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# Enantioselective [2 + 2 + 2] Cycloaddition Reaction of Isocyanates and Allenes Catalyzed by Nickel

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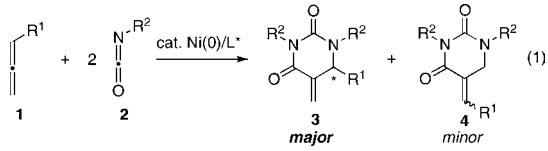
***Abstract:*** The enantioselective intermolecular [2 + 2 + 2] cycloaddition reaction of two molecules of isocyanate and one molecule of allene is catalyzed by a nickel(0)/(*S*,*S*)-*i*-Pr-FOXAP complex, providing an efficient access to enantiomerically enriched dihydropyrimidine-2,4-diones.

Transition-metal-catalyzed [2 + 2 + 2] cycloaddition reactions provide a powerful tool for rapid construction of six-membered ring carbo- and heterocycles.[1] Isocyanates are often employed as the $\pi$ component due to their unique reactivity as well as availability from commercial sources.[2] Transition metal complexes such as cobalt(I),[3] nickel(0),[4] ruthenium(II),[5] and rhodium(I)[6] can catalyze the intermolecular [2 + 2 + 2] cycloaddition reaction of one molecule of isocyanate and two molecules of alkyne, leading to the formation of 2-pyridones.[7] Pyrimidine-2,4-diones were also synthesized by [2 + 2 + 2] cycloaddition of two molecules of isocyanate and one molecule of alkyne.[6a,8] Rovis and co-workers developed a regio- and enantioselective rhodium(I)-catalyzed bimolecular [(2 + 2) + 2] cycloaddition reaction of $\omega$-alkenyl isocyanates with alkynes forming bicyclic lactams or vinylogous amides and applied this strategy to the asymmetric total synthesis of (+)-lasubine II and (−)-209D.[9] Despite numerous studies on the metal-catalyzed [2 + 2 + 2] cycloaddition reactions, however, there has been no report on the use of allenes as the coupling partner of isocyanates.[10,11] Herein, we describe the nickel-catalyzed intermolecular [2 + 2 + 2] cycloaddition reaction of 1 equiv of allene **1** and 2 equiv of isocyanate **2** to afford the corresponding dihydropyrimidine-2,4-dione **3** with high levels of enantioselectivity (eq 1).




Initially, a variety of achiral phosphine ligands were evaluated using nickel(0) as the transition metal and undeca-1,2-diene (**1a**) and tolyl isocyanate (**2a**) as the model substrates; a mixture of **1a** (1.0 equiv) and **2a** (3.0 equiv) in THF was heated at 80 °C in the presence of a nickel(0) catalyst generated *in situ* from $Ni(cod)_2$ (10 mol %) and a phosphine ligand (P/Ni = 4:1). Whereas the use of monophosphine ligands such as $PMe_3$, $PCy_3$, $P(t\text{-}Bu)_3$, and $PPh_3$ resulted in only oligomerization of the allene **1a**,[12] a cycloaddition reaction was observed with bisphosphine ligands such as Dppe and Dppbenz. For example, when Dppe was employed, a mixture of **3aa** and **4aa** (4:1) was produced in 13% combined yield. The products **3aa** and **4aa** are regioisomers, both arising from intermolecular [2 + 2 + 2] cycloaddition between one molecule of allene

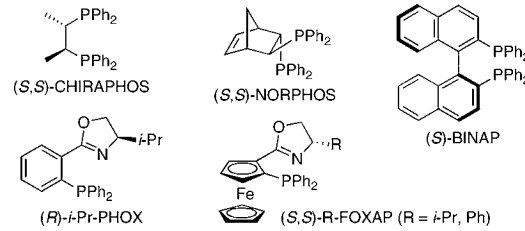
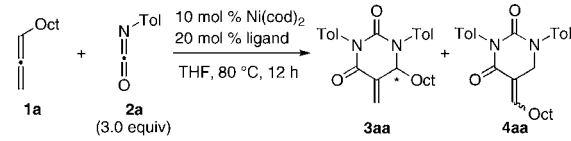



***Figure 1.*** Chiral ligands examined in the optimization studies.

***Table 1.*** Ni(0)-Catalyzed Enantioselective [2 + 2 + 2] Cycloaddition: Screening of Chiral Phosphine Ligands[a]




| entry | chiral ligand | yield (%)[b] | rs (**3:4**)[c] | ee (%)[d] |
|---|---|---|---|---|
| 1 | (*S*,*S*)-CHIRAPHOS | 78[e] | 5:1 | 33 |
| 2 | (*S*,*S*)-NORPHOS | 19 | 4:1 | 19 |
| 3 | (*S*)-BINAP | 43[e] | 2:1 | 5 |
| 4 | (*R*)-*i*-Pr-PHOX | 32 | 16:1 | 87 |
| **5** | **(*S*,*S*)-*i*-Pr-FOXAP** | **68** | **>20:1** | **97** |
| 6 | (*S*,*S*)-Ph-FOXAP | 66 | >20:1 | 67 |

