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Nickel-Catalyzed Desymmetrizing Cyclization of 1,6-Dienes to Construct Quaternary Stereocenters

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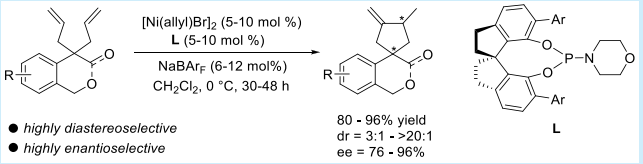
ABSTRACT: A highly enantioselective and diastereoselective nickel-catalyzed desymmetrizing cyclization of 1,6-dienes was developed by using chiral spiro phosphoramidite ligands. The reaction provides a new atom- and step-economical approach to chiral spiro lactones and analogues bearing a quaternary stereocenter.

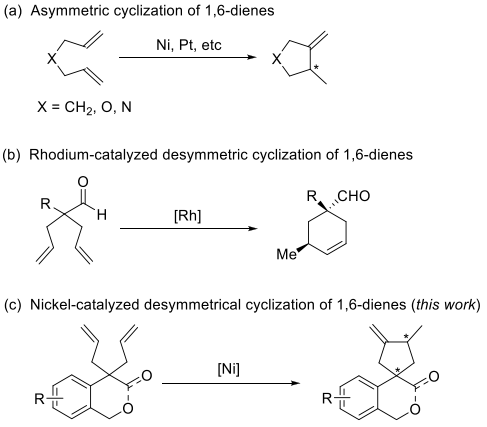


Quaternary stereocenters widely exist in the structures of natural products and pharmaceuticals. For instance, of the top 120 chiral small-molecule pharmaceuticals by retail sales in the United States in 2018, 13% contain a quaternary stereocenter.[1] In organic synthesis, most of the quaternary stereocenter units originate from the natural product precursors. Chemists have been trying to develop efficient methods to construct quaternary stereocenters and have made remarkable progress.[2] At present, there are mainly two strategies for constructing quaternary stereocenters: One is the addition of a carbon nucleophile to a carbon−carbon double bond or to a tricarbon-substituted cation, and the other is the desymmetrization of the prebuilt quaternary center.[3]

Desymmetrization is a unique way to construct quaternary stereocenters, in which the quaternary center is already present in the molecule, and the reaction occurs enantioselectively on one of the side chains. Thus, the nuisance steric hindrance in the formation of a quaternary stereocenter can be avoided. In the past decades, desymmetrization attracted extensive attention for enantioselective preparation of the chiral compounds containing a quaternary stereocenter.[4] For example, in the Hajos−Parrish−Eder−Sauer−Wiechert reaction, the desymmetrizing cyclization of prebuilt α,α-disubstituted 1,3-diketone produced chiral polycyclic molecules,[4a,b] which have been widely applied in the total synthesis of natural products. Desymmetric ring-opening and ring-expanding reactions of small-ring systems containing quaternary centers are also useful reactions in organic synthesis.[4c]

Transition-metal-catalyzed asymmetric cyclization of 1,6-dienes provided an efficient method for the preparation of chiral cyclopentenes (Scheme 1a).[5] However, the desymmetrizing cyclization of 1,6-dienes to construct a quaternary stereocenter has only one example by using a rhodium catalyst (Scheme 1b).[6] In the previous work, we developed a nickel-catalyzed enantioselective cyclization of N- or O-tethered 1,6-dienes to form six-membered chiral heterocycles.[7] Encouraged by this success, we envisioned whether this reaction can be applied to desymmetrizing cyclization of 1,6-dienes containing a quaternary center. Herein, we report a desymmetrizing cyclization of 1,6-dienes to synthesize chiral spiro lactones and analogues in high enantioselecitvity (Scheme 1c).

