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Catalytic Enantioselective 1,4-Iodofunctionalizations of Conjugated Dienes

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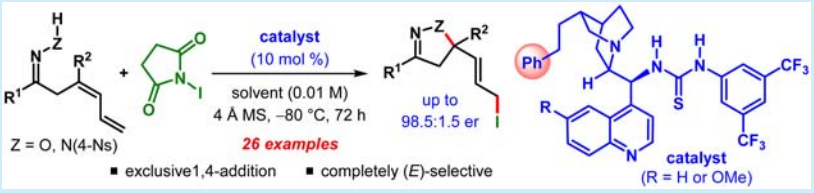
Supporting Information

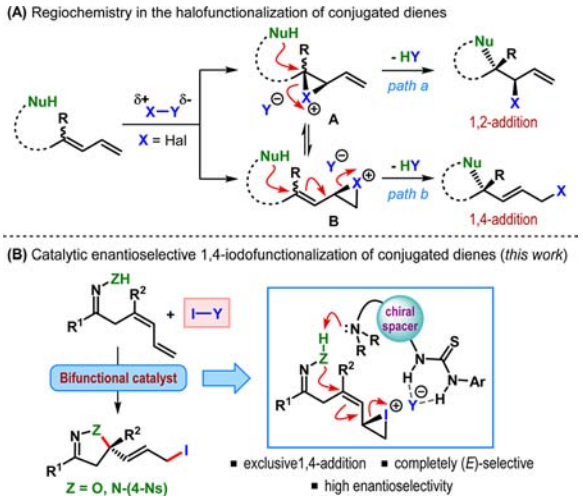


ABSTRACT: The first catalytic enantioselective 1,4-iodofunctionalizations of conjugated dienes have been developed. Starting from $\beta,\gamma,\delta,\varepsilon$-unsaturated oximes and 4-Ns hydrazones, these *N*-iodosuccinimide-mediated reactions are catalyzed by newly modified tertiary aminothiourea derivatives and furnish Δ^2-isoxazoline and Δ^2-pyrazoline derivatives, respectively, containing an (*E*)-allyl iodide group at the quaternary stereogenic center generally in high yield and with excellent enantioselectivity (up to 98.5:1.5 er).

Regioselective 1,4-difunctionalization of 1,3-dienes is a highly desirable class of synthetic transformations since the resulting alkene-containing compounds are versatile building blocks in organic synthesis. Electrophilic halogen-induced nucleophilic addition[1] to 1,3-dienes offers a potential approach toward 1,4-heterodifunctionalization. Catalytic asymmetric halofunctionalization of unactivated olefins has received considerable attention during the past few years.[2] Emergence of new modes of activation and catalysis concepts have led to the rapid expansion of the reaction scope within a short period.[3−5] However, while tremendous advancement in this direction took place for the reactions of various nucleophiles with isolated[6,7] and, to some extent, cumulated π-systems,[8] the enantioselective halofunctionalization reactions involving conjugated π-systems remained far less developed. This is particularly surprising since bromolactonization of conjugated (*Z*)-enynes, reported by Tang et al., was among the first highly enantioselective catalytic halofunctionalizations to be developed.[4] The reason behind this paucity possibly lies in the challenging regiochemical requirement (1,2- vs 1,4-halofunctionalization) associated with such systems. While the regioselectivity issue, in the case of enynes, is resolved due to the affinity of more electron-rich alkynes to electrophilic halogens,[4] the same issue becomes prominent for conjugated dienes due to the presence of two nearly equally reactive olefins (Scheme 1A).[9] In 2013, Toste and co-workers addressed this regioselectivity problem through the use of anionic phase-transfer catalysis and developed an enantioselective 1,4-fluoroaminocyclization of 1,3-dienes.[10] This report, as of today, remained the lone example of catalytic enantioselective 1,4-halofunctionalization of 1,3-dienes.[11]

Encouraged by our recent studies on the highly enantioselective catalytic iodocyclizations of β,γ-unsaturated oximes and hydrazones,[12] we decided to pursue the halocyclization of conjugated dienes using the same nucleophiles. In this report, we describe the first catalytic enantioselective 1,4-iodofunctionalization of conjugated dienes.

