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Nickel(0)/*N*-Heterocyclic Carbene-Catalyzed Asymmetric [2 + 2 + 2] Cycloaddition of Two Enones and an Alkyne: Access to Cyclohexenes with Four Contiguous Stereogenic Centers

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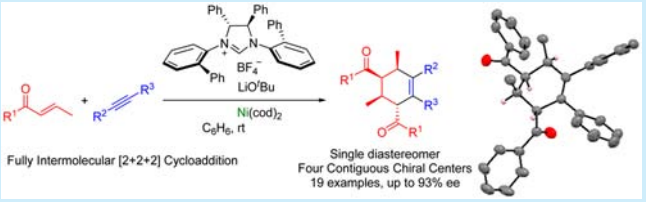
Supporting Information

ABSTRACT: A nickel(0)/chiral *N*-heterocyclic carbene (NHC)-catalyzed fully intermolecular, enantioselective [2 + 2 + 2] cycloaddition of two enones and an alkyne has been developed to access enantioenriched cyclohexenes. A single diastereomer was obtained with a successive generation of four contiguous stereogenic centers. The absolute configuration of cyclohexene derivative **3aa** was determined by X-ray diffraction and circular dichroism (CD) spectral studies.



Cyclohexanes are common structural motifs in many classes of pharmaceutical and natural products such as terpenoids, steroids, and alkaloids (Figure 1).[1] The stereo-

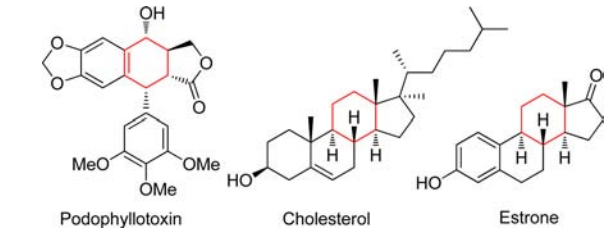
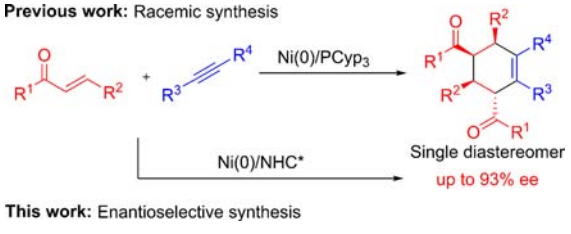


Figure 1. Representative examples of natural compounds having nonracemic chiral cyclohexane ring.

controlled synthesis of a cyclohexane ring with multiple stereogenic centers has long been regarded as a great challenge because an increase in chiral centers is accompanied by an exponential increase in the possible number of stereoisomers. As with Diels–Alder[2a,b] and organocatalytic cascade[2c,d] strategies, transition-metal-catalyzed [2 + 2 + 2] cycloaddition is a powerful tool for the enantioselective synthesis of cyclohexane derivatives using various π-components.[3] To add structural diversity to the products, various intra- and intermolecular reaction patterns and catalytic systems have been developed. Alkenes are usually less reactive than alkynes toward transition metals. Thus, [2 + 2 + 2] cycloadditions between alkene(s) and alkyne(s) have mostly been developed either for fully intramolecular[4] or semi-intermolecular reactions.[5−10] Rh(I)-catalyzed fully intramolecular [2 + 2 + 2] cycloadditions of 1,*n*-dienynes[4a−d] and enediynes[4e] have been reported for the asymmetric synthesis of various polycyclic compounds. As a contribution to semi-intermolecular [2 + 2 + 2] cycloadditions, Montgomery et al. described the Ni(0)/PPh_3-catalyzed [2 + 2 + 2] cycloaddition of an yne-enone with an enone to afford a bicyclic cyclohexene derivative in a diastereoselective manner.[5] Rh(I)/bisphosphine catalytic systems have been explored for semi-intermolecular, enantioselective [2 + 2 + 2] cycloadditions of 1,6-enynes with either an alkyne[6] or an acrylamide[7] and 1,6-diynes with either a reactive olefin (norbornene, acrylate, or acrylamide)[8] or an imine.[9] Alexanian et al. reported an alkyne-free, [2 + 2 + 2] cycloaddition between ene-allenes and allenoates enabling the facile preparation of densely functionalized cyclohexadienes.[10] All of these enantioselective methods are mainly based on Rh(I)/bisphosphine catalysis.[4,6−10] In addition, despite a substantial amount of research on [2 + 2 + 2] cycloadditions using various reaction patterns, fully intermolecular enantioselective reactions have been less explored.[11]

