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Stereospecific Intramolecular Reductive Cross-Electrophile Coupling Reactions for Cyclopropane Synthesis

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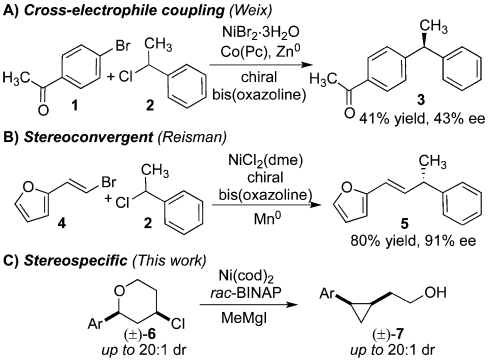
Supporting Information

ABSTRACT: The stereospecific reductive cross-electrophile coupling reaction of 2-aryl-4-chlorotetrahydropyrans to afford disubstituted cyclopropanes is reported. This ring contraction presents surprises with respect to the stereochemical outcome of reaction of the alkyl halide moiety. While cross-coupling and reductive cross-electrophile coupling reactions of alkyl halides are typically stereoablative, using a chiral catalyst to set the stereocenter, this transformation proceeds with high stereochemical fidelity at the alkyl halide and ether bearing stereogenic centers. This approach provides straightforward access to highly substituted cyclopropanes in two steps from commercially available aldehydes.

For miners and organometallic chemists "the devil's copper" can provide intrigue and vexation.[1] In addition to providing inexpensive alternatives to precious palladium catalysts, nickel complexes present a diverse range of elementary reactions, including both polar and single-electron chemistry.[2] Indeed, mechanistic ambiguity has been a challenge in rational design of new catalytic transformations. At the same time, the unique reactivity patterns offered by Ni catalysts can provide advantages in certain settings. For example, Ni catalysts are particularly well suited for reactions employing alkyl halides and pseudohalides, due to their ability to engage sluggish electrophilic partners and reduced propensity for β-hydride elimination.[3] For these reasons, Ni catalysts have been critical for development of cross-coupling reactions of alkyl electrophiles and in recent development of reductive cross-electrophile coupling reactions.[4]

In a reductive cross-electrophile coupling reaction, two electrophilic partners, typically alkyl or aryl halides, are coupled in the presence of exogenous reducing agent. This strategy circumvents synthesis of an organometallic reagent, as would be required for a traditional cross-coupling reaction.[4] Weix et al. pioneered the Ni-catalyzed reductive cross-coupling of aryl and alkyl halides with a variety of electrophilic partners (Scheme 1A).[5] Recently, they reported cross-electrophile coupling of benzylic alcohols and benzylic chlorides with aryl halides.[6] Reisman et al. reported stereoconvergent reductive cross-coupling reactions of racemic benzylic chlorides with acid chlorides or vinyl bromides to provide products with good yield and high ee (Scheme 1B).[7] Stereoconvergent methods capitalize on the stereoablative nature of oxidative addition of Ni complexes with alkyl halides and employ a chiral ligand to set the desired stereocenter.[8]

Scheme 1. Asymmetric Reductive Cross-Electrophile Coupling Strategies



Recent work in our laboratory demonstrated Ni-catalyzed stereospecific cross-coupling reactions of alkyl ethers and esters under Kumada, Negishi, and Suzuki-type conditions.[9] We hypothesized that these electrophiles would also participate in stereospecific cross-electrophile coupling reactions, since oxidative addition of the low-valent Ni catalyst with the benzylic ether should be a common elementary step in both mechanisms.