Scheme 1. Halofunctionalization of Conjugated Dienes



1,1-Disubstituted 1,3-dienes ($R^2 \neq H$; Scheme 1B) were selected as the diene component to facilitate the regiochemical discrimination between the two otherwise similar π-systems. The desired 1,4-halofunctionalization was hypothesized to occur through the reaction of the relatively less hindered haliranium ion **B** (Scheme 1A, path b).

In line with our previous observations,[12] we once again chose tertiary amino(thio)urea derivatives[13] as possible catalyst candidates. We surmised that a combination of Brønsted base

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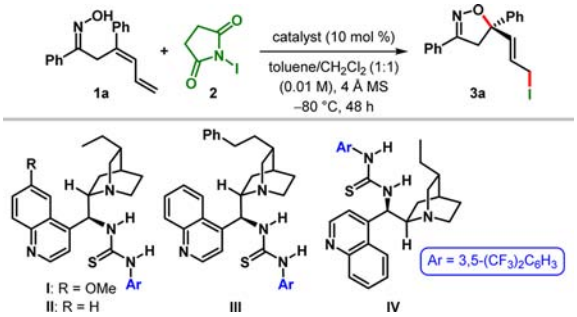
and chiral anion-binding catalysis should be able to discriminate between the two enantiomeric iodiranium cations besides activating the nucleophile (Scheme 1B).[3b,6d,h]

Indeed, the exposure of β,γ,δ,ε-unsaturated oxime **1a** to *N*-iodosuccinimide (NIS) **2** in the presence of 10 mol % of the dihydroquinine-derived thiourea **I** in a 1:1 mixture of toluene and dichloromethane at −80 °C led to 1,4-iodoetherification exclusively. We were delighted to find that the desired Δ^2-isoxazoline **3a** was obtained with substantial er (Table 1, entry 1).

Table 1. Catalytic Enantioselective 1,4-Iodoetherification: Reaction Optimization[a]



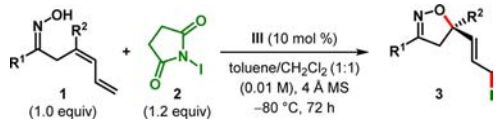
entry	catalyst	conv[b] (%)	er[c]
1	**I**	>95	86:14
2	**II**	>95	87:13
3	**III**	>95	95.5:4.5
4	**IV**	>95	5.5:94.5

[a]Reactions were carried out using 1.0 equiv of **1a** and 1.2 equiv of **2**. [b]Conversion of **1a** as determined by ^{1}H NMR of the crude reaction mixture. [c]Enantiomeric ratio (er) was determined by HPLC analysis using a chiral stationary phase.

No 5-exo or 6-endo cyclization products resulting from 1,2-addition could be detected. The exclusive (*E*)-selectivity of the product alkene is hardly surprising given the concerted nature of the reaction (nucleophilic addition and haliranium opening) and the preference for *s-trans* conformation of the allylic haliranium intermediate **B** (Scheme 1A). Moreover, failure of a thiourea derivative lacking Brønsted basic functionality to induce sufficient enantioselectivity further corroborated our catalytic hypothesis.[14] The dihydrocinchonidine-derived thiourea **II** slightly improved the enantioselectivity (entry 2). Replacing ethyl group on the quinuclidine ring with a bulkier homobenzyl group led to catalyst **III**, which to the best of our knowledge has never been reported in the literature.[15] In the presence of **III** at −80 °C, **3a** was obtained with markedly improved enantioselectivity (95.5:4.5 er; entry 3). All further attempts to boost the enantioselectivity by tweaking other reaction parameters proved futile.[14] The reaction with dihydrocinchonine-derived thiourea **IV** under the same conditions furnished the other product antipode *ent*-**3a** (entry 4), the absolute configuration of which was established as (*S*) through single-crystal X-ray diffraction analysis.[16]