We previously reported the $Ni(cod)_2/PCyp_3$-catalyzed fully intermolecular [2 + 2 + 2] cycloaddition of an alkyne and two enones to yield cyclohexenes with high regio- and diastereoselectivities (Scheme 1).[12] The oxidative cyclization of an enone and an alkyne with a nickel(0) species to give a

Scheme 1. Fully Intermolecular [2 + 2 + 2]-Cycloaddition of Two Enones and an Alkyne



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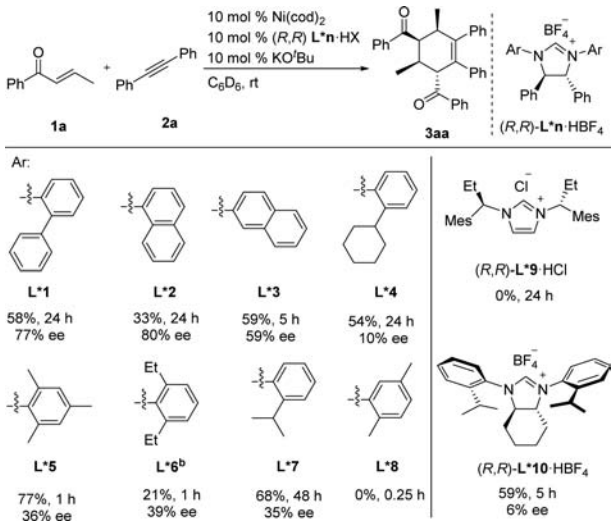
nickelacycle was a key step in this catalytic reaction. The corresponding nickel complex was isolated and its molecular structure was confirmed by X-ray crystallography. Monodentate ligands with high electron-donating abilities such as PCy_3, $PCyp_3$, and IPr effectively promote oxidative cyclization. In pioneering studies by Grubbs et al., chiral *N*-heterocyclic carbenes (NHCs) that are easily derived from chiral C2-diamines were excellent ligands for asymmetric RCM reactions.[13] These ligands also fulfill the electronic and steric requirements of oxidative cyclization reactions. Despite these advantages, however, very few examples of chiral NHCs have been employed for such reactions using nickel(0).[14] Herein, we wish to report an enantioselective version of the fully intermolecular [2 + 2 + 2] cycloaddition of an alkyne with two enones using Ni(0)-chiral NHC to access enantioenriched cyclohexenes for the first time (Scheme 1).

The optimization of catalytic enantioselective [2 + 2 + 2] cycloaddition was carried out using (*E*)-1-phenyl-2-buten-1-one (**1a**) and diphenylacetylene (**2a**). A series of C2-symmetric imidazolinium salts were surveyed in the presence of KO^{t}Bu and Ni(cod)$_2$ (Scheme 2).[15] *N*-2-Biphenyl- (**L*1**) and *N*-1-naphthyl (**L*2**)-substituted NHCs provided **3aa** in moderate yields and promising enantioselectivities (77 and 80% ee, respectively). *N*-2-Naphthyl-substituted NHC (**L*3**), however, gave inferior results in terms of enantioselectivity (59% ee) compared with that of **L*2**. A lower enantioselectivity was obtained with *N*-2-cyclohexylphenyl-substituted NHC **L*4** (10% ee). *N*-Mesityl- (**L*5**), *N*-2,6-diethylphenyl- (**L*6**), and *N*-2-isopropylphenyl (**L*7**)-substituted NHCs afforded **3aa** in moderate enantioselectivities (35−39% ee). *N*-2,5-Dimethylphenyl- (**L*8**) and *N*-(1-mesitylpropyl) (**L*9**)-substituted NHCs did not give the desired cycloaddition product **3aa**, and the oligomerization of **1a** was majorly occurred. The NHC derived from imidazolinium salt with a *trans*-cyclohexanediamine backbone (**L*10**) gave **3aa** with poor enantioselectivity (6% ee). The survey of chiral imidazolinium salts illustrated the best results with **L*1**·HBF$_4$[16] in the presence of KO^{t}Bu.

