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Carbonyl cross-metathesis via deoxygenative *gem*-di-metal catalysis

Lumin Zhang[1,2,*], **David A Nagib**[1,*]

[1]Department of Chemistry and Biochemistry, The Ohio State University, US.

[2]Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai, China.

Abstract

Carbonyls and alkenes are versatile functional groups, whose reactivities are cornerstones of organic synthesis. The selective combination of two carbonyls to form an alkene – a carbonyl cross-metathesis – would be a valuable tool for their exchange. Yet, this important synthetic challenge remains unsolved. Although alkene/alkene and alkene/carbonyl cross-metathesis reactions are known, there is a lack of analogous methods for deoxygenative cross-coupling of two carbonyls. Here, we report a pair of strategies for the cross-metathesis of unbiased carbonyls, allowing an aldehyde to be chemo- and stereo-selectively combined with another aldehyde or ketone. These mild, catalytic methods are promoted by earth-abundant metal salts and enable rapid access to an unprecedentedly broad range of either *Z* or *E* alkenes by two distinct mechanisms – entailing transiently generated: (1) carbenes and ylides (via Fe catalysis) or (2) doubly nucleophilic gem-di-metallics (via Cr catalysis).

Given the synthetic importance of carbonyls and alkenes, mechanistically novel methods for their interchange are highly valued.[1] An important example is alkene metathesis, wherein two alkenes are structurally shuffled (Fig. 1a).[2] Although some methods enable cross-reactivity, an inherent challenge remains in differentiating the two alkenes to favor cross-selectivity over dimerization. Alkene-carbonyl metathesis provides another path by exchanging an alkene with a carbonyl, and valuable catalytic strategies exploit this inherent chemo-selectivity.[3,6–8] Alternatively, the metathesis of carbonyls to form an alkene provides a mechanistically distinct means of differentiating a product alkene from its carbonyl precursors. Deoxygenative carbonyl dimerization has been developed using low-valent titanium (i.e., the McMurry coupling).[9–11] Nonetheless, cross-selectivity remains unsolved.[4,5] Here, we present two, distinct strategies for cross-metathesis of carbonyls, entailing either: (1) carbene-to-ylide transfer or (2) *gem*-di-metalation. By these mechanistically divergent methods, an aldehyde may now be chemo- and stereo- selectively combined with another carbonyl to form either a *Z* or *E* alkene. This transform, an

* zhanglm5618@sioc.ac.cn; nagib.1@osu.edu.

Author contributions.

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endothermic reverse of ozonolysis, is enabled by catalytic transformation of electrophilic carbonyls into either zwitterionic ylides or doubly nucleophilic gem-di-metals.

The challenge of enabling cross-selectivity in the McMurry coupling is tied to its mechanism (Fig. 1b).[9] In it, Ti-mediated reduction of a carbonyl and ketyl radical coupling forms pinacol, which is subsequently deoxygenated as TiO_2 to yield an alkene. Since there is no mechanism for carbonyl selectivity in ketyl formation nor for the ensuing pinacol coupling, a statistical mixture of cross-coupling and dimerization products is inherent. The only exceptions are certain carbonyls (e.g., diaryl ketones, glyoxylates), whose double reductions to anion nucleophiles are thermodynamically biased.[12,13] Other novel alternatives to the McMurry coupling are similarly limited to differentiation by at least one aryl carbonyl partner.[14–17]

Towards broader, chemoselective carbonyl activation, we recently developed an in situ acyl halide addition of aldehydes to form ketyl radicals by atom transfer catalysis.[18] This enables aldehyde cross-coupling with several other electrophiles.[19–23] However, carbonyl olefination also requires a mechanism for oxygen deletion[24,25] (e.g. Ti to TiO_2, in the McMurry reaction). Thus, we developed a method to convert aldehydes to carbenes, wherein aldehydes are deoxygenated via transient α-benzoyl zinc intermediates (Fig. 1b).[26] Notably, we observed stereo-selective carbene dimerization to *E*-alkenes with a Co catalyst. To reverse polarity of these electrophilic carbenes and combine them with another carbonyl, we included sulfide co-catalysts to access sulfonium ylide reactivity.[27] Yet, this strategy affords epoxides rather than alkenes (i.e., only one carbonyl is deoxygenated).[26] Instead, to promote carbonyl metathesis, double deoxygenation of two carbonyls is necessary.

