12]

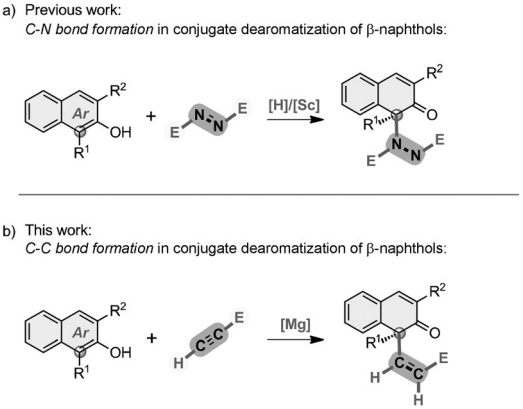

Figure 1. Asymmetric conjugate addition reactions in the dearomatization of β-naphthols.

We began our initial investigations by searching for a suitable in situ generated magnesium catalyst[13] for the conjugate addition reaction of the β-naphthol **1a** (Scheme 1). Several representative chiral oxazoline-OH-type ligands were tested, but these ligands did not introduce high levels of enantioselectivity (**L1**–**L4**). We therefore evaluated the effects of other oxazoline-OH ligands derived from *ortho*-hydroxyphenylacetic acid, which was developed by us recently.[7] The screening process showed that moderate *ee* values could be obtained while introducing this type of chiral ligand into the dearomatization reaction. Fortunately, we identified **L9** as a promising chiral ligand, which led to higher enantioselectivity and *Z*/*E* selectivity. Next we turned to improving the results by evaluating all the reaction parameters. By running the reaction at lower temperatures, we were pleased to observe that the *ee* value increased to 88% along with enhancement of the *Z*/*E* selectivity to 8.5:1

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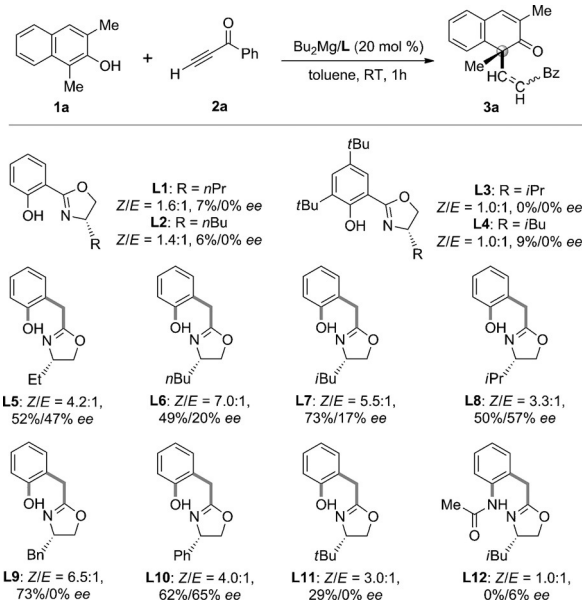
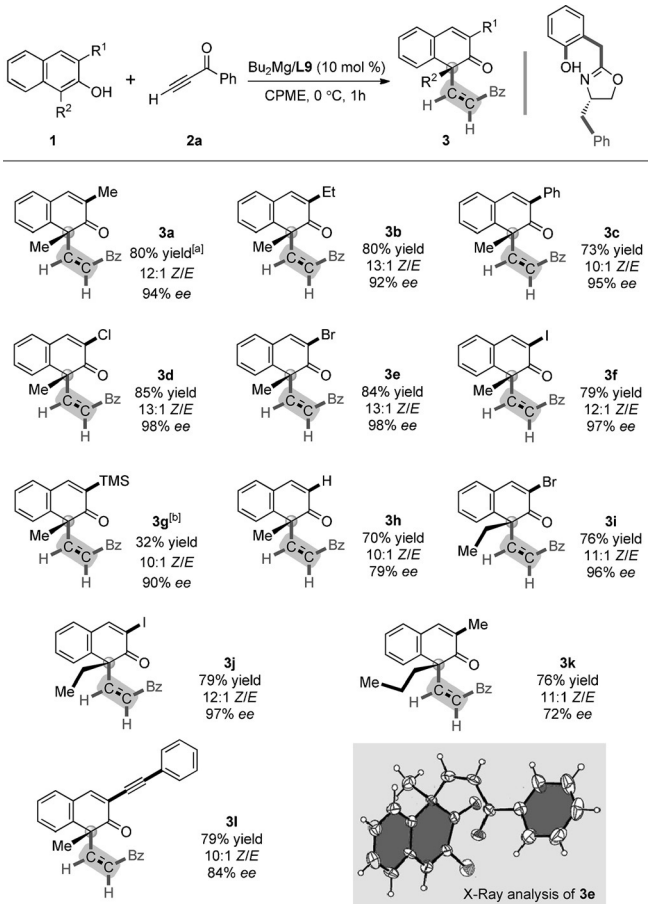


Scheme 1. Searching for suitable in situ generated magnesium catalysts. *Z*/*E* ratio determined by ^{1}H NMR (300 MHz) analysis of the crude reaction mixture. The *ee* values were determined by HPLC using a chiral stationary phase. Bz = benzoyl.