Here we report the stereospecific ring contractions of 2-aryl-4-chlorotetrahydropyrans to afford substituted cyclopropanes (Scheme 1C), via an intramolecular reductive cross-coupling reaction[10] of a benzylic ether and an alkyl halide. Notably, it is strictly stereospecific with respect to *both* electrophilic functional groups. As anticipated at the outset, oxidative addition at the benzylic ether proceeds with high stereochemical fidelity.[9a] One surprising feature of this transformation is that the alkyl halide bearing stereogenic center reacts with high stereospecificity (vide infra). This result is unusual, as prior Ni-catalyzed reactions of alkyl halides were stereoablative.[8]

In addition to affording a stereospecific cross-electrophile coupling, this reaction provides straightforward and scalable access to substituted cyclopropanes, important organic motifs found in many natural products and medicinal agents.[11] The strained nature and reactivity of cyclopropanes make them valuable synthetic intermediates and mechanistic probes, and as such the development of their asymmetric synthesis has been an area of intensive research.[12] By effecting a skeletal rearrangement of the tetrahydropyran starting material, this reductive cross-coupling reaction provides cyclopropanes bearing a synthetic

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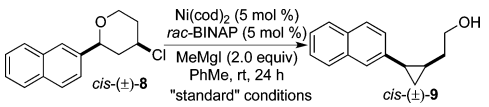
handle appropriate for further functionalization as part of target- or diversity-oriented synthetic strategies.

To test our hypothesis for a stereospecific ring contraction, we designed test substrate tetrahydropyran *cis*-**8**. As a starting point, we examined this substrate under the same catalyst conditions we employed in our previous Kumada-type cross-coupling reactions of aryl-substituted tetrahydropyrans.[9a] Using a combination of $Ni(cod)_2$ and *rac*-BINAP, in the presence of MeMgI, we found that *cis*-**8** afforded *cis*-**9** in excellent yield and as a single diastereomer (Table 1, entry 1). The relative configuration of **9** was assigned as cis by X-ray crystallographic analysis of a derivative and NOE NMR experiments.[13]

Table 1. Optimization of Reaction Conditions



Entry	variation from standard conditions	recovered **8** (%)[a]	yield **9** (%)[a]
1	none	0	98
2	No $Ni(cod)_2$ and *rac*-BINAP	98	0
3	2.5 % $Ni(cod)_2$ and *rac*-BINAP	0	97
4	DPEphos instead of *rac*-BINAP	10	52
5	$Ni(acac)_2$ instead of $Ni(cod)_2$	22	70
6	$Ni(acac)_2$ with 12% 1,5-cyclooctadiene	8	92
7	$Ni(acac)_2$ with 12% 1,5-cyclooctadiene outside glove box[b]	29	71
8	No MeMgI	98	0
9	1.0 equiv MeMgI instead of 2.0 equiv	46	54
10	Commercial MeMgBr	20	80
11	PhMgBr instead of MeMgI	0	97
12	$ZnMe_2$ instead of MeMgI	94	0

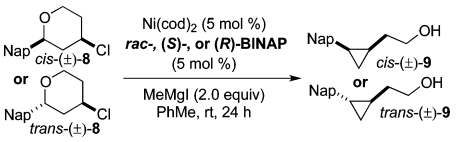
[a]Yield determined by ^{1}H NMR based on comparison to PhTMS as internal standard. [b]All reagents were weighed on the benchtop, and the reaction was purged with N_2 before addition of MeMgI.

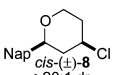
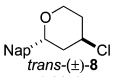
To determine what components of the reaction were necessary, we examined both the Ni catalyst and the Grignard reagent. We first removed $Ni(cod)_2$ and *rac*-BINAP from the reaction and saw no conversion of the starting material, indicating the reaction is indeed Ni-catalyzed (entry 2). We found that catalyst loadings as low as 2.5 mol% resulted in full conversion to product in 24 h at rt (entry 3). Other bidentate phosphine ligands, such as DPEphos, were not as effective in the reaction (entry 4). We also examined alternative Ni precatalysts. We found that $Ni(acac)_2$, a more stable Ni precatalyst, provided lower conversion than $Ni(cod)_2$ (entry 5). However, with the addition of 12 mol% of 1,5-cyclooctadiene conversion to product is restored (entry 6). This catalyst system is also amenable to set up on the benchtop, avoiding use of a glovebox (entry 7).

