

Enantiospecific Intramolecular Heck Reactions of Secondary Benzylic Ethers

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S Supporting Information

ABSTRACT: Enantioenriched methylenecyclopentanes are synthesized by stereospecific, nickel-catalyzed Heck cyclizations of secondary benzylic ethers. The reaction proceeds in high yield and enantiospecificity for benzylic ethers of both π -extended and simple arenes. Ethers with pendant 1,2-disubstituted olefins form trisubstituted olefins with control of both absolute configuration and alkene geometry. Diastereoselective synthesis of a polycyclic furan is demonstrated.

The Mizoroki–Heck reaction is part of the foundation of modern organometallic chemistry and is a key disconnection in the synthetic chemist's repertoire.¹ Creative advances continue to expand our synthetic capabilities and refine our understanding of transition-metal-catalyzed reactions.² Traditional Heck reactions employ an aryl or vinyl halide or pseudohalide. Development of “alkyl–Heck reactions,” where the electrophilic partner is an alkyl halide or pseudohalide, is undergoing revitalization,^{3–7} in part due to synergy with recent advances in alkyl cross-coupling reactions.⁸ Exciting results employing primary alkyl halides have been reported, where catalyst control suppresses undesired side reactions and provides regioselectivity and asymmetric induction in the migratory insertion step.^{6,3d,e} Heck-like reactions of secondary alkyl iodides that proceed through radical intermediates have also been reported and provide substituted tetrahydrofurans and cyclopentanones with high diastereoselectivity.⁷ Important challenges remain. For example, in reactions of secondary alkyl electrophiles, control of the absolute configuration at the site of oxidative addition has not been reported.

We hypothesized that secondary ethers functionalized with a pendant alkene should undergo nickel-catalyzed Heck cyclization and that the reactions would be highly stereospecific (Scheme 1). This work builds on our development of related stereospecific nickel-catalyzed cross-coupling reactions of benzylic ethers.^{9–11} We propose that oxidative addition occurs with inversion, providing a single enantiomer of the key secondary alkylnickel intermediate that can continue through the cross-coupling or Heck catalytic cycle.

We designed substrates to test for stereospecific Heck cyclization, informed by our prior development of stereospecific cross-coupling reactions of esters and ethers. Employing benzylic pivalate **1** with Cs_2CO_3 as the base, however, failed to furnish any of the desired methylenecyclopentane **2** (Table 1, entry 1).¹² Next, dimethylzinc was examined as a terminal

Scheme 1. Stereospecific Nickel-Catalyzed Reactions of Benzylic Ethers and Esters

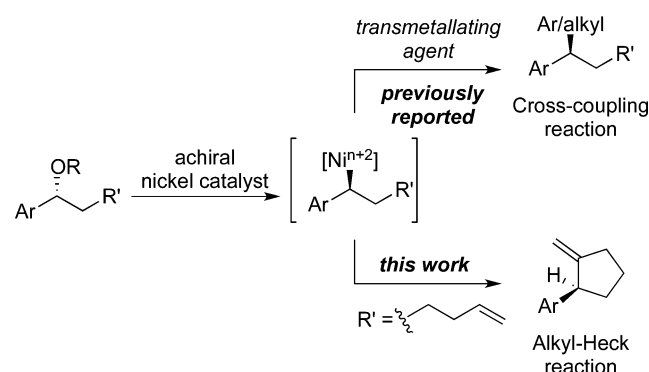
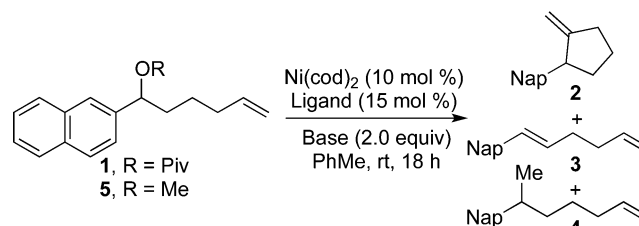


Table 1. Optimization of Reaction Conditions



entry	R	ligand	base	yield 2 (%) ^a	yield 3 (%) ^a	yield 4 (%) ^a
1	Piv	PCy_3	Cs_2CO_3	<2	37	<2
2	Piv	PCy_3	ZnMe_2	7	39	<2
3	Me	PCy_3	MeMgI	64	17	<2
4	Me	PPh_3	MeMgI	18	76	<2
5	Me	DPEphos	MeMgI	4	23	47
6	Me	dppf	MeMgI	<2	27	66
7	Me	$\text{NiCl}_2(\text{PCy}_3)_2$ ^b	MeMgI	82	11	<2