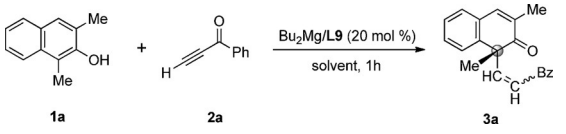
Scheme 2. Scope with respect to the β-naphthols. See the Supporting Information for reaction details. [a] Yield of the isolated of *Z* adduct. *Z*/*E* ratio determined by ^{1}H NMR (300 MHz) analysis of the crude reaction mixture. The *ee* values were determined by HPLC using a chiral stationary phase. [b] With 40 mol% catalyst.

(Table 1, entry 1). By screening solvents, CPME (cyclopentyl methyl ether) was determined to the best solvent with respect to both the *Z*/*E* selectivity and enantioselectivity (entries 2–6). Reduction of the in situ generated magnesium catalyst to 10 mol% did not result in any noticeable deterioration in either yield, *Z*/*E* ratio, or enantioselectivity (entry 9).

With the optimized reaction conditions in hand, we explored the substrate generality of the β-naphthols. The dearomatization proceeds smoothly with β-naphthols bearing alkyl and aryl groups, as well as halogens at C3, thus resulting in good yields (73–85%) and *Z*/*E* ratios (10:1–13:1), and excellent enantioselectivities (92–98%, Scheme 2; **3a**–**3f**). The absolute configuration was determined by X-ray diffraction results.[14] A C3-TMS-substituted β-naphthol was also used in the dearomatization process, and led to the corresponding product **3g** in lower yield with a higher catalyst loading. The asymmetric conjugate addition also occurred with 3-(H)-β-naphthol, thus resulting in acceptable yield and enantioselectivity (**3h**). Moreover, the substituent in C1 of the β-naphthols could be changed to bulkier groups, such as ethyl and propyl, thereby achieving good to excellent enantioselectivities (**3i**–**k**). Lastly, we were pleased to find that phenylethynyl could be tolerated at C3 of the naphthyl ring to furnish the dearomatization product **3l**.

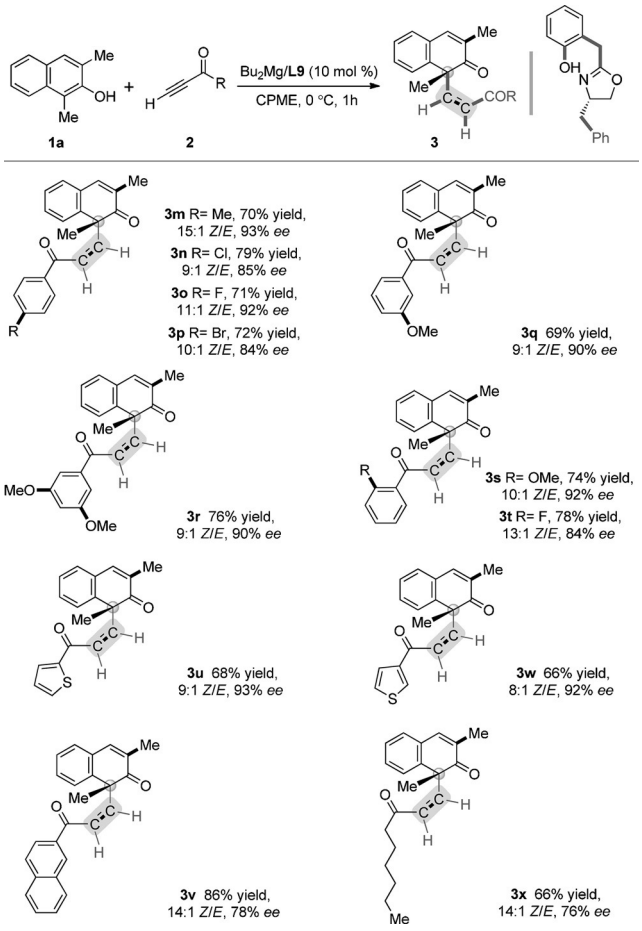
We then investigated the substrate scope with respect to propargylic ketones (Scheme 3). Aryl-alkynyl ketones bearing various substituents were subjected to the conjugate addition reaction. The results show that these propargylic ketones are amenable to the reaction conditions and predominantly gave *Z*-configured adducts with high *ee* values (**3m**–**t**). Propargylic ketones containing heteroaryl units or condensed rings were also tolerated (**3u**–**w**). Notably, an alkyl-alkynyl ketone was also tested in the conjugate reaction