[a] All reactions were carried out on a 0.2 mmol scale. [b] Combined yield of regioisomers. [c] Ratio of regioisomers determined by $^1H$ NMR. [d] Enantiomeric excess determined by chiral HPLC analysis. [e] The product was accompanied with small amounts (~10%) of unidentified compounds.

**1a** and two molecules of isocyanate **2a**. We next extended our ligand survey to chiral phosphine ligands to observe good catalytic activity with the use of $C_2$-symmetric bisphosphine ligands such as (*S*,*S*)-Chiraphos, (*S*,*S*)-Norphos, and (*S*)-Binap (Figure 1). However, both the regioselectivity (**3aa:4aa**) and the enantioselectivity of **3aa** were low (Table 1, entries 1−3). The regioselectivity was significantly improved when unsymmetrical phosphino-oxazoline ligands were used (entries 4−6). Among them, (*S*,*S*)-*i*-Pr-FOXAP[13] proved to be the optimal ligand; **3aa** was obtained in 68% yield with >20:1 regioselectivity, and its enantioselectivity was 97% ee (entry 5).[14]

The results of the reaction with various combinations of allenes **1** and isocyanates **2** using a nickel(0)/(*S*,*S*)-*i*-Pr-FOXAP complex are summarized in Table 2. Monosubstituted allenes **1b**−**d** possessing a primary alkyl group readily reacted with **2a** to afford the corresponding products **3ba**−**da** in good yields with high regio- and enantioselectivities (entries 1−3),[15] whereas the reaction of cyclohexylpropa-1,2-diene (**1e**) was sluggish to give the product **3ea** only in 26% yield (entry 4).[16] Functional groups such as benzyloxy, siloxy, and alkenyl groups were tolerated in the alkyl chain under the reaction conditions (entries 5−7). The



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***Table 2.*** Ni(0)-Catalyzed Enantioselective [2 + 2 + 2] Cycloaddition of **1** ($R^1CH{=}C{=}CH_2$) and **2** ($R^2NCO$)[a]

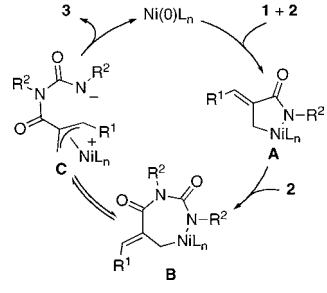
| entry | **1** ($R^1$) | **2** ($R^2$) | **3** | yield (%)[b] | rs (**3**:**4**)[c] | ee (%)[d] |
|---|---|---|---|---|---|---|
| 1 | **1b** (Hex) | **2a** (Tol) | **3ba** | 67 | >20:1 | 96 |
| 2 | **1c** ($CH_2Cy$) | **2a** | **3ca** | 67 | >20:1 | 94 |
| 3 | **1d** ($(CH_2)_2Ph$) | **2a** | **3da** | 65 | >20:1 | 94 |
| 4 | **1e** (Cy) | **2a** | **3ea** | 26 | 5:1 | 97[e] |
| 5 | **1f** ($(CH_2)_4OBn$) | **2a** | **3fa** | 61 | >20:1 | 97[e] |
| 6 | **1g** ($(CH_2)_4OTBS$) | **2a** | **3ga** | 60 | >20:1 | 94 |
| 7 | **1h** ($(CH_2)_2CH{=}CMe_2$) | **2a** | **3ha** | 64 | >20:1 | 99 |
| 8 | **1a** (Oct) | **2b** (4-$Me_2N$-$C_6H_4$) | **3ab** | 57[f] | >20:1 | 98 |
| 9 | **1a** | **2c** (4-MeO-$C_6H_4$) | **3ac** | 65 | >20:1 | 99 |
| 10 | **1a** | **2d** (Ph) | **3ad** | 70 | >20:1 | 98 |
| 11 | **1a** | **2e** (4-Cl-$C_6H_4$) | **3ae** | 73 | >20:1 | 89[e] |
| 12 | **1a** | **2f** (4-$MeO_2C$-$C_6H_4$) | **3af** | 76 | 16:1 | 97[e] |
| 13 | **1a** | **2g** (4-MeCO-$C_6H_4$) | **3ag** | 55 | >20:1 | 94[e] |
| 14 | **1a** | **2h** (4-$CF_3$-$C_6H_4$) | **3ah** | 79 | 6:1 | 88[e] |
| 15 | **1a** | **2i** (3-Me-$C_6H_4$) | **3ai** | 65 | >20:1 | 97 |
| 16 | **1a** | **2j** (2-Naphthyl) | **3aj** | 82 | >20:1 | 97 |
| 17 | **1a** | **2k** (Bn) | **3ak** | 12 | >20:1 | 94 |