^aYield determined by ^1H NMR based on comparison with PhSiMe_3 as internal standard. ^b $\text{NiCl}_2(\text{PCy}_3)_2$ was used in place of $\text{Ni}(\text{cod})_2$ and added ligand.

reductant for the reaction, and a small amount of the desired methylenecyclopentane **2** was observed (entry 2). Encouraged by this result, we replaced dimethylzinc with methylmagnesium iodide, a stronger terminal reducing agent. To avoid unwanted side reactions of the leaving group with a Grignard reagent, we replaced pivalate **1** with methyl ether **5**. Under these

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Table 2. Scope of Intramolecular Heck Cyclization

Entry	Substrate (ee (%)) ^a	Product	yield product (%) ^b	ee (%) ^a	es (%) ^c
1	 5 (99)	 2	74	99	>99
2 ^d	5 (89)	2	73	89	>99
3	 6 (97)	 7	81	97	>99
4	 8 (97)	 9	73	97	>99
5 ^e	 10 (93)	 11	76	93	>99
6	 12 (88)	 13	95	88	>99
7	 14 (85)	 15	74	84	99 ^f
8 ^{g,h}	 16 (93)	 17	36 (64) ⁱ	93	>99
9 ^{g,h}	 18 (94)	 19	35 (60) ⁱ	94	>99
10 ^{g,h}	20 R = H (92)	19 R = H	67 (81) ⁱ	92	>99
11 ^{g,h}	21 R = <i>p</i> -F (90)	22 R = <i>p</i> -F	57 (77) ^j	90	>99 ^f
12 ^{g,h}	23 R = <i>p</i> -TMS (92)	24 R = <i>p</i> -TMS	85	92	>99 ^f

^aDetermined by chiral SFC. ^bIsolated yield after column chromatography. ^cEnantiospecificity (es) = (ee_{product}/ee_{substrate}) × 100. ^dReaction run on 1.0 mmol scale. ^eEnantiomeric excesses determined by chiral GC. ^fEnantiospecificity was determined based on the ee of the corresponding alcohol, rather than the ether. ^gReaction performed at 60 °C. ^hReaction performed with added MgI₂ (1 equiv). ⁱYield determined by ¹H NMR based on comparison with PhSiMe₃ as internal standard.

conditions, consumption of starting material increased significantly (entries 3–6).¹³ When bidentate phosphine ligands were added to the reaction, the undesired product 4, resulting from simple Kumada coupling, was the major product (entries 5 and 6). Remarkably, Kumada product 4 was not observed when catalysts ligated by monodentate phosphines were used in the reaction (entries 3 and 4). The desired Heck cyclization to afford methylenecyclopentane 2 proceeded in good yield with PCy₃ as the ligand (entry 3). Our optimized reaction conditions took advantage of the air-stable NiCl₂(PCy₃)₂ catalyst and afforded the desired product in high yield (entry 7).

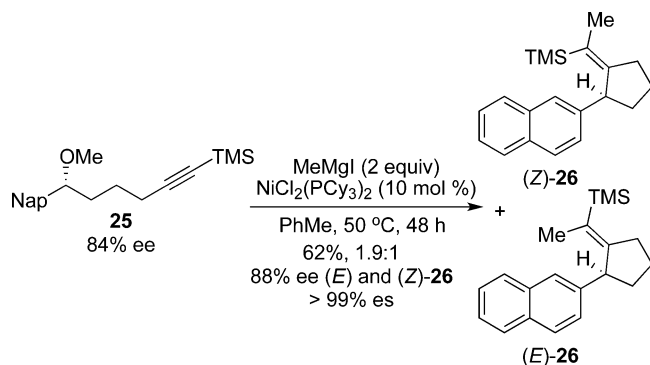
Having established conditions for the cyclization of secondary ether 5, we synthesized enantioenriched (*R*)-5 with the goal of determining the stereospecificity of the reaction. Ether (*R*)-5 was prepared in high enantiomeric excess by CBS reduction of the corresponding ketone.¹⁴ Cyclization of (*R*)-5 resulted in good yield and excellent enantiospecificity to afford the methylenecyclopentane 2 with inversion at the benzylic stereocenter (Table 2, entry 1).¹⁵ The reaction is scalable with no observable deterioration in yield or enantiospecificity when performed on a 1.0 mmol scale of ether 5 (Table 2, entry 2).