Based on our previous development of Ni-catalyzed alkyl-Heck reactions, we hypothesized that the Grignard reagent acts as a reducing agent to effect catalyst turnover.[14] Removing the Grignard reagent resulted in full recovery of starting material; using only 1 equiv resulted in 54% yield (entries 8 and 9, respectively).[15] Use of commercial MeMgBr affords 80% yield of **9** (entry 10). We found that the identity of the Grignard reagent was not crucial. Switching to PhMgBr from MeMgI had no detrimental effect (entry 11). Using PhMgBr, we also isolated 1 equiv of biphenyl side product, supporting our hypothesis that the Grignard reagent acts to reduce the Ni catalyst. Unfortunately, after examining milder reducing agents, e.g., dimethylzinc or manganese powder, we found that a Grignard reagent is required in order for the reaction to proceed (entry 12). While this is not an ideal reducing agent, it is readily available and straightforward to handle.[16]

With optimized reaction conditions in hand, we next examined the stereospecificity of the reaction. Because Ni-catalyzed reactions using alkyl halides are typically stereoconvergent and are thought to proceed through alkyl radical intermediates, we were interested in determining whether *cis*- and *trans*-**8** would afford the same diastereomer of product and whether use of a chiral ligand would influence the diastereomeric ratio. We subjected both *cis*- and *trans*-**8** to reactions employing *rac*-BINAP and were surprised to see that the reaction was not stereoconvergent, but was highly stereospecific with respect to the alkyl halide (Table 2). Chloride *cis*-**8** afforded *cis*-**9** in high yield and

Table 2. Substrate Control of Stereochemistry

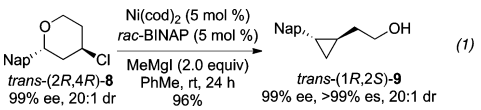


Entry	Starting Material (cis:trans)	Ligand	Yield of **9** (%)[a]	Prod. dr (cis:trans)[b]
1	 *cis*-(±)-**8** >20:1 dr	*rac*-BINAP	94	>20:1
2		(*R*)-BINAP	96	>20:1
3		(*S*)-BINAP	95	>20:1
4	 *trans*-(±)-**8** 1:20 dr	*rac*-BINAP	94	1:20
5		(*R*)-BINAP	97	1:20
6		(*S*)-BINAP	96	1:20

[a]Isolated yield after column chromatography. [b]Determined by ^{1}H NMR. Nap = 2-naphthyl.

excellent dr (entry 1). Similarly, *trans*-**8** yielded *trans*-**9** with high yield and dr (entry 4). Introduction of enantioenriched catalyst does not perturb the high level of stereospecificity: in all cases, the reaction occurred cleanly with inversion at the benzylic ether and retention at the alkyl halide bearing a stereogenic center (entries 2, 3, 5, and 6). These results are not consistent with initiating the reaction by oxidative addition of the alkyl halide moiety.[17] This stereochemical outcome in the reaction of an alkyl halide with a low-valent Ni complex is unusual and has significant implications for the mechanism of this transformation, which is currently under investigation.

To determine whether the reaction proceeds with net inversion or retention at the reactive centers, we prepared enantioenriched *trans*-**8**.[18] As anticipated, ring contraction proceeded with high enantiospecificity (es; eq 1).[19] Product **9** was derivatized, and absolute configuration was assigned by X-ray crystallographic analysis.[13] Surprisingly, we found that reaction at the benzylic ether occurred with net retention.[20] The alkyl chloride moiety reacted with inversion. While this stereochemical outcome is unexpected, it appears to be consistent in this ring contraction (vide infra).