To enable synergistic deoxygenation of a second carbonyl, we have now developed two distinct catalytic strategies to access either a *Z* or *E* alkene stereoselectively (Fig. 1c). The first approach is inspired by a modified Wittig mechanism.[1] In this case, the ensuing deoxygenation is enabled by converting a transient carbene to a phosphonium ylide. This method complements pioneering approaches by Carreira, Lebel, and Aggarwal entailing carbene transfer from diazo reagents,[28–30] by now permitting the use of enolizable alkyl aldehydes as carbene precursors. And for comparison with other modern ylide-based approaches, Silvi recently intercepted the Wittig reaction by decarboxylative radical addition of α-stabilized acids to vinyl phosphoniums,[31] and Ott developed a P=P reagent to promote a double Wittig of aryl aldehydes.[16] Yet, in our proposal, we expected this chemoselective conversion of aldehydes to ylides to now enable catalytic coupling of unbiased, alkyl aldehydes. Moreover, this base-free olefination is expected to be stereoselective – affording *Z*-alkenes, in contrast with diazo-mediated *E*-olefinations.[28–30]

To test our first proposal (Table 1), we converted unbiased, enolizable, alkyl aldehyde **A** to its stable α-benzyloxy bromide by in situ BzBr addition with a $ZnBr_2$ catalyst. This inter-mediate may be purified by column chromatography or recrystallization, and stored cold indefinitely or may be used directly without purification. Upon its Zn-insertion to form alkyl zinc carbenoid, **A'** (mediated by LiCl), an iron catalyst (10% $FeCl_2$), phosphine (Ph_3P), and acceptor aldehyde **B** were added to the mixture and let stir at room temperature. In support of our mechanistic hypothesis, the product alkenes **1–7** are formed with complete

cross-selectivity (>20:1 by ^{1}H NMR) since the phosphonium ylide is exclusively generated from aldehyde **A**, and the ylide does not dimerize, but only reacts with aldehyde **B**. The high efficiency and cross-selectivity observed also indicates that transfer of the iron carbene to Ph_3P outpaces dimerization. To our delight, *Z*-alkene formation is also highly stereoselective (up to >20:1 with LiCl in THF/DMF) in contrast to diazo variants.[28–30] The cross-coupling of two linear *n*-alkyl aldehydes (**1**) yields 9:1 *Z:E* selectivity, and trapping with α-branched (alkyl or aryl) aldehydes affords even higher stereo-selectivity (**2**, 10:1 *Z* and **3**, 16:1 *Z*). Further steric hindrance is also well-tolerated (and more stereoselective), as in the case of pivaldehyde (**4**, >20:1 *Z*) and heterocyclic aldehydes (**5-7**, >20:1 *Z*).

We next sought to develop a parallel strategy to access *E*-alkenes via a distinct deoxygenation mechanism (Fig. 1c). Here, we were inspired by the Takai reaction, wherein *gem*-dimetals stereoselectively olefinate aldehydes.[32,33] In this phosphine-free approach, *gem*-diiodides are converted to dizinc or dichromium intermediates by insertion of either Zn or Cr reductants.[34] Like the reagents developed by Nysted or Tebbe, metal oxide formation drives alkene generation and carbonyl deoxygenation in these cases.[1] Yet, advantages of the Cr-based method include high *E*-selectivity and broad reactivity with either aryl or alkyl aldehydes, including base-sensitive, enolizable ones. Still, the need for unstable *gem*-diiodides, or related precursors, remains a major synthetic limitation since harsh iodination conditions and the potential for elimination typically limit generality and accessibility.[35,36] Motherwell and Boland have each extended this reaction to employ other carbonyl derivatives as the *gem*-di-metal precursor.[37,38] However, neither approach is cross-selective, catalytic, or exhibits the wide synthetic scope of the Takai method. In contrast, we anticipated chemoselective in situ aldehyde preactivation and catalytic stereocontrol could enable a broadly useful carbonyl cross-metathesis.

