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# Nickel-Catalyzed Cross-Electrophile Coupling of Alkyl Fluorides: Stereospecific Synthesis of Vinylcyclopropanes

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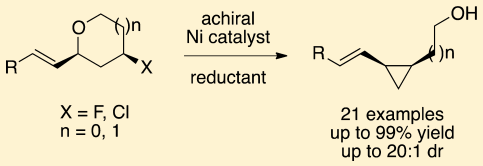
Supporting Information

**ABSTRACT:** The stereospecific reductive cross-electrophile coupling reaction of 2-vinyl-4-halotetrahydropyrans for vinylcyclopropane synthesis is reported. The nickel-catalyzed reaction occurs with both alkyl fluorides and alkyl chlorides. To the best of our knowledge, this is the first reported cross-electrophile coupling reaction of an alkyl fluoride. Ring contraction proceeds with high stereospecificity, providing selective synthesis of either diastereomer of di- and trisubstituted cyclopropanes. The utility of this methodology is demonstrated by several synthetic applications including the synthesis of the natural product dictyopterene A. 2-Vinyl-4-fluorotetrahydrofurans also undergo stereospecific ring contractions, providing access to synthetically useful hydroxymethyl cyclopropanes.

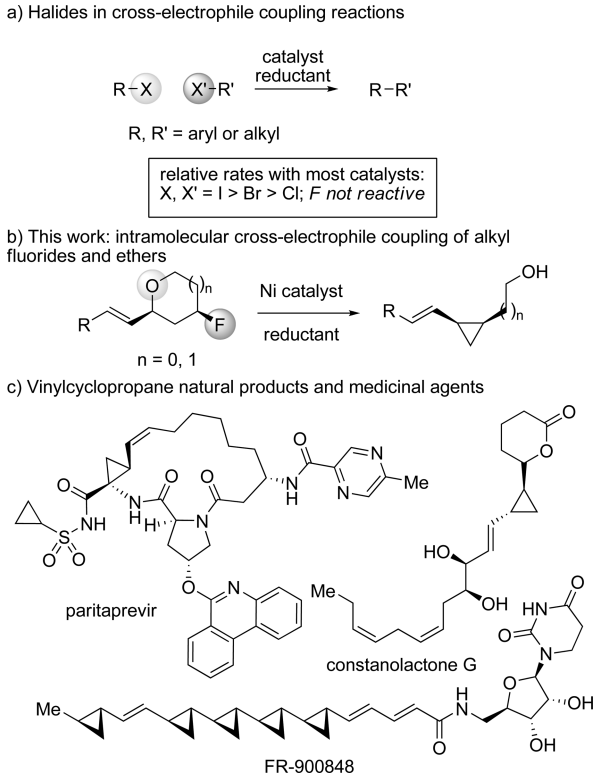



## INTRODUCTION

Alkyl fluorides are typically considered the least reactive of the alkyl halides. Although alkyl iodides and bromides are potent alkylating agents that often possess cytotoxicity, alkyl fluorides are frequently employed as isosteres for the parent hydrocarbons due to the ability of the C−F bond to mask reactive C−H positions in bioactive agents.[1,2] This decrease in reactivity is apparent in transition-metal-catalyzed reactions.[3−5] For example, the use of aryl fluorides in cross-coupling reactions is much less well developed than that of the corresponding cross-coupling reactions of aryl chlorides, bromides, and iodides.[3,6] While alkyl fluoride cross-coupling reactions have been established,[7−9] more commonly, alkyl fluorides are tolerated as unreactive moieties in nickel- and palladium-catalyzed cross-coupling reactions.[10] Similarly, cross-electrophile coupling reactions employ aryl and alkyl iodides, bromides, and chlorides;[11−13] however, to our knowledge, there are no examples that employ fluorides as partners (Scheme 1a). As part of our ongoing interest in the development of stereospecific reactions of alkyl electrophiles,[14] we report a stereospecific ring contraction of 4-fluorotetrahydropyrans to access vinylcyclopropanes (Scheme 1b). Notably, this reaction engages two functional groups that are considered poor electrophiles, an ether and an alkyl fluoride. Consistent with cross-coupling and related reactions of aryl fluorides,[15,16] we find that a first-row transition metal catalyst, specifically a nickel catalyst, is highly effective for this transformation. Control of stereochemistry is robust and predictable, providing straightforward access to either diastereomer of the vinylcyclopropane products.