The optimized catalyst and the reaction conditions (Table 1, entry 3) were then extended to other substrates in order to probe the generality of our intramolecular 1,4-iodoetherification protocol. These reaction conditions were found to be fairly general to an array of β,γ,δ,ε-unsaturated oximes **1**. As shown in Table 2, both electron-deficient and electron-rich aryl substituents on the diene are tolerated and furnished the products **3a**–**c** in good to excellent yields, even though the enantioselectivity varied considerably depending on the electronic nature of the aryl group (entries 1–3). Oximes bearing aryl or heteroaryl substituents were found to be suitable substrates, and regardless of their steric or electronic nature, the Δ^2-isoxazolines were usually obtained in high yield with good to excellent er (entries 4–10). While aliphatic substituent on the diene prevailed with high er (entry 11), a noticeable drop in enantioselectivity was observed for oximes containing an aliphatic substituent (entries 12 and 13).

Table 2. Catalytic Enantioselective 1,4-Iodoetherification: Substrate Scope[a]



entry	R^1	R^2	3	yield[b] (%)	er[c]
1	Ph	Ph	**3a**	87	95.5:4.5
2	Ph	4-FC_6H_4	**3b**	88	93:7
3	Ph	4-MeC_6H_4	**3c**	99	89:11
4	4-FC_6H_4	Ph	**3d**	86	97:3
5	3-FC_6H_4	Ph	**3e**	86	94.5:5.5
6	4-ClC_6H_4	Ph	**3f**	82	96.5:3.5
7	4-$OMeC_6H_4$	Ph	**3g**	76	95.5:4.5
8	4-MeC_6H_4	Ph	**3h**	84	95:5
9	2-naphthyl	Ph	**3i**	96	88:12
10	2-furyl	Ph	**3j**	77	95.5:4.5
11	Ph	Me	**3k**	92	96.5:3.5
12[d]	Me	Ph	**3l**	24 (73)	65:35
13[e]	*c*-Hex	Ph	**3m**	81 (99)	80:20
14	*c*-Hex	Me	**3n**	93	76.5:23.5

[a]Reactions were carried out on a 0.1 mmol scale. Unless stated otherwise, **1** with *E*/*Z* ratio >20:1 was used. [b]Yields correspond to the isolated yield. The values in parentheses are yields based on the reactive geometrical isomer of the substrate. [c]Enantiomeric ratio (er) was determined by HPLC analysis using a chiral stationary phase. [d]*E*/*Z* ratio for **1l** 2:1. [e]*E*/*Z* ratio for **1m** 4.2:1.

The requirement of an aryl or heteroaryl substituent on the oxime for attaining a useful level of er constitutes a current limitation of this protocol. Even though Δ^2-isoxazolines are valuable in their own right,[17] the synthetic utility of our 1,4-iodoetherification adducts was demonstrated through a series of transformations involving **3a** and **3k** (see the Supporting Information).

Having successfully accomplished the catalytic enantioselective 1,4-iodoetherification of β,γ,δ,ε-unsaturated oximes, we turned our attention to the 1,4-iodoaminocyclization of related hydrazone derivatives. To begin with this investigation, analogous β,γ,δ,ε-unsaturated 4-nitrobenzenesulfonyl (4-Ns) hydrazone **4a** was chosen as the model substrate (Table 3). The bifunctional catalyst **V** derived from *trans*-1,2-diaminocyclohexane, which was used in our previously reported enantioselective 1,2-iodoaminocyclization reaction,[12a] turned out to be a potent catalyst and generated the 1,4-iodoaminocyclization adduct Δ^2-pyrazoline derivative **5a** exclusively, without any trace of 1,2-addition products (entry 1). However, the product was obtained with only moderate enantioselectivity. Dihydroquinine-derived thiourea **I**, on the other hand, provided **5a** with a superior er of 81:19 (entry 3). A change in the reaction medium proved crucial, and improved er was observed in a 3:1 mixture of toluene and CH_2Cl_2 (entries 4 and 5). Although the exchange of the ethyl substituent on the quinuclidine of **I** with a

