Selecting Double Bond Positions with a Single Cation-Responsive Iridium Olefin Isomerization Catalyst

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ABSTRACT: The catalytic transposition of double bonds holds promise as an ideal route to alkenes of value as fragrances, commodity chemicals, and pharmaceuticals; yet, selective access to specific isomers is a challenge, normally requiring independent development of different catalysts for different products. In this work, a single cation-responsive iridium catalyst selectively produces either of two different internal alkene isomers. In the absence of salts, a single positional isomerization of 1-butene derivatives furnishes 2-alkenes with exceptional regioselectivity and stereoselectivity. The same catalyst, in the presence of Na^+, mediates two positional isomerizations to produce 3-alkenes. The synthesis of new iridium pincer-crown ether catalysts based on an aza-18-crown-6 ether proved instrumental in achieving cation-controlled selectivity. Experimental and computational studies guided the development of a mechanistic model that explains the observed selectivity for various functionalized 1-butenes, providing insight into strategies for catalyst development based on non-covalent modifications.

1. INTRODUCTION

Olefins are essential intermediates and products in the fragrance, commodity chemicals, and pharmaceutical industries.[1] Positional isomerization of double bonds offers a highly attractive route to internal olefins, given the wide availability of terminal olefins and the perfect atom economy of double bond transposition.[2–8] However, preparing specific isomers with high stereo- and regioselectivity remains a major challenge in catalyst design.

When the desired olefin is by far the most stable isomer, classical methods that use strong acid or high temperature work well.[9,10] Isomerization of allylbenzene derivatives is a prime example, with only two possible products and (*E*)-β-methylstyrene strongly thermodynamically favored.[4] When there are many energetically similar possible products of double bond positional isomerization, conversely, a poorly selective distribution of alkenes is typically obtained. Transition metal catalysts with custom-tailored supporting ligands can facilitate selective isomerization, exemplified by systems capable of a single double bond transposition to (*E*)-2-alkenes[11–16] or (*Z*)-2-alkenes.[17–19]

The current paradigm for controlling selectivity is that for each different product, a new metal/ligand combination is needed (Figure 1A). An alternative approach uses a single metal/ligand combination in conjunction with external additives to control the selectivity (Figure 1B).[20–25] Non-covalent modification has been particularly impactful in the field of alkene hydroformylation, with additives (including alkali metal cations)[26–31] interacting with the catalyst to tune the aldehyde product regioselectivity between terminal or secondary positions.[32] Finding a single catalyst that can access two states capable of a dramatic switch in regioselectivity remains a challenge in hydroformylation.[32,33] The challenge seems even more daunting for olefin isomerization, where two states must discriminate between sterically similar internal olefins. We are not aware of any examples of olefin isomerization catalysts with additive-responsive selectivity.

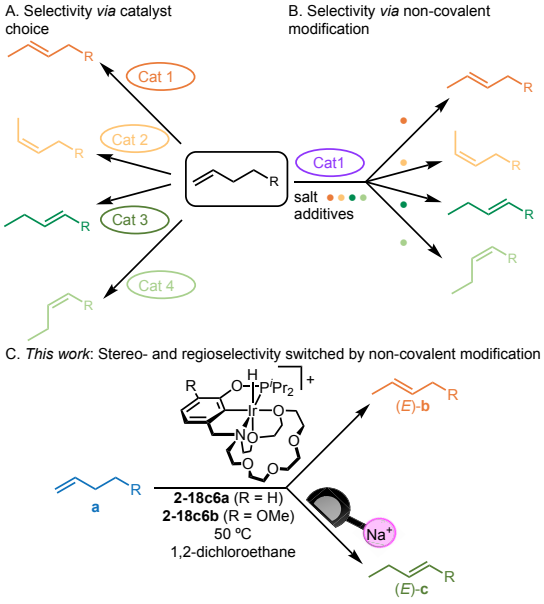


Figure 1. Product selectivity can be tuned via the traditional approach involving preparation of several new synthetically modified catalysts (A) or via an emerging approach based on non-covalent modifications of a single catalyst system (B).

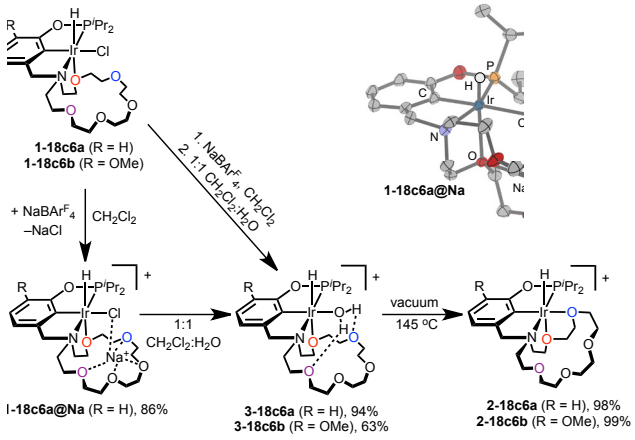
Herein, we introduce new pincer-crown ether iridium hydride catalysts featuring hemilabile aza-18-crown-6 ether receptors that enable olefin isomerization with cation-programmable regioselectivity. In its native state, the pincer-crown ether catalyst isomerizes a range of 1-butenes to the 2-butene regioisomer with high *E* stereoselectivity (Figure 1C). In the presence of Na^+ salts, however, the same catalyst produces 3-butenes, exhibiting high degrees of regioselectivity control between two internal double bond positions. Experimental and computational studies provide insight into catalyst design principles and thermodynamic landscapes required to access high selectivity in 1-butene isomerizations.