We next examined the cyclizations of a range of enantioenriched benzylic ethers. Benzylic methyl ethers of π -extended arenes proceed in excellent yield to afford highly enantioenriched methylenecyclopentanes (entries 1 and 3). Simple heteroarenes such as thiophene 8 and furan 10 also perform well under the reaction conditions (entries 4 and 5). Taking advantage of the Thorpe–Ingold effect by substitution of the alkyl chain with geminal dimethyl substituents improves the yield of the cyclization in general (entry 6).¹⁶ Simple benzylic substrates such as 16 presented a challenge, where high enantiospecificity but modest conversion was typically observed (entry 8). In this case, geminal disubstitution failed to improve yield (entry 9), but modification of the ether provided a solution (entries 10–12). Our laboratory has previously developed the methoxyethyl ether as a traceless directing group that accelerates sluggish cross-coupling reactions.^{9b} This strategy proved fruitful in the context of Heck reactions as well; methoxyethyl ethers 20, 21, and 23 afforded the desired methylenecyclopentanes at 60 °C (entries 6–8). Yields of 17, 19, 22, and 24 could typically be further improved by approximately 10% with the addition of MgI₂ (1 equiv).^{17,18}

To further test the limits of the transformation, an alkyne insertion/Kumada domino reaction was examined.¹⁹ Benzylic ether 25 bearing a tethered TMS-protected alkyne was subjected to the reaction conditions to afford tetrasubstituted olefin 26 in good yield and excellent enantiospecificity (Scheme 2). A 1.9:1 mixture of stereoisomers was obtained which could be separated by flash column chromatography with silver nitrate impregnated silica gel.²⁰ We hypothesize that the migratory insertion step proceeds with syn selectivity.²¹ Therefore, the stereoisomeric mixture of products present in the cyclization of alkyne 25 is predicted to be the result of isomerization of the vinylnickel intermediate prior to reductive elimination.²²

Trisubstituted olefins are valuable synthetic targets found in natural products, intermediates in biosynthetic pathways of steroids, and important building blocks for further functionalization by asymmetric catalysis.^{23,24} Heck cyclization of 1,2-disubstituted olefins affords a strategy for the synthesis of trisubstituted olefins as single stereoisomers, based on the stereochemical requirements of migratory insertion and β -

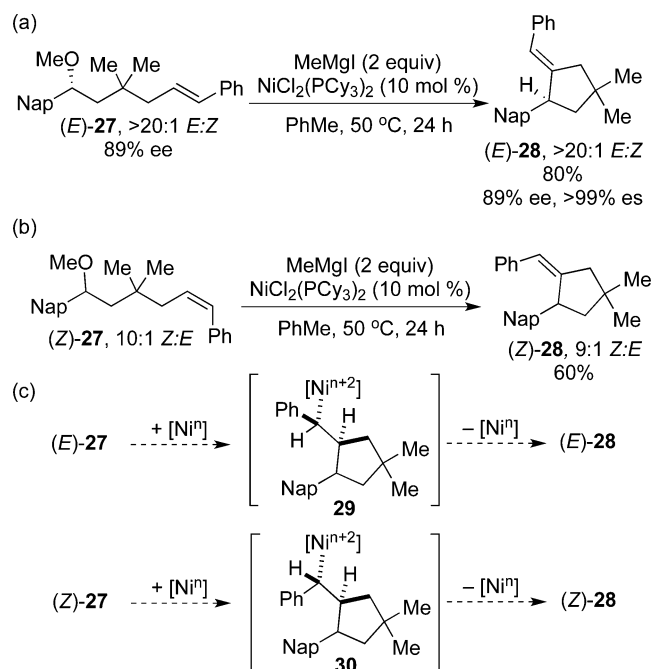
Scheme 2. Alkyne Insertion–Kumada Reaction