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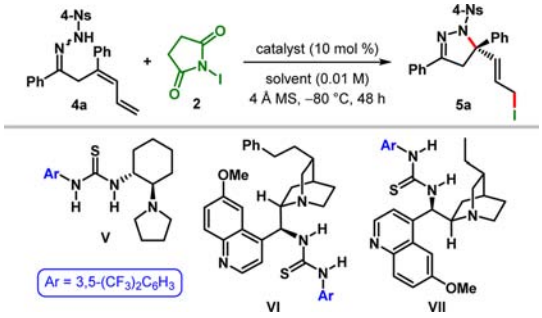
Table 3. Catalytic Enantioselective 1,4-Iodoaminocyclization: Reaction Optimization[a]



entry	catalyst	solvent	conv[b] (%)	er[c]
1	**V**	toluene/CH_2Cl_2 (1:1)	>95	75:25
2	**II**	toluene/CH_2Cl_2 (1:1)	>95	71.5:28.5
3	**I**	toluene/CH_2Cl_2 (1:1)	>95	81:19
4	**I**	toluene/CH_2Cl_2 (2:1)	>95	89:11
5	**I**	toluene/CH_2Cl_2 (3:1)	>95	92:8
6	**VI**	toluene/CH_2Cl_2 (3:1)	>95	93:7
7	**VI**	toluene/$CHCl_3$ (3:1)	>95	98.5:1.5
8	**VII**	toluene/$CHCl_3$ (3:1)	>95	9:91

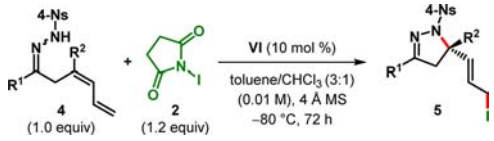
[a]Reactions were carried out using 1.0 equiv of **4a** and 1.2 equiv of **2**. [b]Conversion of the reactive geometrical isomer (*E*)-**4a** as determined by ^{1}H NMR of the crude reaction mixture. [c]Enantiomeric ratio (er) was determined by HPLC analysis using a chiral stationary phase.

homobenzyl group (in **VI**) marginally improved the er, a combination of this catalyst (**VI**) and a more polar medium (3:1 toluene/$CHCl_3$) provided **5a** with excellent enantioselectivity (entries 6 and 7). The enantiomeric product *ent*-**5a** could be accessed under the same conditions, albeit with lower er, using dihydroquinidine-derived thiourea **VII** (entry 8).

With the optimum catalyst and the reaction conditions (Table 3, entry 7) in hand, we examined the scope of this catalytic enantioselective 1,4-iodoaminocyclization reaction. The inseparable *E*/*Z* mixtures (with respect to C═N) obtained during the preparation of hydrazone in most cases[18] initially appeared as potentially problematic. However, only the (*E*)-isomer was found to undergo the desired iodoaminocyclization, and the unreactive (*Z*)-hydrazone could be recovered in most cases.[18] As depicted in Table 4, the optimized reaction conditions were found to be suitable for *β*,*γ*,*δ*,*ε*-unsaturated 4-nitrobezenesulfonyl (4-Ns) hydrazone containing both aromatic and aliphatic substituents. Electronically diverse aryl substituents on either hydrazone or diene furnished the Δ^2-pyrazoline derivatives in good to excellent enantioselectivities. Moreover, this 1,4-iodoaminocyclization reaction stands in sharp contrast to the 1,4-iodoetherification, discussed above, in that the high level of enantioselectivities was preserved for substrates containing alkyl groups on either positions (R^1 and R^2) (Table 4, entries 10 and 11). The compatibility of a more challenging substrate (R^1 = Me, R^2 = Ph) could not be tested as the hydrazone was formed exclusively as the undesired (*E*)-isomer (see the Supporting Information). However, the dialkylated hydrazone (**4l**) afforded the desired product (**5l**) with reasonably high er (entry 12). The absolute configuration of the products was assigned by comparison with that of **5a**, obtained by single-crystal X-ray diffraction analysis.[16]

In addition to being completely regioselective, a common feature of both the iodoetherification and iodoaminocyclization is that, irrespective of the nature of the substituents, all the