Vinylcyclopropanes occur in natural products such as *trans*-chrysanthemic acid, FR-900848, ambruticin S, and constanolactone G and in medicinal agents including NS3 serine protease inhibitors paritaprevir and simeprevir (Scheme 1c).[17,18] Vinylcyclopropanes are also valuable synthetic intermediates that participate in a broad range of transformations, including transition-metal-catalyzed rearrangements

**Scheme 1. Reductive Cross-Electrophile Coupling and Important Vinylcyclopropanes**

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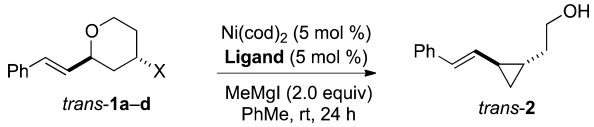
and cycloaddition reactions.[19−21] This reactivity has been utilized in the synthesis of a variety of natural products including linear triquinanes and *Melodinus* alkaloids.[22] As such, considerable synthetic effort has been directed toward synthesis of vinylcyclopropanes. They can be prepared from dienes and highly reactive α-diazocarbonyls or carbenoids or from enones via Michael-initiated ring closing reactions.[23,24] The majority of these syntheses result in formation of hydroxymethyl- or acyl-substituted vinylcyclopropanes. A strategy that provides vinylcyclopropanes with different substituent patterns would therefore be desirable.

## RESULTS AND DISCUSSION

We recently reported a reductive cross-electrophile coupling strategy toward the synthesis of arylcyclopropanes from 2-aryl-4-chlorotetrahydropyrans.[25] This strategy employs stable and readily available starting materials and provides access to a broad range of substituent patterns with predictable control of stereochemistry. Since allylic ethers undergo facile nickel-catalyzed cross-coupling reactions,[26] we hypothesized that 4-halo-2-vinyltetrahydropyrans would undergo ring contraction to generate vinylcyclopropanes (Table 1). To test our hypothesis, we utilized *trans*-4-fluoro-2-((*E*)-styryl)tetrahydro-2H-pyran (*trans*-**1a**). This compound is readily prepared by a Prins reaction of the corresponding aldehyde in the presence of $HBF_4{\cdot}OEt_2$.[27,28] A series of nickel catalysts prepared in situ from $Ni(cod)_2$ and bidentate ligands were evaluated. Using a BINAP-ligated nickel complex we obtained a 75% yield of the desired vinylcyclopropane *trans*-**2** with high diastereoselectivity (entry 1). Alternative ligands including Xantphos and pyridine-derived ligands BPhen and bipy resulted in diminished yield and stereospecificity (entries 2−4).[29] Use of $Ni(cod)_2$ with no additional ligand provided a greatly diminished yield of the desired product (entry 5). Utilizing a nickel(II) precatalyst with the addition of Xantphos as a ligand resulted in comparable yield and dr (entry 6). Analysis of NOE data verified the relative configuration, confirming that *trans*-**1a** resulted in *trans*-**2**. To the best of our knowledge, this is the first reported reductive cross-electrophile coupling with an alkyl fluoride.

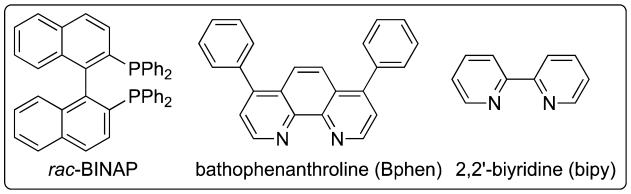
To evaluate the breadth of the methodology we examined a series of tetrahydropyrans where the alkyl fluoride was replaced with another halide or pseudohalide leaving group. Utilizing alkyl chloride *trans*-**1b**, we were pleased to see both high yield and stereochemical fidelity when pyridine-based ligand, BPhen, was employed (Table 1, entry 9). The more reactive alkyl bromide *trans*-**1c** resulted in high yields of the vinylcyclopropane; however, only modest levels of diastereoselec-