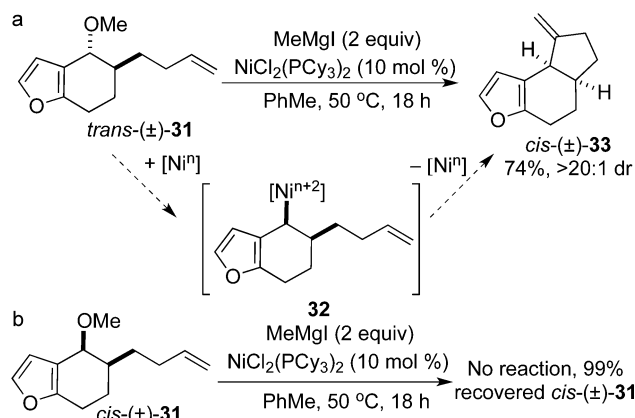
hydride elimination.^{21,25} Indeed, when **(E)-27** is subjected to the reaction conditions, the trisubstituted olefin **(E)-28** is formed in high yield and with high enantiospecificity at the benzylic stereocenter. The product is formed as a single olefin isomer in >20:1 dr (Scheme 3a). Next, **(Z)-27** was cyclized in good yield to form **(Z)-28** (Scheme 3b). Therefore, either isomer of the product can be accessed simply by selecting the appropriate isomer of starting material.

The classic Heck reaction has had a transformative impact on natural product synthesis because it can provide rapid assembly of complex polycyclic architectures.^{1d} To challenge our alkyl-Heck reaction, we synthesized **trans-31** from the corresponding dihydrobenzofuranone by α -alkylation and reduction.²⁶ Cyclization of **trans-31** provided **cis-33** as the major product in >20:1 diastereoselectivity (Scheme 4a). The ring fusion was assigned as *cis* based on NOE correlations and a comparison of the *J*-coupling constants to calculated values for **33** and to literature values for related tricyclic terpenoids.²⁶ Tricyclic **cis-33** maps onto the core of furan terpenoid natural products such as pseudoferic acid **C**, and lactones such as nepalensolides **A–C** and brothenolide.^{27–29}

Scheme 3. Stereoselective Synthesis of Trisubstituted Olefins

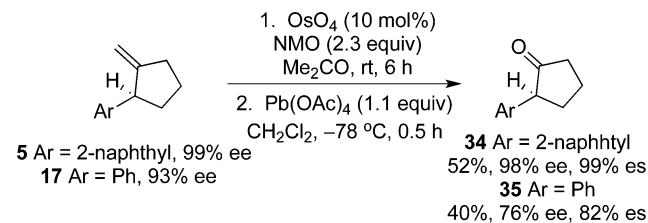


Scheme 4. Diastereoselective Tricyclic Ring Formation with Inversion at the Benzylic Position



This substrate class also provides mechanistic insight into the stereochemical and mechanistic aspects of the Heck cyclization. Cyclization of **trans-31** to afford **cis-33** is consistent with inversion at the benzylic stereogenic center. We attribute this outcome to inversion during the oxidative addition event to generate a *cis* substituted benzylnickel intermediate (**32**). Subsequent steps in the catalytic cycle, migratory insertion and β -hydride elimination, should not affect the benzylic stereogenic center. When the diastereomer, **cis-31**, was subjected to cyclization conditions, starting material was recovered in quantitative yield (Scheme 4b). It is worthwhile to note that **cis-31** does not appear to undergo side reactions such as elimination or Kumada coupling.³⁰ This observation is consistent with coordination of the olefin to the catalyst prior to oxidative addition.

Methylenecyclopentanes are valuable synthetic intermediates; the exocyclic olefin provides a synthetic handle for further elaboration to more complex products. For example, methylenecyclopentanes **5** and **17** are readily converted to the corresponding enantioenriched α -aryl cyclopentanones by a two-step procedure. Dihydroxylation of the olefin with OsO_4 followed by mild oxidative cleavage of the resultant diol with $\text{Pb}(\text{OAc})_4$ affords α -aryl cyclopentanones **34** and **35** in good to excellent levels of enantiopurity (Scheme 5).

Scheme 5. Synthesis of Enantioenriched α -Aryl Cyclopentanones

In summary, selective formation of methylenecyclopentanes containing tertiary stereocenters has been achieved by stereospecific, nickel-catalyzed intramolecular Heck cyclization of secondary ethers. The reaction proceeds in high yield and enantiospecificity and has been applied to the formation of synthetically challenging trisubstituted olefins. An alkyne insertion–Kumada domino reaction to prepare tetrasubstituted olefins is also demonstrated. Efforts to expand the scope of the transformation and elucidate mechanistic details are underway.

■ ASSOCIATED CONTENT

■ Supporting Information

Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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