Table 4. Catalytic Enantioselective 1,4-Iodoaminocyclization: Substrate Scope[a]



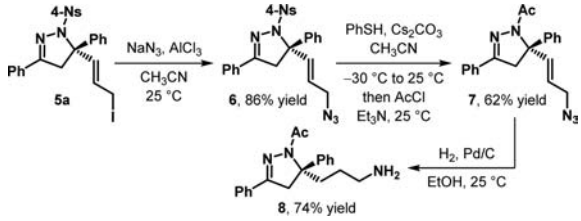
entry	R^1	R^2	5	yield[b] (%)	er[c]
1[d]	Ph	Ph	**5a**	54 (87)	98.5:1.5
2[e]	Ph	4-FC_6H_4	**5b**	32 (71)	96.5:3.5
3[f]	Ph	4-MeC_6H_4	**5c**	31 (77)	91:9
4	4-FC_6H_4	Ph	**5d**	61	91:9
5[g]	2,5-$F_2C_6H_3$	Ph	**5e**	52 (80)	93:7
6[h]	4-ClC_6H_4	Ph	**5f**	34 (79)	95:5
7[i]	4-$OMeC_6H_4$	Ph	**5g**	33 (69)	93:7
8[j]	4-MeC_6H_4	Ph	**5h**	37 (75)	96.5:3.5
9	2-naphthyl	Ph	**5i**	74	97:3
10	*c*-Hex	Ph	**5j**	66	95:5
11[k]	Ph	Me	**5k**	61	96.5:3.5
12[k,l]	*c*-Hex	Me	**5l**	43 (99)	89:11

[a]Reactions were carried out on a 0.1 mmol scale. Unless stated otherwise, **4** with *E*/*Z* ratio >20:1 was used. [b]Yields correspond to the isolated yield. The values in parentheses are yields based on the reactive geometrical isomer (*E*) of the substrate. [c]Enantiomeric ratio (er) was determined by HPLC analysis using a chiral stationary phase. [d]*E*/*Z* ratio for **4a** 1.7:1. [e]*E*/*Z* ratio for **4b** 1:1.2. [f]*E*/*Z* ratio for **4c** 1:1.5. [g]*E*/*Z* ratio for **4e** 1.7:1. [h]*E*/*Z* ratio for **4f** 1:1.3. [i]*E*/*Z* ratio for **4g** 1:1.1. [j]*E*:*Z* ratio for **4h** 1:1. [k]Reaction was conducted at −60 °C. [l]*E*/*Z* ratio for **4l** 1:1.3.

products were formed as a single diastereomer with respect to the olefin geometry in the allylic unit.

Having verified the scope of the enantioselective 1,4-iodoaminocyclization reaction, the product Δ^2-pyrazoline derivative (**5a**) was applied in a number of transformations (see the Supporting Information). In particular, protecting group exchange of the azide derivative **6** in a one-pot manner followed by hydrogenation furnished an *N*-acetyl 3,5-diaryl Δ^2-pyrazoline **8** having a structure similar to that of a potent kinesin spindle protein (KSP) inhibitor (Scheme 2).[19] No trace of racemization was observed during any of these transformations.[18]

Scheme 2. Conversion of 5a to a KSP Inhibitor Analogue (8)



In summary, we have achieved the first catalytic enantioselective 1,4-iodocyclizations of conjugated dienes with the help of newly modified bifunctional tertiary aminothiourea catalysts. Under the mild reaction conditions with NIS as the electrophilic iodine source, *β*,*γ*,*δ*,*ε*-unsaturated oximes and 4-Ns-hydrazones underwent cyclization exclusively in a 1,4-fashion to furnish Δ^2-isoxazoline and Δ^2-pyrazoline derivatives, respectively, containing a quaternary stereogenic center generally in high yield with good to excellent enantioselectivity and impeccable diastereoselectivity.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02026.

Experimental details, characterization data, and crystallographic data (PDF)
NMR spectra of obtained compounds (PDF)
X-ray data for compound *ent*-**3a** (CIF)
X-ray data for compound **5a** (CIF)

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Notes

The authors declare no competing financial interest.

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