Table 1: Optimization of the reaction details.



Entry[a]	Solvent	*T* [°C]	Conversion [%][b]	*Z*/*E*[b]	*ee* [%][c]
1	toluene	0	>95	8.5:1	88
2	THF	0	31	2.3:1	69
3	CH_2Cl_2	0	>95	6.1:1	85
4	ether	0	86	8.7:1	91
5	*t*BuOMe	0	78	7.0:1	85
6	CPME	0	>95	12:1	94
7	CPME	0	89	12:1	89[d]
8	CPME	−20	84	12:1	92
9	CPME	0	>95	12:1	94[e]

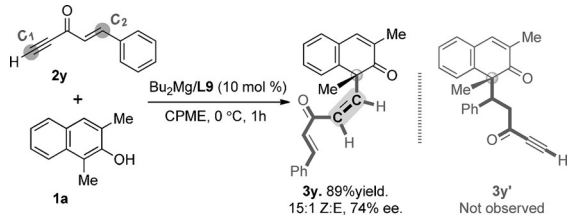
[a] Reactions were performed with β-naphthol (**1a**, 0.20 mmol) and ketone (**2a**, 0.24 mmol) in solvent (2.0 mL) in the presence of Bu_2Mg (20 mol%) and ligand (20 mol%). [b] Determined by ^{1}H NMR (300 MHz) analysis of the crude reaction mixture. [c] Analyzed by HPLC using a chiral stationary phase. [d] In 4.0 mL CPME. [e] With 10 mol% catalyst. THF = tetrahydrofuran.



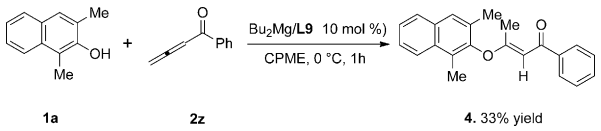
Scheme 3. Scope with respect to propargylic ketones. Yield is that of the isolated *Z* isomer. *Z*/*E* ratio determined by ^{1}H NMR (300 MHz) analysis of the crude reaction mixture. The *ee* values were determined by HPLC using a chiral stationary phase.

and provided the *Z*-adduct **3x** predominantly, with 76% *ee*. To our disappointment, internal propargylic ketones could not undergo the conjugate reaction using the current catalytic system.[15]

Furthermore, when the propargylic ketone **2y**, bearing two electrophilic sites, was employed in the conjugate reaction, only the acetylenic carbon atom (C1) participated in the asymmetric dearomatization process (Scheme 4). When the allenic ketone **2z** was used under the same reaction conditions, it only generated the adduct **4** and some unidentified dimers of **2z** (Scheme 5). The C–C double bond in **4** was determined to be *E* by NOESY analysis.[16]

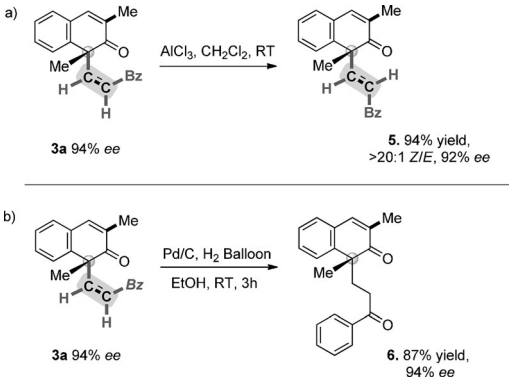


Scheme 4. Ketone bearing two electrophilic sites in the conjugate addition.



Scheme 5. Allenic ketone in the conjugate addition.

Next we attempted transformations of the dearomatization product. The *Z*-configured C–C double bond could be converted into to *E*-adduct **5** in the presence of $AlCl_3$ under ambient conditions (Scheme 6a). In contrast, the *Z*-configured C–C double bond could be easily reduced using H_2 to furnish the compound **6** (Scheme 6b).