2. RESULTS

Synthesis of Catalysts Based on Aza-18-crown-6 Ether. Previous studies focused on aza-15-crown-5-ether-based pincer complexes, which performed a single positional isomerization of allylbenzene with rate acceleration by Li^+ salts (but without any change in selectivity).[34,35] We hypothesized that iridium complexes containing an aza-18-crown-6 ether would show higher activity, based on binding affinity studies showing very strong and selective binding of Na^+,[36,37] enabling the transposition of double bonds over multiple positions.

The synthetic route to cationic hydride complexes amenable to olefin binding is summarized in Figure 2. Complexes with methoxy groups in the arene backbone of the pincer ligand (labelled "**b**") were compared with unsubstituted variants (labelled "**a**"), based on recent studies showing that methoxy substitution prevents side reactions during catalysis.[38,39] A biphasic synthesis proved essential for removal of chloride, with treatment of the previously reported aza-18-crown-6-ether-based chloride complexes **1-18c6a/b**[40] with $NaBAr^F_4$ (Ar^F = 3,5-bis(trifluoromethyl)phenyl) in 1:1 CH_2Cl_2:H_2O producing cationic aqua hydride complexes **3-18c6a/b** (Figure 2). Heating solid samples of **3-18c6a/b** at 145 °C under vacuum overnight yielded the desired complexes **2-18c6a/b** (Figure 2). The complexes were characterized by multinuclear NMR spectroscopy, high-resolution mass spectrometry, and single crystal X-ray crystallography. The purity of the methoxy-containing complexes was established by NMR spectroscopy and elemental analysis; the purity of the unsubstituted variants, which were not used in the following catalysis studies, was assessed by NMR spectroscopy.

Initial attempts at chloride abstraction from **1-18c6a** using $NaBAr^F_4$ (Figure 2) gave a single product, but an X-ray diffraction study of the resultant crystals revealed a Na^+ adduct, [κ⁴-(¹⁸c⁶NCOP^{iPr})Ir(H)(Cl)@Na][BAr^F_4] (**1-18c6a@Na**, Figure 2), with Na^+ unexpectedly intercalated by the crown ether and the (unabstracted) Cl^- bridging to the Ir center. Similar species were proposed as intermediates in on/off rate-switchable isomerization by the 15-crown-5-based catalyst,[34] although these were not structurally characterized.



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and molecular structure of **1-18c6a@Na** from X-ray diffraction study (BAr^F_4 anion and cocrystallized solvent omitted for clarity, ellipsoids at 50% probability); the hydride was located in the difference map.

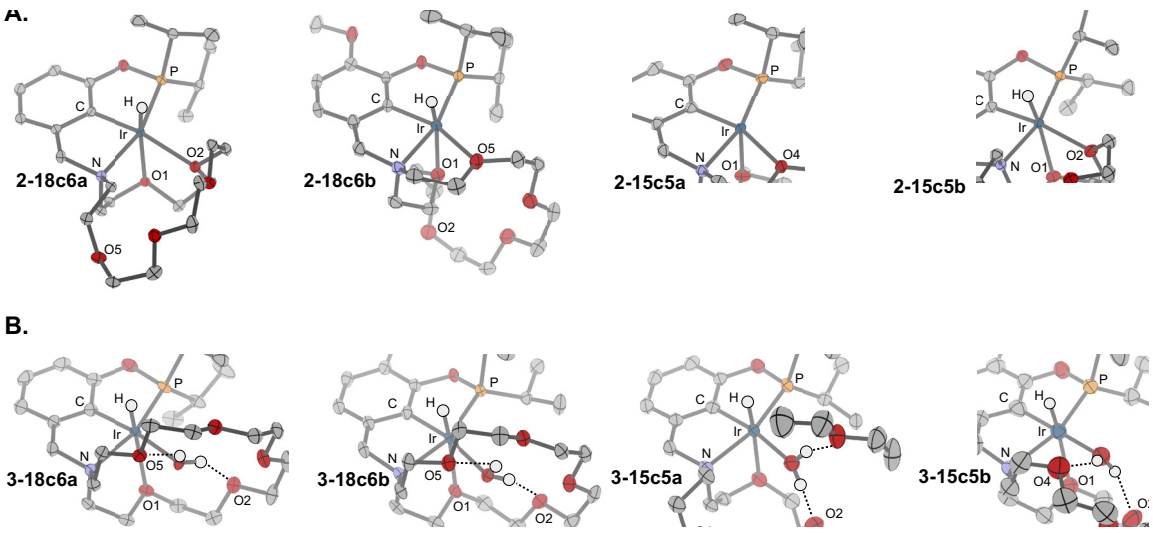


Figure 3. Molecular structures of (A) **2-18c6a/b**, previously published **2-15c5a**,[41] and **2-15c5b**; and (B) **3-18c6a/b** and **3-15c5a/b** from X-ray diffraction. Thermal ellipsoids at the 50% probability level. BAr^F_4⁻ counteranions and cocrystallized solvent are omitted for clarity. See SI for more details.

Both of the pentadentate-bound cationic hydride complexes **2-18c6a/b** exhibit dynamic behavior in NMR studies. A single broad resonance is observed in each $^{31}P\{^{1}H\}$ NMR spectrum, and each ^{1}H NMR spectrum exhibits broadening in many resonances of the crown ether ring. Dynamic behavior was seen as low as –70 °C, suggesting crown ether oxygen hemilability with facile exchange between bound and free oxygen atoms.

Comparative X-ray diffraction (XRD) studies provided further insight into linkage isomers. The solid-state structure of **2-18c6a** features two crown ether oxygen atoms donating to the Ir center (Figure 3A), the oxygen closest to the amine (O1) and its nearest neighbor (O2). Complex **2-18c6b**, however, adopts a different linkage isomer in the solid state, with the two oxygen atoms proximal to the amine (O1 and O5) donating to Ir. Distinct linkage isomers were also observed in the structures of previously reported complexes **2-15c5a** and **2-15c5b**.[39,41] Computational studies are consistent with the linkage isomers being energetically similar (within 3 kcal/mol), slightly favoring the isomer with amine-adjacent ethers bound to iridium (Figure S55).