We envisioned that this reaction would provide a robust and scalable strategy to synthesize single diastereomers of cyclopropanes from commercially available aldehydes. To demonstrate that this strategy is amenable to larger scale, we performed the two-step sequence on a 5.3 mmol scale (Scheme 2). Prins cyclization of **10** with 3-buten-1-ol employing $ZnCl_2$ and *p*-TSA proceeded smoothly to afford *cis*-**8** in 80% yield and 20:1 dr.[21]

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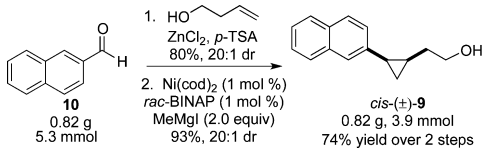
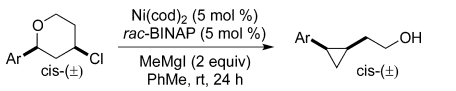
Scheme 2. Amenability to Scale Up

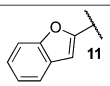
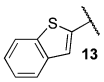
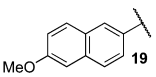
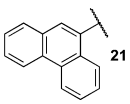


With 1 g of *cis*-**8** in hand, we determined that ring contraction with only 1 mol% catalyst provides *cis*-**9** in 93% yield and 20:1 dr. This strategy provides a straightforward method for conversion of the requisite aldehyde to the cyclopropane in two steps and with reliable control of relative stereochemistry.

Having established the robustness of this reaction, we turned our attention to determining the scope. We examined a range of aryl-substituted tetrahydropyrans (Table 3). Reactions of

Table 3. Scope of Ring Contraction Reaction



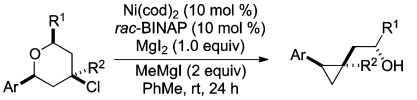
Entry	Ar	Product	Yield (%)[a]	S.M. dr (cis:trans)[b]	Prod. dr (cis:trans)[b]
1		**12**	68	20:1	20:1
2	*trans*-(±)-**11**	*trans*-(±)-**12**	55	1:8	1:8
3		**14**	80	16:1	10:1
4		**16**	91	20:1	20:1
5		**18**	96	20:1	15:1
6		**20**	97	20:1	20:1
7[c]	**19**	**20**	94	20:1	20:1
8	*trans*-(±)-**19**	*trans*-(±)-**20**	97	1:20	1:20
9		**22**	98	20:1	20:1

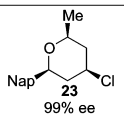
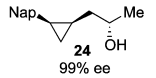
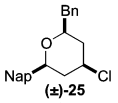
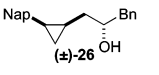
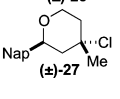
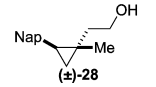
[a]Isolated yield after column chromatography. [b]Determined by ^{1}H NMR. [c]Reaction performed on a 1.0 mmol scale.

benzofuran- and benzothiophene-substituted tetrahydropyrans proceed in good yields and dr (entries 1–3). In an effort to challenge the transformation, we examined simple furan-containing substrates **15** and **17**. Both 2- and 3-substituted furans yielded desired product in excellent yield and with transfer of stereochemical information (entries 4 and 5). We found that 6-methoxy-2-naphthalene substituted THP *cis*-**19** proceeded in 97% yield and 20:1 dr and was amenable to a larger 1.0 mmol scale reaction (entries 6 and 7). Reaction of *trans*-**19** likewise proceeded with clean transfer of stereochemical information to afford *trans*-**20** in 97% yield (entry 8).