Scheme 6. Transformations of the dearomatization product.

Finally, a plausible mechanism for this dearomatization was proposed on the basis of our previous work[7] and studies of the phenol/Mg crystallographic structures.[17] As illustrated in Figure 2, after reaction between **L9** and Bu_2Mg, either the precatalyst A or its dimer **B** is formed.[18] Then the β-naphthols are activated by the precatalyst **A** to give **C**. Next propargylic ketones coordinate to the magnesium center (**D**) and furnish the C–C bond (**E**). To better understand the stereocontrol, calculation experiments were performed. The calculation data indicate that the (*R*)-IM transition state, which leads to the formation of the major product observed experimentally, is much more stable than (*S*)-IM. The methyl group of the β-naphthol in (*R*)-IM does not have any obvious steric interactions with the chiral ligand. But the calculation results for (*S*)-IM showed steric interactions between the methyl group of the β-naphthol and the benzyl group of **L9**. The calculated free-energy gap between these two transition states is 0.67 kcal mol^{-1}.[19] This computational investigation is in accordance with our aforementioned experimental results. Lastly, another molecular of β-naphthol participates in the catalytic cycle and promotes release of the product.

In summary, we have achieved the application of a C–C bond-forming conjugate addition in the dearomatization of β-naphthols. An in situ generated magnesium catalyst was employed to realize the highly enantioselective dearomatization process. Transformations of the dearomatization product and investigations of the stereocontrolling elements were explored. Further studies on the dearomatization of β-naphthols are under investigation.

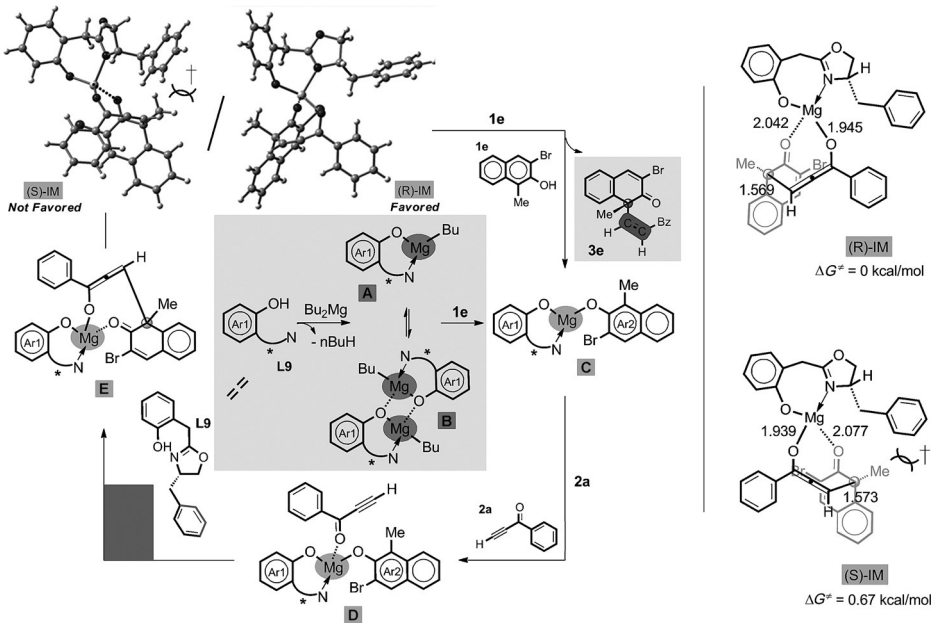


Figure 2. Proposed mechanism and results from the computational investigation.

Keywords: arenes · aromaticity · DFT calculations · magnesium · naphthols

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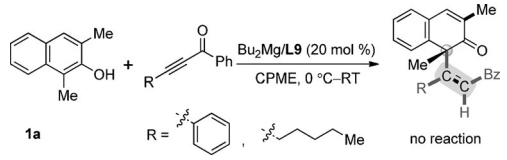
[13] We found Bu_2Mg to play a key role in this reaction. It should be noted that older Bu_2Mg, which was stored for about two months, could still mediate the reaction efficiently without influencing of the *ee* values, but it did lead to lower *Z*/*E* ratios. The reaction worked well with Bu_2Mg purchased from suppliers such as Sigma–Aldrich and Acros-Organics.
[14] CCDC 1048396 (**3e**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.
[15] There is no reaction between these substrates:



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[18] Positive nonlinear effect was observed in our previous study to illustrate the dimer or polymer species of catalyst should be generated.
[19] For calculations on two other transition states, see the Supporting Information.

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