**Table 1. Examination of Leaving Groups and Ligands for *trans*-4-Halotetrahydropyran**




| entry | X | SM | ligand | yield (%) | **1** dr (*trans*/*cis*) | **2** dr (*trans*/*cis*) |
|---|---|---|---|---|---|---|
| 1 | F | **1a** | *rac*-BINAP | 75 | 20:1 | 20:1 |
| 2 | F | **1a** | Xantphos | 67 | 20:1 | 17:1 |
| 3 | F | **1a** | BPhen | 42 | 20:1 | 13:1 |
| 4 | F | **1a** | bipy | 21 | 20:1 | 13:1 |
| 5 | F | **1a** | none | 14 | 20:1 | 20:1 |
| 6[a] | F | **1a** | Xantphos | 60 | 20:1 | 17:1 |
| 7 | Cl | **1b** | *rac*-BINAP | 61 | 20:1 | 4:1 |
| 8 | Cl | **1b** | Xantphos | 0 | 20:1 | |
| 9 | Cl | **1b** | BPhen | >99 | 20:1 | 20:1 |
| 10 | Cl | **1b** | bipy | 97 | 20:1 | 7:1 |
| 11 | Br | **1c** | *rac*-BINAP | 98 | 20:1 | 4:1 |
| 12 | Br | **1c** | Xantphos | 82 | 20:1 | 2:1 |
| 13 | Br | **1c** | BPhen | 83 | 20:1 | 5:1 |
| 14 | Br | **1c** | bipy | 99 | 20:1 | 4:1 |
| 15 | OTs | **1d** | *rac*-BINAP | 16 | 20:1 | 20:1 |
| 16[b] | OTs | **1d** | Xantphos | 35 | 20:1 | 4:1 |
| 17 | OTs | **1d** | BPhen | 0 | 20:1 | |
| 18 | OTs | **1d** | bipy | 0 | 20:1 | |

[a]$NiCl_2$(dme) used instead of $Ni(cod)_2$. [b]Yield determined by $^1H$ NMR based on comparison to PhTMS as internal standard.




**Scheme 2. Stereochemical Outcome of Ring Contraction**

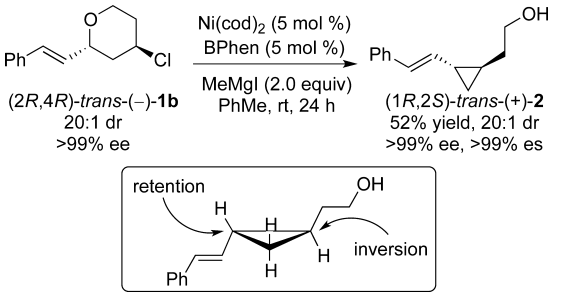
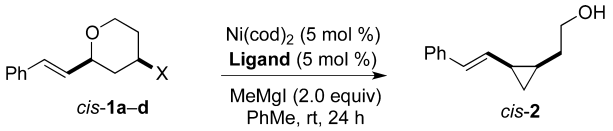



**Table 2. *cis*-4-Halotetrahydropyran Ligand and Leaving Group Screen**




| entry | X | SM | ligand | yield (%) | **1** dr (*cis*/*trans*) | **2** dr (*cis*/*trans*) |
|---|---|---|---|---|---|---|
| 1 | F | **1a** | Xantphos | 56 | 20:1 | 20:1 |
| 2 | F | **1a** | *rac*-BINAP | 41 | 20:1 | 9:1 |
| 3 | F | **1a** | Phen | 26 | 20:1 | 9:1 |
| 4 | Cl | **1b** | Xantphos | 47 | 20:1 | 20:1 |
| 5 | Cl | **1b** | *rac*-BINAP | 71 | 20:1 | 4:1 |
| 6 | Cl | **1b** | Phen | 92 | 20:1 | 6:1 |
| 7 | Br | **1c** | Xantphos | 30 | 20:1 | 2:1 |
| 8 | Br | **1c** | *rac*-BINAP | 58 | 20:1 | 2:1 |
| 9[a] | Br | **1c** | *rac*-BINAP | 65 | 20:1 | 5:1 |
| 10 | Br | **1c** | Phen | 68 | 20:1 | 2:1 |
| 11 | OTs | **1d** | *rac*-BINAP | 8 | 8:1 | 1:1 |

[a]$Bu_4NBr$ (1.0 equiv) added.