To synthesize cyclopropanes with a more complex range of substituent patterns, we examined a series of trisubstituted tetrahydropyrans (Table 4). Subjecting enantioenriched 2,4,6-trisubstituted tetrahydropyran **23** to the standard reaction conditions resulted in only partial conversion. However, adding

Table 4. Scope of Trisubtituted Tetrahydropyrans



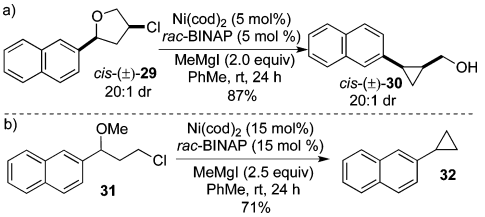
Entry	Starting Material	Product	Yield (%)[a]	S.M. dr[b]	Prod. dr[b]
1	 **23** 99% ee	 **24** 99% ee	88	13:1	20:1
2	 (±)-**25**	 (±)-**26**	85	20:1	20:1
3[c]	 (±)-**27**	 (±)-**28**	62	9:1	8:1

[a]Isolated yield after column chromatography. [b]Reported as (cis:trans) determined by ^{1}H NMR. [c]Reaction performed without addition of MgI_2 and with 5 mol% catalyst loading. Nap = 2-naphthyl.

1 equiv of MgI_2 afforded cyclopropane **24** in 88% yield and >99% es (entry 1). In related Kumada-type cross-coupling reactions, we observed that MgI_2 accelerates reactions of sluggish substrates.[22] We hypothesize that the Lewis acidic salts coordinate the benzylic ether, facilitating oxidative addition of the C–O bond. Derivatization and X-ray crystallographic analysis demonstrated that the reaction occurred with retention at the benzylic ether and inversion at the alkyl chloride.[13] This stereochemical outcome is consistent with our earlier observations (eq 1). Adding MgI_2 also resulted in good conversion of **25**, with a larger substituent at the C6 position, to **26** (entry 2). To challenge the reaction, we examined if substitution at the reactive centers would be tolerated. The use of tertiary chloride **27** afforded **28**, containing a quaternary center, in 62% yield and good transfer of stereochemical information (entry 3).

In beginning to examine the broader scope, we set out to determine if the tetrahydropyran scaffold was integral to reactivity. We first examined a smaller cyclic ether, tetrahydrofuran **29**. Subjecting tetrahydrofuran *cis*-**29** to the reaction afforded *cis*-**30** in 87% and 20:1 dr (Scheme 3a), indicating that

Scheme 3. Application to Alternative Substrate Classes



decreasing the carbon tether is not detrimental to the reaction. We were also interested if an unstrained, acyclic scaffold would provide substrates that are competent in the reaction. We subjected primary chloride **31** to standard reaction conditions (Scheme 3b). Cyclopropane **32** was obtained in 71%, indicating that acyclic primary chlorides are indeed tolerated.

As our reaction is amenable to cyclopropanes bearing simple heteroaromatic rings, we sought to exploit these functional groups to obtain alkyl-substituted cyclopropanes. Kobayashi et al. demonstrated that 2-substituted furans can be oxidized to form 2-enonic acids.[23] This functionality translates nicely as a

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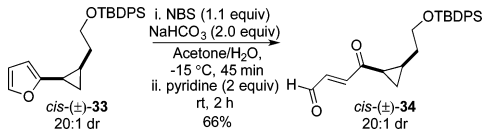
building block to prepare biologically active scaffolds, such as halicholactone, a lipoxygenase inhibitor, and its family members.[24] We envisioned that our method could be used to synthesize analogs of this class of natural products. 2-Furan-substituted cyclopropane *cis*-**33** was oxidized using the reported conditions (Scheme 4). 2-Enonic acid **34** was obtained in 66% yield with no loss of stereochemistry.

Scheme 4. Oxidation of Furan 33



In summary, stereospecific synthesis of di- and trisubstituted cyclopropanes is achieved via a Ni-catalyzed reductive cross-electrophile coupling of 2-aryl-4-chlorotetrahydropyrans. The ring contraction is stereospecific with respect to both the benzylic ether and the alkyl halide moieties. Efforts to expand the scope and elucidate the mechanism of the transformation are underway.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details and characterization data. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b03870. For crystallographic data see also CCDC 1059382, 1413565, and 1414041.

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Notes

The authors declare no competing financial interest.

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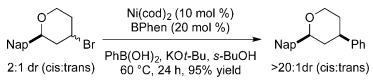

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