Scheme 2. Catalytic Enantioselective [2 + 2 + 2] Cycloaddition: Survey of Imidazolinium Salt[a]



[a]General reaction conditions: (*R*,*R*)-**L*n**·HX, KO^{t}Bu, Ni(cod)$_2$ (0.02 mmol each), **1a** (0.2 mmol), **2a** (0.2 mmol), and C_6D_6 (0.5 mL). All experiments were conducted in a NMR tube equipped with a J. Young valve. Isolated yields are given. Ee's were determined by HPLC using chiral stationary phase. [b]Opposite enantiomer was obtained as a major product.

In order to improve both the yield and the enantioselectivity of **3aa**, the reaction conditions were further optimized with **L*1**·HBF$_4$ by varying the reaction parameters such as base, solvent, and temperature (Table 1).[17] The NHC derived from **L*1**·HBF$_4$ resulted in inferior enantioselectivity in the presence of NaO^{t}Bu (61% ee). An improvement in enantioselectivity was observed with LiO^{t}Bu (85% ee) and was probably the result of a stronger interaction by the Lewis acidic Li cation with an enone compared with that of Na and K cations (entries 1−3). As for solvents, toluene and THF gave moderate yields, but inferior results (29% yield, 70% ee) were obtained with acetonitrile (entries 4−6). The effect of the temperature on enantioselectivity was critical to the present catalytic reaction. The enantioselectivity was improved to 92% by elevating the reaction temperature to 30 °C (entry 7). However, a further increase in the temperature to 40 °C showed a depletion of the enantioselectivity to 74% ee (entry 8). At 10 °C, **3aa** was obtained in only an 11% yield with 80% ee (entry 9). Remarkably, stirring the reaction mixture at 30 °C improved the yield of **3aa** with no erosion of enantioselectivity (84% yield, 92% ee, entry 10). This result might have been due to the low solubility of an imidazolinium salt and base in benzene. Thus, the optimized reaction conditions were determined as follows: 10 mol % of Ni(cod)$_2$, (*R*,*R*)-**L*1**·HBF$_4$ and LiO^{t}Bu in benzene at 30 °C with stirring.

Table 1. Further Optimization with Imidazolinium Salt L*1·HBF$_4$[a]

entry	base	solvent	temp (°C)	time (h)	yield (%)	ee (%)
1	KO^{t}Bu	C_6D_6	rt	24	58	77
2	NaO^{t}Bu	C_6D_6	rt	24	47	61
3	LiO^{t}Bu	C_6D_6	rt	48	56	85
4	LiO^{t}Bu	toluene-d_8	rt	48	46	70
5[b]	LiO^{t}Bu	THF	rt	48	54	85
6	LiO^{t}Bu	CD_3CN	rt	20	29	70
7	LiO^{t}Bu	C_6D_6	30	48	52	92
8	LiO^{t}Bu	C_6D_6	40	24	72	74
9	LiO^{t}Bu	C_6D_6	10	48	11	80
10[b]	LiO^{t}Bu	benzene	30	24	84	92

[a]All experiments were conducted in an NMR tube equipped with a J. Young valve. Isolated yields are given. Ee's were determined by HPLC using chiral stationary phase. [b]Reaction was performed with vigorous stirring.

The scope and limitation of the present enantioselective reaction was examined with various enones **1** and alkynes **2**, as summarized in Scheme 3. The reaction of **1a** with bis(*p*-tolyl)acetylene (**2b**) and bis(*m*-tolyl)acetylene (**2c**) gave **3ab** (95% yield, 76% ee) and **3ac** (58% yield, 74% ee), respectively. On the other hand, bis(*o*-tolyl)acetylene (**2d**) was unsuccessful in attempts to produce the respective cycloaddition product **3ad**, probably due to the bulkiness of the *o*-tolyl group. Alkynes bearing electron-deficient aryl groups such as bis(*p*-fluorophenyl)acetylene (**2e**) and bis(*p*-trifluoromethylphenyl)-acetylene (**2f**) gave **3ae** and **3af** in moderate to good yields and enantioselectivities (69 and 52% ee, respectively). In contrast, bis(*p*-anisyl)acetylene (**2g**) resulted in no reaction possibly due to the low coordination ability of an electron-rich substrate with