Structural comparisons of the aqua complexes are also instructive. As shown in Figure 3B, the large macrocycle-containing complexes **3-18c6a** and **3-18c6b** feature one crown ether oxygen (O1) binding to the Ir center in the primary coordination sphere, while the bound water engages in hydrogen bonding with two other crown ether oxygen atoms (O2 and O5). The hydrogen bonding network in the secondary coordination sphere draws the crown ether macrocycle around the metal center. The flexibility of the larger 18-crown-6 macrocycle enables the ring to fully encapsulate the water ligand, a motif also seen in large metallo-crown complexes with water ligands.[42] The 15-crown-5 macrocycle only interacts with the water ligand from one side.

An important conclusion of the synthetic and structural studies is that the size of the macrocycle and the presence of a methoxy group in the pincer backbone induce only subtle changes in catalyst structure and hemilability dynamics. Thus, we anticipated that differences in catalytic activity would be dominated by changes in cation–macrocycle binding affinity. In light of previous results showing superior performance for **2-15c5b** over **2-15c5a**,[39] subsequent studies focused on methoxy-containing catalysts.

Influence of Macrocycle Size on Cation-Controlled Olefin Isomerization. To assess the performance of the new 18-crown-6-based catalysts, isomerization of 4-phenyl-1-butene (**4a**) to 4-phenyl-2-butene (**4b**) was monitored at room temperature by NMR spectroscopy (Figure 4A). For simplicity, terminal olefins are labeled **a**, the isomer with the double bond in the adjacent internal position is labeled **b**, and the next internal position is labeled **c**. In the absence of salt, 1 mol% **2-18c6b** catalyzed the isomerization of **4a** to **4b** with exceptional 23:1 *E*:*Z* stereoselectivity ($t_{1/2}$ = 190 h, TOF = 0.44 h^{-1}). The addition of $NaBAr^{F}_4$ led to a 4,500-fold rate enhancement ($t_{1/2}$ = 0.042 h, TOF = 1800 h^{-1}). The stereoselectivity of **2-18c6b** also changes in the presence of $NaBAr^{F}_4$: even at early times, (*E*)-**4b** is only moderately favored (*E*:*Z* = 5:1), while **2-18c6b** without salt additives produced *E*-**4b** with *E*:*Z* ratios of 23:1 throughout the reaction (Figure 4B/C). Aqua complex **3-18c6b** is drastically inhibited relative to **2-18c6b** in the absence of salts ($t_{1/2}$ = 2200 h, TOF = 0.031 h^{-1}). Yet, surprisingly, **3-18c6b** is only slightly slower than water-free catalyst **2-18c6b** in the presence of $NaBAr^{F}_4$ ($t_{1/2}$ = 0.14 h, TOF = 510 h^{-1}, Figure S21).

The new 18-crown-6-based catalyst is superior to the previously reported 15-crown-5-based catalyst in several facets: **2-18c6b** isomerizes **4a** up to 10 times faster; the commercially available salt $NaBAr^{F}_4$ can be used; and enhanced water tolerance is evident in the salt-promoted reactivity of **3-18c6b**. In considering cation-responsive catalysis to produce different internal olefins, the ability of Na^{+} to alter the activity and stereoselectivity of **2-18c6b** was promising. The reaction profile suggested that salt-free conditions might produce a single stereoselective isomerization, with salt-promoted conditions giving multiple isomerizations.

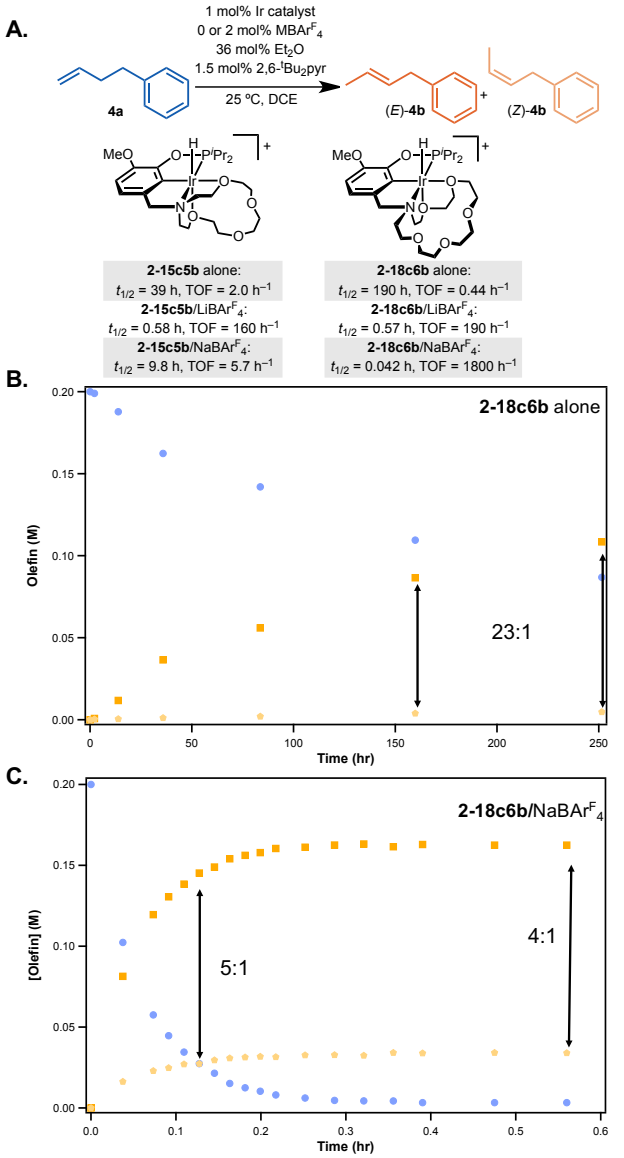
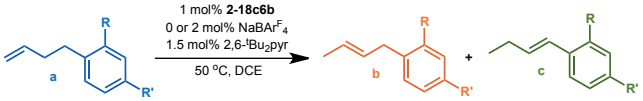