To examine our proposed *E*-selective cross-metathesis (Table 2), aldehyde **A** was converted to its α-OBz bromide and added to aldehyde **B** and $CrCl_2$ in a 1:1:1 ratio. In this preliminary stoichiometric example, we were pleased to see complete cross-selectivity (>10:1) and stereoselectivity (>20:1) in the formation of alkene **8**. Toward a catalytic variant, we were inspired by how Fürstner rendered the Nozaki−Hiyama−Kishi reaction catalytic in Cr by incorporating a Mn reductant and chlorosilane.[39] Recent examples have also shown the value of bipyridyl ligands and coordinating solvents to enable reductive catalytic turnover of Cr.[40–42] We investigated several ligands and reductants and found the combination of Mn, LiI, Me_3SiCl, and 4,4′-di-*t*-butyl-bipyridyl ligand (dtbbpy) to be most effective. Upon inclusion of 10% dtbbpy in THF, Cr catalyst loading may be reduced to 25% $CrCl_2$. Yet, while product **8** forms efficiently (79%) in this case, cross- (8:1) and stereo- (10:1 *E*) selectivity are diminished for this dichromium-mediated reaction. Thus, 50% $CrCl_2$ was selected to enable broad, robust efficiency (>90% yield) and selectivity (>10:1 cross; >20:1 *E:Z*).

To evaluate the synthetic utility of this Cr-catalyzed carbonyl cross-metathesis (Fig. 2a), a diverse range of aldehydes were investigated as the donor (**A**) and acceptor (**B**) components. Both were shown to have broad scope and generality. For example, acceptor **B** may consist of linear (**9–12**) and branched (**13–20**) aldehydes, including isotopes of formaldehyde (**9**), *d*-acetaldehyde (**10**), and citronellal (**12**), as well as medicinally relevant, small rings and

heterocycles (**14–18**). Large sterics are also well-tolerated (**19–20**). In each of these cases (**8, 13–20**), high chemo- and stereo- selectivity is observed (>10:1 cross; >20:1 *E:Z*). Conversely, aryl and heteroaryl aldehydes are also efficient and cross-selective but lack stereoselectivity (**21–27**). Notably, ketones may also be employed as acceptors (**28–34**) with their efficiency illustrating the robustness of this dichromium reactivity.

To probe the mildness and unique tunability of the aldehyde activation, the donor component **A** of this cross-metathesis was also varied (Fig. 2b). These experiments show a similarly broad scope. For example, formaldehyde (**35**) may be employed, as well as aldehydes containing reactive functional groups, such as alkenes (**36**) or halides (**37**). Moreover, sterically hindered, α-branched and enolizable aldehydes are tolerated (**38–40**) – overcoming significant limitations of the Wittig reaction.[1] Complex aldehydes were also coupled to form a heteroatom-rich alkene (**41**) and showcase the synthetic utility of this mild, catalytic protocol (Fig. 2c). Finally, ring-closing metathesis was performed on a molecule bearing an aldehyde and ketone to generate α-pinene **42**.

To benchmark the unprecedented cross-selectivity of these two new strategies, we evaluated the metathesis of aldehydes using other current state-of-the-art methods. First, our previous Co-catalyzed carbene dimerization method (Fig. 3a) yields a 4:1 mixture of dimers (**43** and **44**) to cross-coupled alkene **8** since there is no mechanism for cross-selectivity. Surprisingly, the Ti-mediated McMurry coupling does not afford any alkene when two alkyl aldehydes (**A** and **C**) are employed (Fig. 3b). Yet, if a more easily reduced aryl aldehyde **D** is combined with aldehyde **A**, then a 1:1 mixture of **D**-**D** dimerization (**45**) and **A**-**D** cross-coupling (**21**) is observed. In this case, although there is a method for differentiating Ti-ketyl radical generation (favoring **D** > **A**), there is no selectivity mechanism for its cross-coupling.

Since we have already shown selective formation of these two products (**3**, **8**, **21**) with >10:1 cross-selectivity, we next sought to evaluate the rate of reactivity between aldehyde and ketone acceptors in our Cr-catalyzed method (Fig. 3c). In this case, when donor aldehyde **A** (1 equiv.) is subjected to two acceptors, aldehyde **C** and ketone **E** (1 equiv. each), the aldehyde partners are exclusively coupled with >20:1 aldehyde:ketone selectivity and >20:1 cross-selectivity. When aryl aldehyde **D** and ketone **F** (1 equiv. each) are employed as acceptors in this three-component competition, the same >20:1 aldehyde:ketone chemoselectivity is observed.