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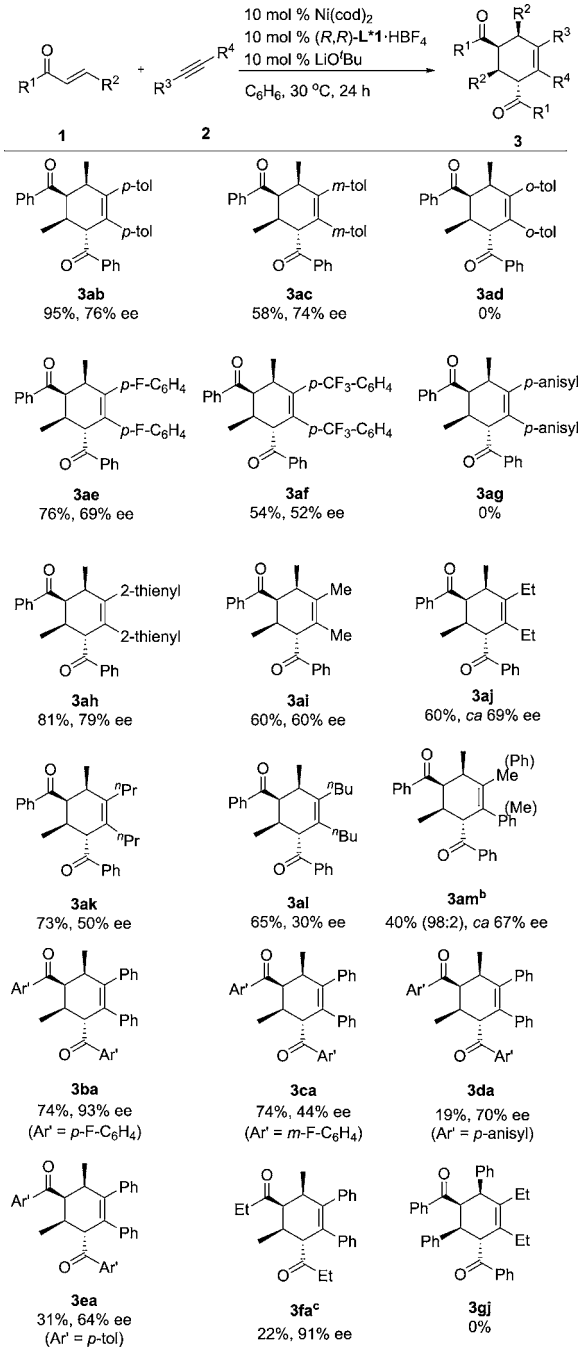
Scheme 3. Ni(0)/NHC-Catalyzed Enantioselective [2 + 2 + 2] Cycloaddition[a]



[a]General reaction conditions: (*R*,*R*)-**L*1**.HBF$_4$, LiO^{t}Bu, Ni(cod)$_2$ (0.05 mmol each), enone (**1**, 0.5 mmol), alkyne (**2**, 0.5 mmol). Isolated yields are given. Ee's were determined by HPLC equipped with chiral stationary phase. [b]Substituents of minor regioisomer are in parentheses and ee was measured for major regioisomer. [c]Stirred it for 72 h.