Figure 4. Isomerization of **4a** (blue circles) to (*E*)-**4b** (dark orange squares) to (*Z*)-**4b** (light orange pentagons) by Ir catalysts at 25 °C. Summary of catalytic results (A), and NMR time courses of **2-18c6b** alone (B) and in the presence of $NaBAr^{F}_4$ (C).

Cation-Switchable Regioselectivity in the Isomerization of 4-Phenyl-1-Butene Derivatives. To probe the ability of **2-18c6b** to produce different internal olefins with different additives, a variety of 4-aryl-1-butenes were treated

with 1 mol% **2-18c6b** at 50 °C, with or without $NaBAr^F_4$. Table 1 shows that Na^+ controls the regioselectivity *and* stereoselectivity of the isomerization product. Regioisomer **b** is formed in 84 to 95% yield and 7:1 to 15:1 *E*:*Z* selectivity in the absence of salts; changing conditions to include $NaBAr^F_4$ results in formation of regioisomer **c** in 79 to 96% yield and 36:1 to >90:1 *E*:*Z* selectivity (excepting substrate **12**). The regioselectivity changes more than 900-fold in most cases.

Table 1. Cation-responsive isomerization of butenyl arenes to either internal isomer.[a]



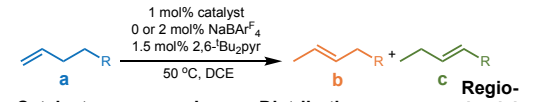
R,R'	Salt Added	Time (h)	b (*E*:*Z*)	c (*E*:*Z*)	b : c
H, H (**4**)	–	48	94% (14 : 1)	<1%	>90 : 1
	Na^+	24	7% (4 : 1)	93% (50 : 1)	1 : 10
H, OMe (**5**)	–	48	92% (14 : 1)	<1%	>90 : 1
	Na^+	24	6% (5 : 1)	94% (>90 : 1)	1 : 20
OMe, H (**6**)	–	48	95% (14 : 1)	2%	60 : 1
	Na^+	24	10% (4 : 1)	89% (50 : 1)	1 : 8.9
H, F (**7**)	–	216	93% (15 : 1)	1%	90 : 1
	Na^+	24	4% (4 : 1)	96% (50 : 1)	1 : 20
H, Br (**8**)	–	216	95% (10 : 1)	1%	90 : 1
	Na^+	24	7% (4 : 1)	93% (70 : 1)	1 : 9
H, Cl (**9**)	–	216	88% (14 : 1)	2%	40 : 1
	Na^+	24	4% (4 : 1)	96% (60 : 1)	1 : 20
Cl, H (**10**)	–	120	91% (15 : 1)	<1%	>90 : 1
	Na^+	48	20% (4 : 1)	79% (30 : 1)	1 : 4
H, CF_3 (**11**)	–	216	84% (12 : 1)	<1%	>80 : 1
	Na^+	24	7% (3 : 1)	84% (40 : 1)	1 : 12
H, COOEt (**12**)	–	216	92% (7.1 : 1)	1%	60 : 1
	Na^+	216	40% (3.4 : 1)	58% (5.1 : 1)	1 : 1.5

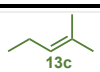
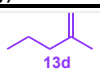
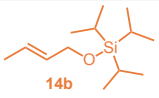
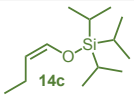
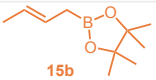
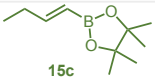
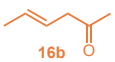
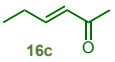
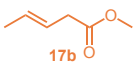
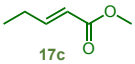
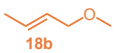
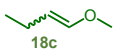
[a] yield of internal isomers; remaining mass balance is starting terminal olefin (see SI Section II for details).

While in principle one could imagine simply running the salt-promoted reaction for short times to obtain the same distribution of **b** isomer (and for long times to obtain the **c** isomer), this is not possible in practice. The **2-18c6b**/Na^+ system produces **b** isomers with poor stereoselectivity (see Figure 4C above). Similar product distributions favoring the (*E*)-**c** isomer were obtained when $LiBAr^F_4$ was used in place of $NaBAr^F_4$ with **2-18c6b** (Table S3), but for simplicity subsequent studies focused only on the Na^+ salt. The distinct *stereoselectivity* of the two catalyst states leads to the ability to produce either of two olefin products with high regioselectivity *and* high stereoselectivity — simply by addition of a Na^+ salt. The selectivity can also be switched *in situ*, if desired. Isomerization of **4a** by **2-18c6b** alone resulted in 95% yield of **4b**; addition of $NaBAr^F_4$ to the mixture flipped the regioselectivity towards **4c** (94% yield after 24 h, Table S1). This result also confirms that **4b** is a viable intermediate in the production of **4c**.

The ester-functionalized arene **12a** reacted slower than other electron-deficient substrates, even in the presence of Na^+. Evidence for inhibition by ester coordination to the catalyst was obtained in the reaction of a 1:1 mixture of ethyl acetate and **4a**. After 120 hours at 50 °C, only 6% of (*E*)-**4c** isomer was observed, with the dominant product being **4b** (93%).