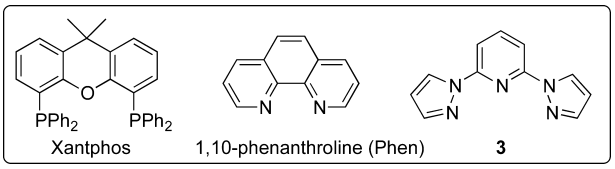





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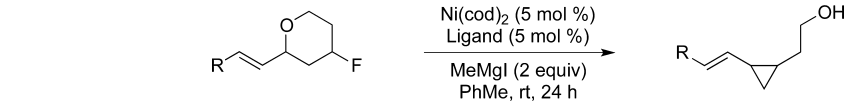
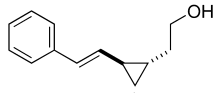
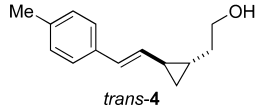
**Table 3. Substrate Scope**



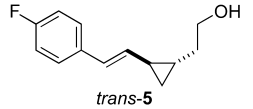

a) Starting from trans-substituted THPs



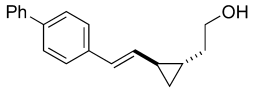
*trans*-**2**
75%, 20:1 dr (20:1 dr)
with *rac*-BINAP



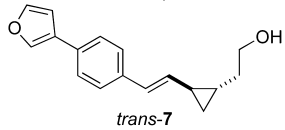
*trans*-**4**
58% yield, 20:1 dr (20:1 SM dr)
with Xantphos



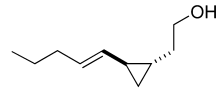
*trans*-**5**
63% yield, 20:1 dr (20:1 SM dr)
with bipy



*trans*-**6**
77% yield, 15:1 dr (15:1 SM dr)
with Xantphos

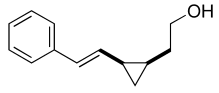


*trans*-**7**
64% yield, 20:1 dr (20:1 SM dr)
with Xantphos

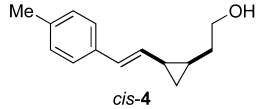


*trans*-**8**
87% yield, 5:1 dr (20:1 SM dr)
with **3**

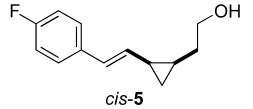
b) Starting from cis-substituted THPs



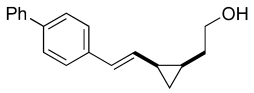
*cis*-**2**
56% yield, 20:1 dr (20:1 SM dr)
with Xantphos



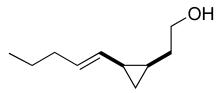
*cis*-**4**
61% yield, 19:1 dr (20:1 SM dr)
with Xantphos[a]



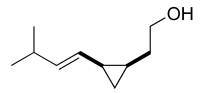
*cis*-**5**
64% yield, 9:1 dr (12:1 SM dr)
with Phen[a]



*cis*-**6**
72% yield, 11:1 dr (12:1 SM dr)
with Xantphos



*cis*-**8**
66% yield, 4:1 dr (20:1 SM dr)
with **3**



*cis*-**9**
55% yield, 3:1 dr (20:1 SM dr)
with BPhen

[a]Reactions were performed with 10 mol % loading of $Ni(cod)_2$ and ligand.

tivity were obtained (entries 11−14).[29] A substrate bearing a pseudohalide leaving group, alkyl tosylate *trans*-**1d**, provided low yield with *rac*-BINAP and Xantphos (entries 15 and 16). No product was observed with any pyridine-based ligands (entries 17 and 18). Therefore, we concluded that fluoride- and chloride-substituted tetrahydropyrans were suitable substrates for the ring contraction.