Scheme 1. Transition-Metal-Catalyzed 1,6-Diene Cyclizations



We began by exploring the desymmetrizing cyclization of 1,6-diene **1a**. The reactions were performed in CH_2Cl_2 at 20 °C with a nickel catalyst prepared in situ from 2.5 mol % of $[Ni(allyl)Br]_2$, 5 mol % of monodentate phosphine ligand, and 6 mol % of sodium tetrakis(3,5-bis(trifluoromethyl)phenyl)-borane ($NaBAr_F$). First, various chiral spiro monodentate phosphorus ligands[8] developed in our laboratory were evaluated (see the Supporting Information for details). Phosphonite ligand **L1** and phosphoramidite ligands **L2** and

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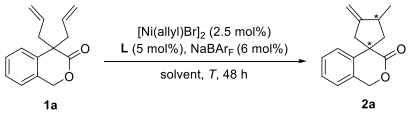
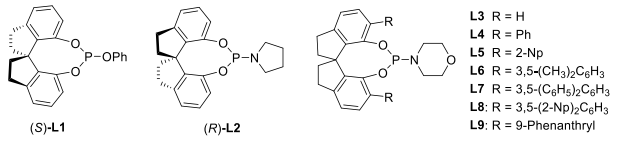
L3 provided low yield and poor enantioselectivity (Table 1, entries 1−3). The substitution at the 6,6′-position of the

Table 1. Nickel-Catalyzed Desymmetrizing Cyclization of 1,6-Diene 1a: Optimization of Reaction Conditions[a]





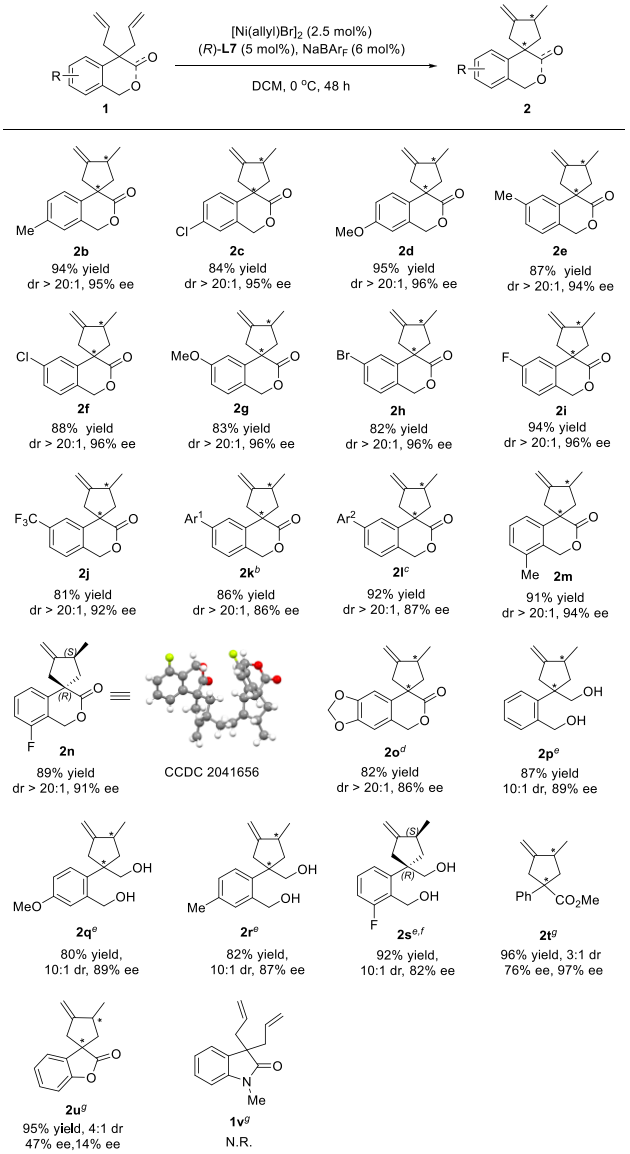
entry	L	T/°C	solvent	yield (%)	dr	ee
1	(*S*)-**L1**	20	CH_2Cl_2	36	>20:1	20
2	(*R*)-**L2**	20	CH_2Cl_2	56	>20:1	6
3	(*R*)-**L3**	20	CH_2Cl_2	76	10:1	20
4	(*S*)-**L4**	20	CH_2Cl_2	80	10:1	19
5	(*S*)-**L5**	20	CH_2Cl_2	82	>20:1	30
6	(*R*)-**L6**	20	CH_2Cl_2	82	>20:1	63
7	(*S*)-**L7**	20	CH_2Cl_2	90	>20:1	82
8	(*R*)-**L8**	20	CH_2Cl_2	87	>20:1	85
9	(*S*)-**L9**	20	CH_2Cl_2	70	>20:1	79
10	(*S*)-**L7**	0	CH_2Cl_2	90	>20:1	96
11	(*R*)-**L8**	0	CH_2Cl_2	85	>20:1	96
12	(*S*)-**L7**	0	toluene	57	>20:1	94
13	(*S*)-**L7**	0	THF	N.R.	—	—
14	(*S*)-**L7**	0	hexane	N.R.	—	—