Table 2. Cation-responsive isomerization of 1-butenes to either 2- or 3-butenes.[a]



Catalyst (time)	Isomer Distribution (*E*:*Z* selectivity)			Regio-selectivity (b:c)
	 13b	 13c	 13d	
2-18c6b (120 h)	**94% (13:1)**	<1%	<1%	>100 : 1
2-18c6b/ Na^+ (48 h)	12% (7:1)	**75%**	13%	1 : 7.5
	 14b	 14c		
2-18c6b (120 h)	**89% (18:1)**	1% (1:1)		90 : 1
2-18c6b/Na^+ (24 h)	4% (2:1)	**96% (1:2)**		1 : 30
	 15b	 15c		
2-18c6b (24 h)	**76% (16:1)**	12% (8 :1)		6.4 : 1
2-18c6b/Na^+ (24 h)	35% (3.4:1)	**64% (16:1)**		1 : 1.8
	 16b	 16c		
3-18c6b (120 h)	**92% (6:1)**	3%[b]		30 : 1
3-18c6b/Na^+ (216 h)[c]	**72% (2.7:1)**	26%[b]		2.7 : 1
	 17b	 17c		
3-18c6b (120 h)	**88% (4.9:1)**	5%[b]		20 : 1
3-18c6b/Na^+ (216 h)[c]	**52% (2.9:1)**	46%[b]		1.1 : 1
	 18b	 18c		
3-18c6b (120 h)[d]	**88% (10:1)**	5% (1:1)		10 : 1
3-18c6b/Na^+ (216 h)[e]	**49% (6:1)**	46% (2.1:1)		1.1 : 1

[a] yield of internal isomers; remaining mass balance is starting terminal olefin (see SI Section II for details). [b] no *Z* isomer detected. [c] 5 mol% $NaBAr^F_4$. [d] 2.5 mol% catalyst. [e] 2.5 mol% catalyst, 5 mol% $NaBAr^F_4$.

A broader range of 1-butene derivatives was examined next, with the results summarized in Table 2. The aliphatic substrate 4-methyl-1-pentene (**13a**) could be transposed to either internal regioisomer by cation-responsive catalyst **2-18c6b**. Without salts, singly isomerized product **13b** was obtained in 94% yield (13:1 *E*:*Z*); in the presence of $NaBAr^F_4$, the doubly isomerized product **13c** was obtained in 75% yield (along with some disubstituted terminal alkene **13d**).[10] Both allyl and vinyl silyl ethers were accessible from the triisopropylsilyl (TIPS)-ether-protected alcohol (**14a**) using **2-18c6b** with the appropriate salt (Table 2). In this case, the *Z* isomer of **14c** was the major product in the presence of $NaBAr^F_4$.[43,44] The representative boronic ester **15a** underwent

isomerization with **2-18c6** to give 76% yield of **15b** (16:1 *E*:*Z*). In the presence of Na^+, **15c** is formed in 64% yield with excellent stereoselectivity (16:1 *E*:*Z*, Table 2). Olefins with terminal acetal, trimethylsilyl, or acetoxy groups converted to distributions favoring the **b** isomer, both with and without salts (Table S2). The salt-free conditions still gave the **b** isomer in excellent *E* selectivity.

Next we turned to olefins containing Lewis bases, 5-hexen-2-one (**16a**), methyl pentenoate (**17a**), and 4-methoxy-1-butene (**18a**). Initial studies using catalyst **2-18c6b** revealed sluggish reactivity, even in the presence of $NaBAr^F_4$ (Figure S46-S48). We hypothesized that the Lewis basic groups on the substrate were forming a stable chelate, preventing product release and inhibiting catalysis. Thinking that a small amount of water could act as a non-chelating ligand to facilitate product release, we turned to the aqua complex **3-18c6b**. Whereas <5% **c** isomer was observed in each case with **2-18c6b**/Na^+, switchable regioselectivity was observed with aqua catalyst **3-18c6b**/Na^+. Table 2 shows that isomerization of ketone-containing **16a** gave 92% yield of **16b** without $NaBAr^F_4$ and 26% yield of **16c** with $NaBAr^F_4$; isomerization of ester-containing **17a** gave 88% yield of **17b** without $NaBAr^F_4$ and 46% yield of **17c** with $NaBAr^F_4$; and ether-containing **18a** gave 88% yield of **18b** without salts and 46% yield of **18c** with $NaBAr^F_4$. Control reactions showed no isomerization when several of the substrates described above were treated with $NaBAr^F_4$ or $LiBAr^F_4$ in the absence of any iridium catalyst.

Computational Studies of Relative Energetics of Olefin Isomers. DFT computations were carried out to examine the relative stability of regioisomers of the 1-butene derivatives examined in the catalytic studies. Compared to MP2[45–48]/aug-cc-pVDZ[49], previously used to examine long-chain functionalized olefins,[50] B3LYP/6-311++G(d,p) more accurately reflected experimental values and was therefore utilized here (with DCE solvent modeled as a polarizable continuum, see SI Section III for full details).[51,52]

Figure 5 summarizes the computational results. The 1-butene derivatives can be organized into two categories based on their computed thermodynamic distributions of regioisomers. Seven substrates had a distribution where the **c** regioisomer was the lowest energy species, while three substrates showed a thermodynamic preference for the **b** regioisomer (Figure 5).