We set out to determine the absolute configuration of an enantioenriched product to determine the stereochemical course of the reaction. Based on our previous work with 2-aryl-4-chlorotetrahydropyrans,[25] we hypothesized that this reaction would proceed with retention at the allylic ether and inversion at the alkyl halide. In order to test this hypothesis, enantioenriched *trans*-**1b** was synthesized.[30] The absolute configuration of *trans*-**1b** was assigned via X-ray crystallographic analysis of a precursor.[31] The reaction of *trans*-**1b** yielded *trans*-**2** with complete retention of dr and ee. Derivatization of *trans*-**2** provided a crystalline solid for X-ray analysis[31] which affirmed the absolute configuration of *trans*-**2** (Scheme 2). As anticipated, the reaction proceeds with retention at the allylic ether and inversion at the alkyl chloride. These results are consistent with our prior work in ring contraction of aryl-substituted tetrahydropyrans.[25] Experiments to further refine the mechanism of the ring contraction are ongoing.

After establishing the optimal conditions and determining the stereochemical outcome for *trans*-**1a−d**, we turned to the more challenging synthesis of *cis*-disubstituted cyclopropanes. These substrates provide a more stringent test of the reaction's stereospecificity, since the *cis* diastereomers of cyclopropanes are disfavored from a thermodynamic perspective. With most of the *cis*-substituted tetrahydropyran substrates (*cis*-**1a−d**), the prior conditions provided low yield or low diastereoselectivity.[31] With 4-fluorotetrahydropyran *cis*-**1a**, we observed acceptable yield and high stereospecificity with Xantphos (Table 2, entry 1). Here, both *rac*-BINAP and Phen provided decreased yield and dr compared with Xantphos (entries 2 and 3). Xantphos would prove to be our most consistent and versatile ligand, performing best for the majority of our substrates (vide infra). When Xantphos provided unsatisfactory yields or dr with other substrates, we typically evaluated alternative ligands *rac*-BINAP, bipy, BPhen, Phen, and **3**. 4-Chlorotetrahydropyran *cis*-**1b** provided high stereospecificity and moderate yield with Xantphos (entry 4)[32] and high yield and moderate stereospecificity with Phen (entry 6), indicating a trade-off between yield and selectivity for this substrate. 4-Bromotetrahydropyran *cis*-**1c** afforded a moderate yield and low stereospecificity with *rac*-BINAP and Phen (entries 8 and 10). The addition of tetrabutylammonium bromide as an additive resulted in a modest increase in yield and stereospecificity (entry 9).[33] As anticipated, a low yield was observed when tosylate *cis*-**1d** was subjected to the reaction conditions (entry 11). Generally, reactions featuring low yields were either the result of byproduct formation or low reactivity of the starting material.[32]

With conditions in hand for ring contraction to generate both *cis*- and *trans*-substituted cyclopropanes, we aimed to expand the scope of the reaction. We focused our studies on alkyl fluorides due to ease of synthesis and potential use in a wide range of synthetic applications. We synthesized several substrates with both aryl and alkyl substituents on the vinyl moiety, beginning with a variety of *para*-substituted cinnamal-



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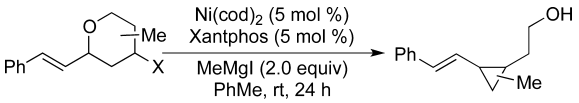
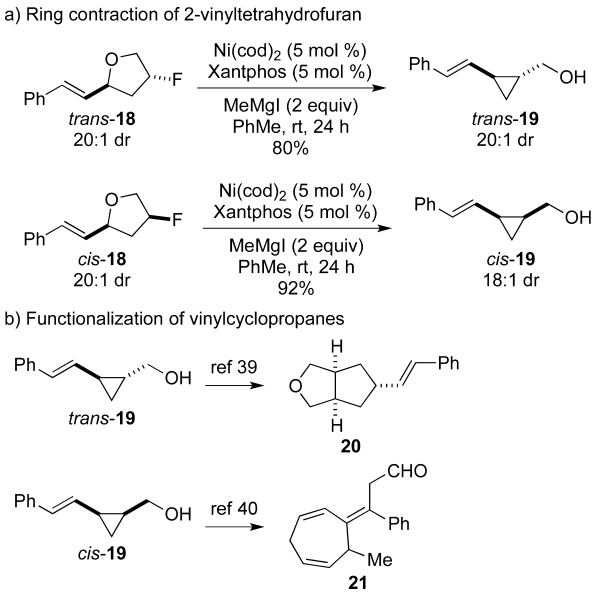
**Table 4. Ring Contractions of Trisubstituted THPs**