[a]Reaction conditions: $[Ni(allyl)Br]_2$ (0.0025 mmol), ligand (0.005 mmol), $NaBAr_F$ (0.006 mmol), **1a** (0.10 mmol), 48 h. Isolated yield. The dr values were determined by ^1H NMR. The ee values were determined by HPLC on a chiral stationary phase.

phosphoramidite ligands (**L4**−**L9**) has a significant influence on the enantioselectivity of the reaction (entries 4−9). Ligands **L7**, **L8**, and **L9**, which have bulky groups at the 6,6′-position, exhibited high yield, high enantioselectivity, and excellent diastereoselectivity (entries 7−9). Moreover, the enantioselectivity of the reaction can be improved by lowering the reaction temperature. At 0 °C, with **L7** and **L8** as ligands, the enantioselectivity of the reaction reached 96% ee (entries 10 and 11). Solvent effect was studied by using ligand **L7**. In addition to CH_2Cl_2, toluene can also be used, but the conversion and yield are lower (entry 12). However, the reaction does not occur in THF or hexane.

Under the optimal reaction conditions (Table 1, entry 10), various isochromanone-derived 1,6-dienes **1** were studied. The 1,6-dienes bearing either an electron-rich or an electron-deficient group on the arene ring performed well to afford the corresponding spiro lactone products in good yield (81−95%) with high enantioselectivity (86−96% ee) and excellent diastereoselectivity (dr >20:1) (Scheme 2, **2b**−**2o**). A variety of functional groups, such as halogen (**2c**, **2f**, **2h**, **2i**), methoxy (**2d**, **2g**), nitro (**2k**), ester (**2l**), and piperonyl (**2o**), were tolerated under the reaction conditions. The absolute configuration of the product **2n** was determined by single-crystal X-ray diffraction analysis. We then investigated the desymmetrizing cyclization of 1,6-dienes containing diol. For these noncyclic substrates, **L8** was the most efficient ligand, affording cyclized products (**2p**−**2s**) in good yield (80−92%)

Scheme 2. Nickel-Catalyzed Desymmetric Cyclization of 1,6-Dienes[a]



[a]Reaction conditions: $[Ni(allyl)Br]_2$ (0.0025 mmol), (*R*)-**L7** (0.005 mmol), $NaBAr_F$ (0.006 mmol), **1** (0.10 mmol), in 1.5 mL of CH_2Cl_2, at 0 °C, 48 h. Isolated yield. The dr values were determined by ^1H NMR. The ee values were determined by HPLC. [b]Ar^1 = 4-$NO_2C_6H_4$. [c]Ar^2 = 4-$(CO_2Me)C_6H_4$. [d]1 mmol of **1o** was used. [e]5 % mol $[Ni(allyl)Br]_2$ was used. Ligand (*R*)-**L8** was used. The use of (*R*)-**L7** provides **2p** in 84% yield, 10:1 dr, and 84% ee. [f]The absolute configuration was determined by reducing **2n** with $LiAlH_4$ and comparing the HPLC chart of the product with that of **2s**. [g]Use ligand (*S*)-**L9**, at 20 °C, 30 h.