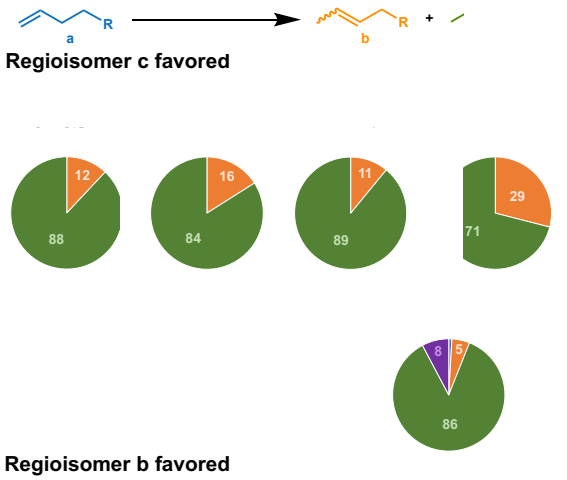
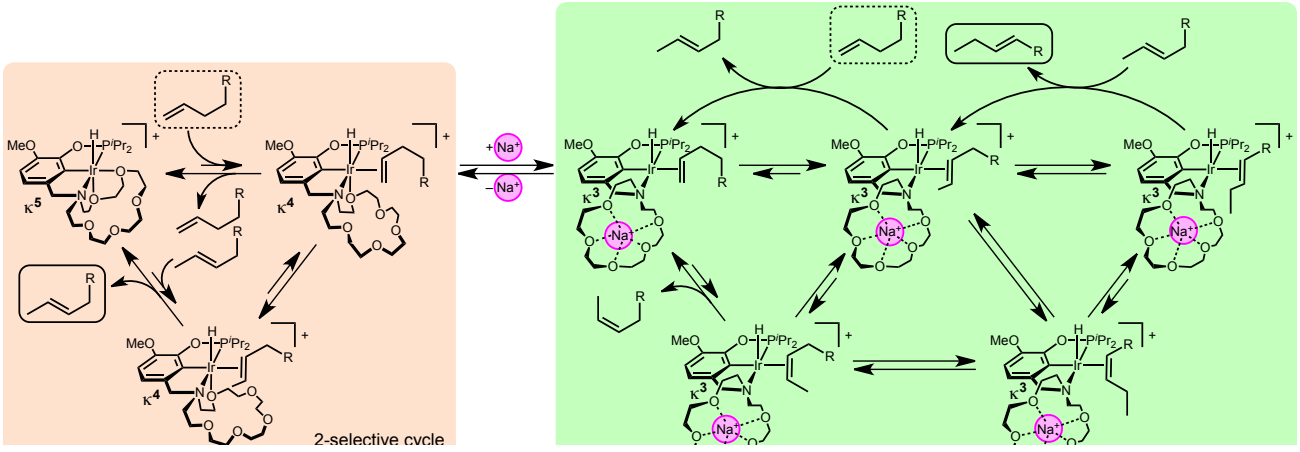


Figure 5. Thermodynamic distributions of 1-butenes from DFT (B3LYP/ 6-311G++(d,p) at 50 °C, and 1,2-dichloroethane continuum solvent model). The disubstituted terminal olefin derived from 4-methyl-1-butene is shown in purple.

3. DISCUSSION

Proposed mechanism of olefin isomerization and influence of crown ether size. The new complex **2-18c6** is not only a rare catalyst capable of a single positional isomerization with exceptional *E* stereoselectivity, but also a unique example of a single catalyst that be modified through non-covalent interactions to produce either of two internal isomers. Scheme 1 proposes a mechanism that accounts for the distinct cation-controlled product distributions. Given the important role of steric interactions in directing selectivity in isomerization,[17,53] we propose that the 2-selective isomerization stems from a catalyst state featuring a tetradentate (κ^4) binding mode with one crown ether oxygen bound during turnover, while the 3-selective isomerization takes place from a catalyst state with a tridentate (κ^3) binding mode. Spectroscopic monitoring is consistent with a change in resting state, with sharp signals for

Scheme 1. Proposed mechanism of cation-responsive isomerization by iridium pincer-crown ether catalysts.



2-18c6b present in salt-free conditions and only very broad resonances detectable in the presence of $NaBAr^F_4$. Substrates containing Lewis basic functional groups are proposed to form chelates, filling the vacant coordination site apparent in several intermediates of Scheme 1, slowing product release and inhibiting catalysis.

The cation-responsive reactivity of the 18-crown-6-based catalysts was predicted by earlier binding affinity studies of model complexes.[36,37] Previous binding affinity studies of model nickel and iridium complexes revealed that 15-crown-5-based pincer-crown ether complexes bind Li^+ stronger than Na^+, aligning with the high Li^+ specificity in rate-tunable allylbenzene isomerization with **2-15c5**.[36,37] Previous studies of structurally related model pincer complexes containing an 18-crown-6 ether group revealed a similar binding affinity for Li^+ (K_a = 34 M^{-1}) compared to 15-crown-5-based complexes (K_a = 76 M^{-1}).[36] This led to the successful prediction of similar rates of olefin isomerization for **2-15c6b** (TOF = 160 h^{-1}) or **2-18c6b** (TOF = 190 h^{-1}) in the presence of $LiBAr^F_4$. We also successfully predicted that **2-18c6** would have much higher Na^+-promoted activity than **2-15c5**, based on the huge difference in binding affinity in model complexes with aza-15-crown-5 ($K_a(Na^+)$ = 19 M^{-1}) and aza-18-crown-6 ($K_a(Na^+)$ = 15,000 M^{-1}) groups.[37] Indeed, the new catalyst **2-18c6b** (TOF = 1800 h^{-1}) isomerizes olefins ca. 300 times faster than **2-15c5b** (TOF = 5.7 h^{-1}) in the presence of $NaBAr^F_4$. The distinct reactivity of the salt adduct interplays with thermodynamics of the olefinic products to explain the observed switchable behavior.