| Entry | Starting Material | Product | Yield (%) | SM dr | Prod. dr |
|---|---|---|---|---|---|
| 1 | *cis*-**10a** | *cis*-**11** | 68 | 20:1 | 20:1 |
| 2 | *cis*-**10b** | *cis*-**11** | 44 | 20:1 | 20:1 |
| 3 | **12a** | **13** | 72 | 10:1 | 10:1 |
| 4 | **12b** | **13** | 91[a] | 20:1 | 20:1 |
| 5 | **14** | **15** | 86[a] | 20:1 | 20:1 |
| 6 | **16** | **17** | 86 | 15:1 | 15:1 |

[a]Reactions performed at a scale of >1 g.

**Scheme 3. Hydroxymethylcyclopropanes**




dehyde derivatives (Table 3). For all substrates, NOE's were measured to assign the relative configuration of both starting materials and products. Using Xantphos as the ligand, *trans*-**4** was generated in good yield and diastereoselectivity. Interestingly, when we subjected the *cis* diastereomer to identical reaction conditions, we observed a decreased dr. We found that increasing the catalyst loading to 10 mol % resulted in formation of *cis*-**4** with significantly improved diastereoselectivity.[34] To evaluate the chemoselectivity of the reaction, we prepared a substrate featuring an aryl fluoride in addition to the alkyl fluoride. Employing bipy in the ring contraction of the trans diastereomer, the desired product *trans*-**5** was obtained in modest yield with retention of the diastereomeric ratio. No reaction occurred at the aryl fluoride, despite the presence of Grignard reagent in the reaction mixture.[6] For the *cis* diastereomer, *cis*-**5** was obtained with high stereospecificity by employing 10 mol % catalyst with Phen as the ligand of choice. A series of 4-arylcinnamaldehyde derivatives were examined; products *trans*-**6**, *cis*-**6**, and *trans*-**7** were formed in good yields and high diastereoselectivity using Xantphos as the ligand.

We aimed to expand the scope beyond substrates containing the styrenyl motif to include other vinyl tetrahydropyrans (Table 3). After evaluation of a series of ligands, 2,6-dipyrazol-1-ylpyridine (**3**) was identified as the optimal ligand for the ring contraction to afford *trans*-**8** in excellent yield and 5:1 dr. Ligand **3** was also the most effective ligand in the ring contraction to afford the *cis* diastereomer (*cis*-**8**). Branched product *cis*-**9** was generated in a modest yield. We attribute the decrease in yield for *cis*-**9** compared to *cis*-**8** to steric encumbrance that interferes with ligation of the olefin to the nickel catalyst.[26] Increasing the catalyst loading had no effect on dr or yield with any of these nonstyrenyl substrates.

In order to broaden the applications of this chemistry, we examined substrates containing additional substitution on the tetrahydropyran ring to access more highly substituted cyclopropanes (Table 4). As we observed with most disubstituted tetrahydropyrans, Xantphos proved to be the ideal ligand for these systems. Formation of secondary alcohol **11** using C-6-substituted tetrahydropyrans **10a** and **10b** (entries 1 and 2) proceeded in excellent stereospecificity, with a higher yield being obtained using alkyl fluoride **10a** (entry 1). To challenge the method with synthesis of trisubstituted cyclopropanes we examined a series of 3-methyl and 4-methyltetrahydropyrans (**12**, **14**, and **16**, entries 3–6). These reactions also evaluate the impact of additional stereogenic centers on the stereospecificity of the reaction. Consistent with our prior work in ring-opening reactions of related substrates,[25,35] reactions were highly stereospecific, allowing for controlled synthesis of either **13** or **15** by selection of the appropriate starting material. Due to the typical difficulty of synthesizing quaternary stereocenters, one of our priorities was to utilize this chemistry to synthesize a vinylcyclopropane product that featured a quaternary stereocenter. Tertiary alkyl chloride **16** provided an excellent yield and diastereomeric ratio of trisubstituted cyclopropane **17** bearing a quaternary stereogenic center (entry 6). Additionally, ring contractions of substrates **12b** and **14** were performed on a >1 g scale without diminished yield or stereospecificity, indicating that the method is amenable to large-scale reactions (entries 4 and 5). These results indicate that our methodology can tolerate substitution around the ring, enabling facile and selective synthesis of stereoisomeric trisubstituted vinylcyclopropanes.