with high enantioselectivity (82−89% ee) and satisfactory diastereoselectivity (dr = 10:1). The desymmetrizing cyclization of the diene having an ester group (**1t**) by using ligand **L9** afforded the cyclization product **2t** in high yield (96%) with good enantioselectivity (76% ee and 97% ee) and moderate diastereoselectivity (dr = 3:1). We also studied the desymmetrizing cyclization of benzofuranone-derived and lactam-derived 1,6-dienes **1u** and **1v**. The cyclization of **1u** produced the desired product **2u** in high yield (95%) with low enantioselectivity (47% ee and 17% ee) and moderate

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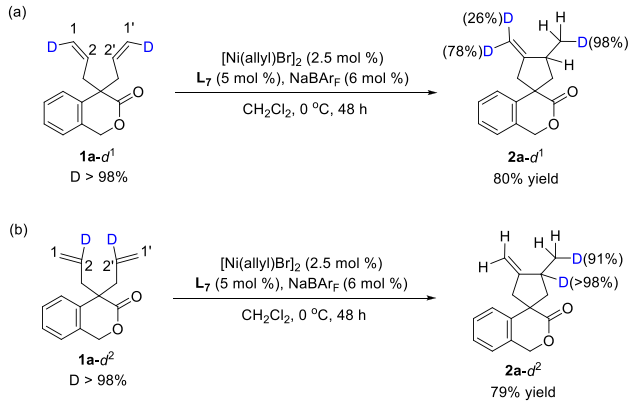
diastereoselectivity (dr = 4:1). However, **1v** could not afford the cyclized product.

To gain mechanistic insight into the desymmetrizing cyclization reaction, deuterium-labeling experiments were performed with deuterated diene substrates **1a**-d^1 and **1a**-d^2 (Scheme 3). ^{1}H NMR spectroscopy analysis of the products

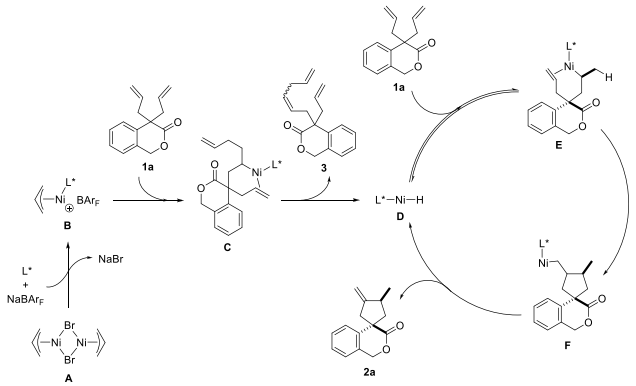
Scheme 3. Deuterium-Labeling Experiments



indicated that the deuterium atom at the terminal position of diene **1a**-d^1 was not transferred (Scheme 3a), and the deuterium atom at the 2-position of diene **1a**-d^2 was transferred to the 1′-position of the cyclized product **2a**-d^2 (Scheme 3b).

Based on the previous studies[7] and the above experimental results, we proposed a mechanism for the nickel-catalyzed desymmetrizing cyclization of 1,6-dienes (Scheme 4). In the

Scheme 4. Proposed Mechanism



presence of the phosphine ligand and $NaBAr_F$, allyl nickel bromide dimer **A** dissociates to allyl nickel **B**. The migratory insertion of the C=C bond of the diene into the nickel–carbon bond of **B** generates alkyl nickel intermediate **C**. Then, a β-H elimination of intermediate **C** forms Ni–H species **D**.[9] The migratory insertion of the C=C bond of the diene **1a** into the Ni–H bond of **D** generates the alkyl nickel intermediate **E**. Next, cyclization of **E** forms alkyl nickel intermediate **F**. Finally, β-H elimination of the intermediate **F** gives product **2a** and regenerates the active Ni–H species **D**.

In conclusion, we have developed a highly enantioselective and diastereoselective nickel-catalyzed desymmetrizing cyclization of 1,6-dienes. The reaction provides an efficient method for the preparation of chiral spiro lactones and analogues bearing a quaternary stereocenter. These chiral spiro lactones and analogues also afford potential candidates for drug screening.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c00796.

Experimental procedures and spectral data (PDF)

Accession Codes

CCDC 2041656 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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■ DEDICATION

Dedicated to the 100th Anniversary of Chemistry at Nankai University.

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