Understanding Regioselectivity Control. Switchable regioselectivity is accessed across a wide range of butenes. In the absence of salts, the catalyst **2-18c6b** (or **3-18c6b**) facilitates a single isomerization of the double bond to the first internal position, producing the **b** isomer in high yield and with high regioselectivity and high stereoselectivity (favoring the *E* isomer). The ratio of **b**:**c** regioisomers without salts often exceeded 40:1. In the presence of $NaBAr^F_4$, the doubly isomerized product is formed instead, also in high yield and favoring the *E* isomer (**b**:**c** ratio typically beyond 1:8).

The crux of the switchable reactivity is the thermodynamic landscape of olefin isomerization. Comparing the computed regioisomer distributions with the experimental outcomes under different conditions, it is clear that the catalytic reactions in the presence of $NaBAr^F_4$ generate the most thermodynamically favored isomer (the "thermodynamic product"). Conversely, the regio- and stereoselectivity of reactions catalyzed by **2-18c6b** in the absence of salts are consistent with a high degree of kinetic control: the thermodynamic product is not obtained, and instead a specific and less stable isomer is produced. Thus, *the switchable selectivity stems from a cation-induced change between kinetic control and thermodynamic control.*

The general features of the reaction coordinate diagrams depicted in Figure 6A are shared by each substrate for which switchable regioselectivity was observed. A "stair-step" stability pattern is apparent on the basis of computed thermodynamic parameters (see Figure 5 above): the starting terminal olefin **a** being the least stable, isomer **b** being intermediate, and isomer **c** being the thermodynamic product (due to π-conjugation or hyperconjugation). The experimental studies show that, in the absence of a salt, the kinetic barrier to convert **a** to **b** is surmountable, but further isomerization to regioisomer **c** is not observed (even with prolonged reaction times). The kinetic product **b** is thus obtained, and **2-18c6b** alone produces high yields of this isomer with exquisite regioselectivity (and stereoselectivity, see below). If instead the reaction is performed with $NaBAr^F_4$, the barriers for all isomerizations are reduced dramatically, and the reaction proceeds under thermodynamic control to the most stable regioisomer. Even with $NaBAr^F_4$, butenes containing Lewis basic groups faced kinetic barriers when using **2-18c6b**. Better control over regioselectivity was obtained with the aqua catalyst **3-18c6b**.

The non-cation-responsive reactivity of butenes with silyl, acetyl, and ketal substituents can be explained by a change in thermodynamic landscape: DFT calculations reveal that isomer **c** is *not* the most stable species in these cases, with **b** being favored instead. As shown in Figure 6B, the same regioisomer will be produced regardless of whether the reaction is under kinetic or thermodynamic control.

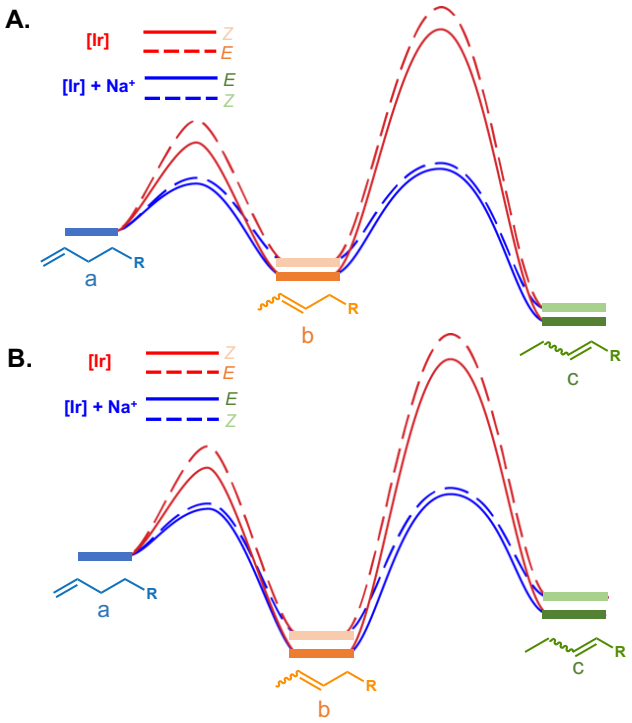


Figure 6. Simplified reaction coordinate diagrams for olefin isomerization depicting the case where cation-controlled selectivity is possible (A) and the case where thermodynamic limitations prevent access to the **c** isomer (B).

Rationalizing Unique Stereoselectivity in Each Catalytic State. The pincer-crown ether catalyst **2-18c6b** is one of a select few catalysts capable of facilitating a single positional isomerization with exceptional stereoselectivity for the *E*-isomer.[11,13,14,16,53,54] The high stereoselectivity of pincer-crown ether catalysts in the absence of salts (*E*:*Z* ratios often exceeding 15:1 even at 50 °C) was not previously recognized because prior studies focused on isomerization of allylbenzene:[34] the *E* isomer of the product β-methylstyrene is highly favored thermodynamically (*E*:*Z* ca. 20:1 at 25 °C), obscuring any kinetic selectivity of the catalyst.[55] The butene-containing substrates, in contrast, have only a moderate thermodynamic preference for the *E* isomer (ca. *E*:*Z* 4:1).[54,56]

The high stereoselectivity of **2-18c6b** in the absence of salts is proposed to originate from steric congestion of the crown ether (Scheme 1). Computational studies have shown that the Ir-O bond *trans* to phenyl is easiest to dissociate, which can open up a binding site for alkene to bind.[41] Without salts, we hypothesize that one crown ether oxygen remains bound to the Ir center during catalysis, providing additional steric pressure that can influence selectivity by favoring the transition state that forms the *E* isomer and disfavoring internal olefin binding.