We sought to apply the ring contraction to the synthesis of hydroxymethyl vinylcyclopropanes (e.g., **19**). This substituent pattern is present in natural products such as chrysanthemol and madolin H. Furthermore, hydroxymethyl vinylcyclopropanes and close derivatives have been employed as starting materials for a wide range of transition metal and Lewis acid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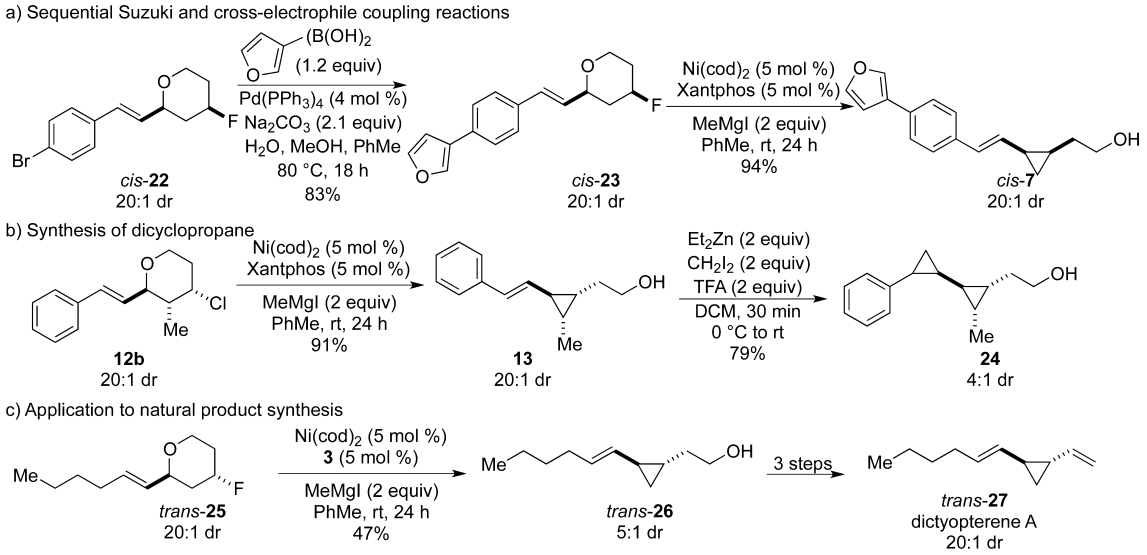
**Scheme 4. Synthetic Applications of Stereospecific Reductive Ring Contractions**




catalyzed addition reactions and rearrangements.[20] These compounds are traditionally prepared by Simmons–Smith or carbene-mediated reactions;[23,24] we envisioned that they would be straightforward to prepare from suitably substituted tetrahydrofurans. Both diastereomers of 2-vinyl-3-fluorotetrahydrofuran **18** were prepared to evaluate the stereospecificity of the reaction.[36−38] We were pleased to see that each diastereomer reacted with high stereospecificity (Scheme 3a). Under standard reaction conditions employing the ligand Xantphos, *trans*-**18** provided *trans*-**19** in excellent yield and diastereoselectivity. Similarly, *cis*-**18** gave *cis*-**19** in 92% yield and 18:1 dr. Both diastereomers of **19** have been utilized in late-metal-catalyzed rearrangement reactions. For example, *trans*-**19** has been alkylated by 3-iodopropane and subjected to a rhodium-catalyzed rearrangement to provide bicyclic ether **20** (Scheme 3b).[39] Likewise, a derivative of *cis*-**19** undergoes a gold-catalyzed rearrangement to form cycloheptadiene **21**.[40]