[a] The reaction was carried out with **1** (0.2 mmol), **2** (0.6 mmol), $Ni(cod)_2$ (10 mol %), *i*-Pr-FOXAP (20 mol %) in THF (1 mL) at 80 °C for 12 h, unless otherwise noted. [b] Combined yield of regioisomers. [c] Ratio of regioisomers determined by $^1H$ NMR. [d] Enantiomeric excess determined by chiral HPLC analysis. [e] Using 1,4-dioxane (1 mL) at 100 °C. [f] $^1H$ NMR yield using $CHBr_2CHBr_2$ as an internal standard.

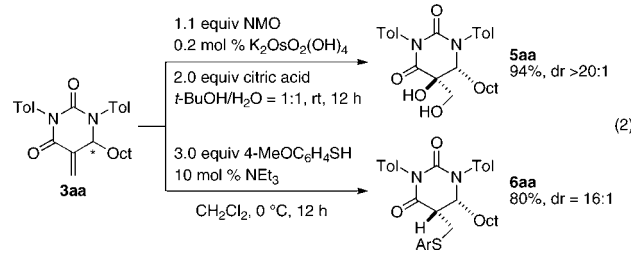
cycloaddition reaction of **1a** with a diverse array of aryl isocyanates **2b**−**j** proceeded well to give the corresponding products **3ab**−**aj** in yields ranging from 55 to 82% with enantioselectivities ranging from 88 to 99% ee (entries 8−16). Higher regioselectivity was observed with electron-rich aryl isocyanates than with electron-deficient aryl isocyanates. In the reaction of benzyl isocyanate (**2k**) with **1a**, large amounts of isocyanate oligomers were produced together with a small amount of the cycloadduct **3ak**, which was isolated in only 12% yield (entry 17). Other alkyl isocyanates including hexyl isocyanate, cyclohexyl isocyanate, and *tert*-butyl isocyanate all failed to undergo the cycloaddition reaction.

A plausible mechanism for the production of dihydropyrimidine-2,4-dione **3** from allene **1** and isocyanate **2** is depicted in Scheme 1.[17] Initially, the intermolecular oxidative cyclization of a heteropair of **1** and **2** occurs on nickel(0) to give five-membered ring azanickelacyclic intermediate **A**.[18,19] Subsequent insertion of another molecule of **2** into the nickel−nitrogen bond expands **A** to seven-membered ring azanickelacycle **B**, which is in equilibrium with zwitterionic $\pi$-allylnickel species **C**. Finally, intramolecular recombination occurs at the more substituted carbon of the allyl moiety to afford **3** along with nickel(0).

***Scheme 1.*** Proposed Mechanism for Ni(0)-Catalyzed Synthesis of **3** from **1** and **2**




The synthetic utility of the enantiomerically enriched dihydropyrimidine-2,4-dione **3aa** was exemplified by further transformations (eq 2).[20] Highly stereoselective functionalization of the olefin could be achieved.




In summary, we have developed a highly enantioselective nickel-catalyzed [2 + 2 + 2] cycloaddition of two molecules of isocyanate and one molecule of allene, providing an efficient access to enantiomerically enriched dihydropyrimidine-2,4-diones. Further investigation on the reaction mechanism, the substrate scope, and the utilization of dihydropyrimidine-2,4-diones as chiral building blocks are underway.

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**Supporting Information Available:** Experimental procedures, spectral data for the new compounds, and details of the X-ray analysis. This material is available free of charge via Internet at http://pubs.acs.org.

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(14) When the cycloaddition of entry 5 of Table 1 was carried out on a 1.0 mmol scale, the product was obtained in 62% (>20:1) and 98% ee. A similar result (65% (>20:1) and 97% ee) was obtained when 10 mol % of (*S*,*S*)-*i*-Pr-FOXAP and 10 mol % of $Ni(cod)_2$ were used.

(15) The absolute configuration of **3ca** was determined by an X-ray crystal structure analysis of its derivative formed by a conjugate addition of a thiol. See the Supporting Information for details.
(16) Under our standard conditions, 1-methoxypropa-1,2-diene and 1-(*tert*-butyldimethylsilyl)propa-1,2-diene were not suitable coupling partners.
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