The stereoselectivity of **2-18c6b** changes upon the addition of $NaBAr^F_4$, leading to thermodynamic distributions of *E* and *Z* isomers. For example, isomerization of **4a** with **2-18c6b**/$NaBAr^F_4$ produces **4b** with selectivity close to the expected thermodynamic distribution (*E*:*Z* = 4:1). As shown in Scheme 1, we propose that Na^+ binding leads to cleavage of both Ir–O bonds and release of steric pressure near the active site. This is consistent with prior studies of model complexes showing negligible cation binding by pincer-crown ether complexes with tetradentate (κ^4) or pentadentate (κ^5) binding modes, but strong binding when tridentate (κ^3) binding modes with no bound ether oxygens are adopted.[36] The mechanistic model of Scheme 1 helps explain why shortening the reaction time of **2-18c6b**/Na^+-catalyzed reactions would not produce the same outcome as the salt-free system: *each catalytic state has a distinct structure and thus distinct stereoselectivity*.

Design Principles for Non-Covalent Catalyst Modification. The prevailing paradigm in catalyst design involves synthetic tuning of supporting ligands. In this work, we explore a complementary strategy based on non-covalent modification of the catalyst structure.[20–25] There are no prior examples of a single catalyst that can produce either of two internal olefin isomers through the influence of non-covalent interactions, to our knowledge. Thus, our mechanistic insight can provide some initial design principles for how cation-controlled selectivity in isomerization reactions may be achieved.

A catalyst should be able to access two states, each with unique reactivity. One state must provide high selectivity for a kinetic product; the other state can provide selectivity for a different kinetic product or for the thermodynamic product. Knowledge of the thermodynamic landscape of the isomers under consideration is helpful in this regard: in our case, computational investigations rapidly identified systems with appropriate relative thermodynamics. An additional requirement is that the two states must not interconvert rapidly. In this case, strong cation–macrocycle interactions maintain the second state.

Steric factors have proven essential in controlling the selectivity in positional olefin isomerization. Ruthenium catalysts exhibit distinct selectivity based on the cyclopentadienyl substitution pattern,[57,58] for example, and the regioselectivity in cobalt-catalyzed isomerization is dramatically impacted by the steric profile of bi- and tridentate phosphine-based ligands.[14,59] These observations suggest that the two catalyst states in a responsive system should be sterically distinct. Here we propose that the change in selectivity stems from a structural change in the primary coordination sphere via changes in ether ligand hemilability. When one ether remains bound to the catalyst, the kinetic product is obtained; when no ethers are bound to the catalyst, the thermodynamic product is instead produced. Thus, modifications that alter ligand lability or the primary coordination sphere may be expected to have strong impacts on reaction selectivity in other catalysts as well.

Changing the primary coordination sphere via external additives in order to control selectivity is notably distinct from the prevailing approach to non-covalent catalyst modification. Typically, additives interact with the supporting ligand (or two supporting ligands interact with each other) to change the overall steric profile or the ligand bite angle, without altering the coordination number. This strategy has been highly effective in tuning the linear/branched regioselectivity in alkene hydroformylation,[23,33] including examples of cation–crown interactions tuning ligand bite angle.[26,27,30] Because the macrocycle in pincer-crown ether is directly bound to the catalyst, cation binding influences the primary coordination sphere, which we propose to be essential for controlling regioselectivity and stereoselectivity between two sterically similar internal olefin isomers.

4. CONCLUSIONS

A single cation-responsive pincer-crown ether iridium catalyst can produce either of two internal isomers using appropriate external additives. In the absence of salts, **2-18c6b** isomerizes 1-butene derivatives to the corresponding 2-butene (allyl derivatives) with exceptional regio- and stereoselectivity. Under otherwise identical conditions, but in the presence of $NaBAr^F_4$, the doubly isomerized 3-butenes (vinyl derivatives) are produced. Combined experimental and computational studies guided the development of a model that explains the selectivity outcomes. Two distinct catalytic state are accessed, one (salt-free) that exhibits high kinetic selectivity for a single *E*-selective isomerization, and another (salt-activated) that exhibits thermodynamic selectivity. Cation–macrocycle interactions are proposed to change the pincer ligand binding mode, resulting in distinct activity and selectivity traits. Selective generation of individual internal olefin isomers from a single catalyst offers promise for the diversification of olefins relevant to the fragrance, and pharmaceutical, and other industries.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at http://pubs.acs.org.

Experimental details and characterization data (PDF)

Crystallographic data (CIF)

Coordinates of optimized geometries of iridium complexes (XYZ)

Coordinates of optimized geometries of olefins (XYZ)

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Notes

The authors declare no competing financial interests.

ACKNOWLEDGMENT

The work was supported by the National Science Foundation under CAREER award Grant No. CHE-1553802. The authors thank M. ter Horst for assistance with NMR spectroscopy experiments and B. Ehrmann for assistance in the RISE Catalysis Center within the Department of Chemistry Mass Spectrometry Core Laboratory. The NMR spectroscopy was supported by the National Science Foundation under Grant No. CHE-1828183 and Grant No. CHE-0922858. The mass spectrometry was supported by the National Science Foundation under Grant No. CHE-1726291.

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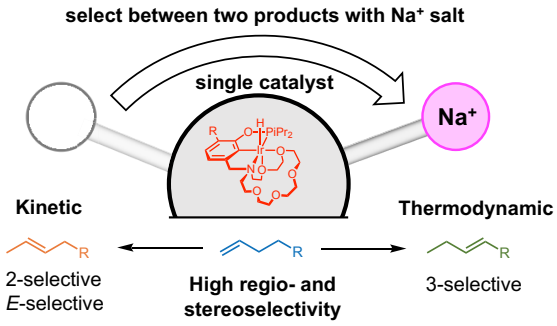
TOC Graphic


select between two products with Na+ salt
single catalyst
Na+
Kinetic
Thermodynamic
2-selective
E-selective
High regio- and
stereoselectivity
3-selective