With the nickel-catalyzed ring contraction method developed, we aimed to demonstrate its synthetic utility. One benefit of utilizing alkyl fluorides as electrophiles is their lack of reactivity under many common reaction conditions. To demonstrate orthogonal cross-coupling reactions, we designed substrate *cis*-**22**, which displays the requisite functional groups for a traditional cross-coupling reaction as well as the ring contraction. We subjected *cis*-**22** to Suzuki–Miyaura cross-coupling reaction conditions, which yielded *cis*-**23**.[41] As anticipated, palladium-catalyzed cross-coupling proceeded smoothly at the aryl bromide, and no reaction occurred at the alkyl fluoride or allylic ether (Scheme 4a). Subsequent submission to ring contraction conditions resulted in excellent yields and diastereoselectivity of *cis*-**7**. Therefore, the cross-electrophile coupling is orthogonal to standard cross-coupling reactions. The ring contraction can also be used sequentially with other cyclopropanation reactions for synthesis of polycyclopropanes such as the natural products U-106305 and 3-myliene. For example, ring contraction of the requisite tetrahydropyran provided vinylcyclopropane **13** (Scheme 4b). A subsequent Simmons–Smith reaction under standard conditions provided dicyclopropane **24**.[42]

The new cross-electrophile coupling reaction can also be employed as a key step in the synthesis of the seaweed pheromone dictyopterene A.[43,44] Several previous synthetic approaches have utilized diazo or carbenoid reagents to furnish the cyclopropane moiety. Our route to this natural product began with a Prins cyclization of the commercially available *trans*-2-heptenal to provide tetrahydropyran *trans*-**25** (Scheme 4c). Subjection of **25** to the nickel-catalyzed ring contraction gave alcohol **26**, which upon further synthetic manipulation afforded (±)-dictyopterene A (**27**).[45,46] Spectral data were consistent with those previously reported.[46] Notably, this synthesis proceeded in five steps from commercially available material, and yielded the natural product in excellent diastereoselectivity.

## ■ SUMMARY

We report the nickel-catalyzed reductive cross-electrophile coupling of 2-vinyl-4-halotetrahydropyrans to access vinylcyclopropanes. The ring contraction is stereospecific at both the allylic ether and alkyl halide, providing controlled access to di- and trisubstituted cyclopropanes. This is the first reported reductive cross-electrophile coupling reaction to utilize fluoride as a leaving group. Orthogonal reactions, including Suzuki cross-coupling and cyclopropanation reactions are demonstrated, and the reaction is applied in the synthesis of a natural product, dictyopterene A. Further development of alkyl fluoride cross-electrophile coupling reactions and mechanistic studies to further elucidate the mechanism of the ring contraction are underway.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b07567.

Crystallographic information file for *cis*-(−)-**1D** (CIF)

Crystallographic information file for *trans*-(−)-**SI-4** (CIF)

Crystallographic information file for *cis*-(+)-**SI-3** (CIF)

Experimental details and characterization data (NMR spectra and SFC traces) (PDF)



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### Notes

The authors declare no competing financial interest.

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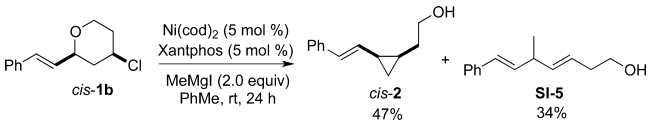
(31) See the Supporting Information for more details.
(32) For example, reaction of substrate *cis*-**1b** provided the following product distribution:




(33) Other standard additives such as $MgI_2$ and CsF provided lower yields and/or diastereoselectivity; see the Supporting Information for details.
(34) With 5 mol % catalyst, cyclopropane *cis*-**4** was obtained in 4:1 dr (53% yield); with 10 mol % catalyst, it was obtained in 19:1 dr (61%).
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## NOTE ADDED AFTER ASAP PUBLICATION

Structures in Table 1 and Table 2 were inadvertently omitted and have been restored in the version reposted on October 13, 2016.



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