the nickel(0) species. However, the reaction of bis(2-thienyl)-acetylene (**2h**) gave **3ah** in both a good yield and enantioselectivity (81% yield and 79% ee). The alkyl group substituted alkynes were also examined. 2-Butyne (**2i**) and 3-hexyne (**2j**) gave the corresponding cycloaddition products **3ai** and **3aj** in a 60% yield each along with a moderate degree of enantioselectivities (60 and 69% ee, respectively). Longer alkyl group-substituted alkynes such as 4-octyne (**2k**) and 5-decyne (**2l**), however, resulted in the desired products **3ak** and **3al** in good yields, but in lower enantioselectivities (50 and 30% ee, respectively). These tendencies indicate that both the steric and electronic nature of alkynes influence both the yield and the enantioselectivity. 1-Phenyl-1-propyne (**2m**) gave the corresponding cycloadduct **3am** in a 40% yield with a high degree of regioselectivity (98:2). The major regioisomer was isolated with ca 67% ee. Next, the scope of enones was studied. The reaction between (*E*)-1-(*p*-fluorophenyl)but-2-en-1-one (**1b**) and **2a** gave **3ba** with high enantioselectivity (93% ee). Moderate enantioselectivity was observed with the *m*-fluorophenyl analogue (**3ca**, 44% ee), but good yields were obtained in both cases (**3ba** and **3ca**; 74%). Electron-rich aryl groups on an enone, such as *p*-anisyl (**1d**) and *p*-tolyl groups (**1e**), gave **3da** and **3ea** in moderate yields and enantioselectivities (70 and 64% ee, respectively). Aliphatic enone 4-hexen-3-one (**1f**) and **2a** afforded **3fa** in a low yield (22%) with high enantioselectivity (91% ee). The reaction of chalcone (**1g**) with 3-hexyne (**2j**) did not proceed at all. The absolute configuration of the major enantiomer of **3aa** were determined to be *R*,*R*,*S*,*R* by X-ray diffraction study, which was further supported by circular dichroism (CD) spectrum analysis.[17] The experimental CD pattern of **3aa** was in agreement with the theoretical CD spectra (Figure 2).

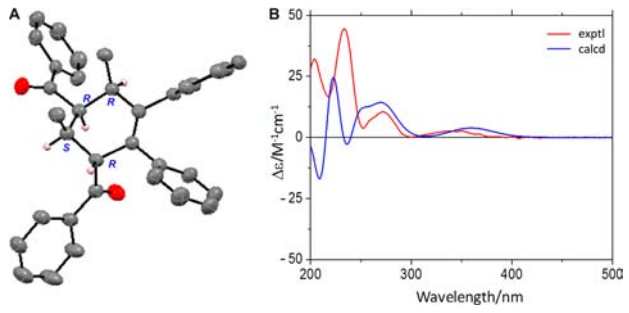
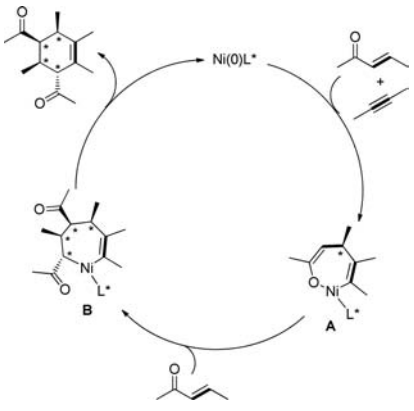


Figure 2. (A) Molecular structure of **3aa** with thermal ellipsoids at the 50% probability level (Flack parameter = 0.14(12)). H atoms are omitted for clarity except those bound to the chiral carbon atom. (B) Comparison of the experimental and the theoretical CD spectra for **3aa**, calculated at the RI-CC2/def2-TZVPP//DFT-D3-TPSS/def2-SVP level (0.3 eV red-shifted, 1/2 scaled, fwhm = 0.5 eV).

The reaction might proceed as follows (Scheme 4).[5,14c,18] The oxidative cyclization of an enone and an alkyne with a

Scheme 4. Plausible Reaction Mechanism



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nickel(0)/**L*1** fragment gives an enantioenriched η^1-*O*-nickelenolate intermediate **A**, which reacts with the second enone in a diastereoselective manner to generate a seven-membered nickelacycle intermediate **B**, which on reductive elimination gives a [2 + 2 + 2] cycloaddition product **3** and generates a total of four stereogenic centers.

In summary, we have developed a nickel(0)/NHC-catalyzed fully intermolecular, enantioselective [2 + 2 + 2] cycloaddition of two enones and an alkyne to yield a variety of cyclohexene derivatives with the successive generation of four contiguous stereogenic centers. The absolute configuration of **3aa** was determined by X-ray diffraction and CD spectral analyses. Detailed studies of the reaction mechanism are 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/acs.orglett.5b02983.

Condition optimization, experimental procedures, and characterization data for all new compounds(PDF)
X-ray data for **3aa** (CIF)

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Notes

The authors declare no competing financial interest.

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