Next, we sought to support our mechanistic hypotheses by isolating key intermediates of each method (Fig. 3d). When aldehyde **A** is subjected to the *Z*-selective conditions in the absence of an acceptor aldehyde **B**, the phosphonium ylide is expected to be present stoichiometrically, even with 20% Fe catalyst. In fact, quenching with HCl yields alkyl phosphonium **46** in >95% isolated yield – validating the intermediacy of an ylide in this *Z*-selective reaction. In parallel, aldehyde **A** was subjected to the *E*-selective reaction, albeit with stoichiometric $CrCl_2$ to isolate a transient organometallic intermediate. If α-OBz-Cr-carbenoid (via only one Cr reduction) predominates, then HCl quenching should yield the reduced benzoate ester. However, this product was not observed. Instead, acidic quenching yields a fully deoxygenated product **47**, which results from the doubly reduced

gem-dichromium intermediate. Since LiI accelerates this stoichiometric $CrCl_2$ reaction, we expect it also plays a role in activating the α-OBz species for reduction by Cr.

Given these observations, we propose the following two mechanisms (Fig. 3e). For the Fe-catalyzed carbene/ylide strategy (shown on the left), in situ activation of aldehyde **A** by BzBr (with $ZnBr_2$ catalyst) yields α-OBz bromide **I**. Next, Zn insertion of **I** affords carbenoid **II**. Transmetallation with the Fe catalyst then yields α-OBz organoiron **III**, which may rapidly α-eliminate the OBz anion to generate Fe-carbene **IV**. Upon carbene transfer to Ph_3P, phosphonium ylide **V** is formed (as observed by its protonated analog **46**), which can chemoselectively combine with aldehyde **B** to form *Z*-alkene while recycling the Fe catalyst. Conversely, in the *gem*-di-metal, Cr-catalyzed mechanism (shown on right), α-OBz bromide **I** may be directly and chemoselectively reduced by Cr(II) to Cr-carbenoid **VI** – accelerated by LiI, and in the presence of acceptor aldehyde **B**. A second Cr-mediated reduction yields the key *gem*-dichromium **VII**, which enables deoxgenative olefination of aldehyde **B** to afford the *E*-alkene and a chromium oxide. By combination of Mn, LiI, and TMSCl, this CrO_n is reduced back to Cr(II) to turn over the Cr catalytic cycle.

In conclusion, two catalytic methods have been developed for the chemo- and stereo-selective cross-metathesis of carbonyls. These deoxygenative strategies enable the reverse of modern ozonolysis reactions[43,44] by combining two carbonyls to form an alkene – a valuable addition to the synthetic toolkit.

Methods.

Cr-catalyzed cross-metathesis (*E*-selective):

To $ZnBr_2$ (5 mol%) in a dry vial, was added CH_2Cl_2 (0.2 mL) and BzBr (1.2 equiv.). Next, aldehyde **A** (0.2 mmol, 1 equiv.) was added slowly and stirred at −10 °C for 2 h, then purified by chromatography or recrystallization, or used crude. Separately, to a dry vial of $CrCl_2$ (50 mol%), dtbbpy (10 mol%), Mn (2 equiv.), LiI (3 equiv.), Me_3SiCl (2 equiv.), THF (1 mL), and a stir bar, was added aldehyde **B** (1 equiv.). The aldehyde **A** mixture was then added with THF (1.5 mL), stirred at 60 °C for 4–12 h, then quenched and purified by chromatography to afford the *E*-alkene product.

Fe-catalyzed cross-metathesis (*Z*-selective):

To $ZnBr_2$ (2 mol%) in a dry vial, was added CH_2Cl_2 (0.6 mL) and BzBr (1.2 equiv.). Aldehyde **A** (0.2 mmol, 1 equiv.) was added slowly and stirred at −10 °C for 2 h, then purified by chromatography. Next, this *α*-OBz bromide (2 equiv.) in THF (1 mL) was slowly added to a dry vial of LiCl (2 equiv.) and Zn dust (3 equiv.), then stirred at room temperature for 8 h. The filtrate of this alkyl zinc carbenoid solution was then transferred to $FeCl_2$ (10 mol%), Ph_3P (2 equiv.), aldehyde (1 equiv.), THF/DMF (2 mL/0.5 mL), and then stirred at room temperature for 12 h. Purification by chromatography affords the *Z*-alkene product.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data availability.

The data supporting the findings of this study are included in the Supplementary Information.

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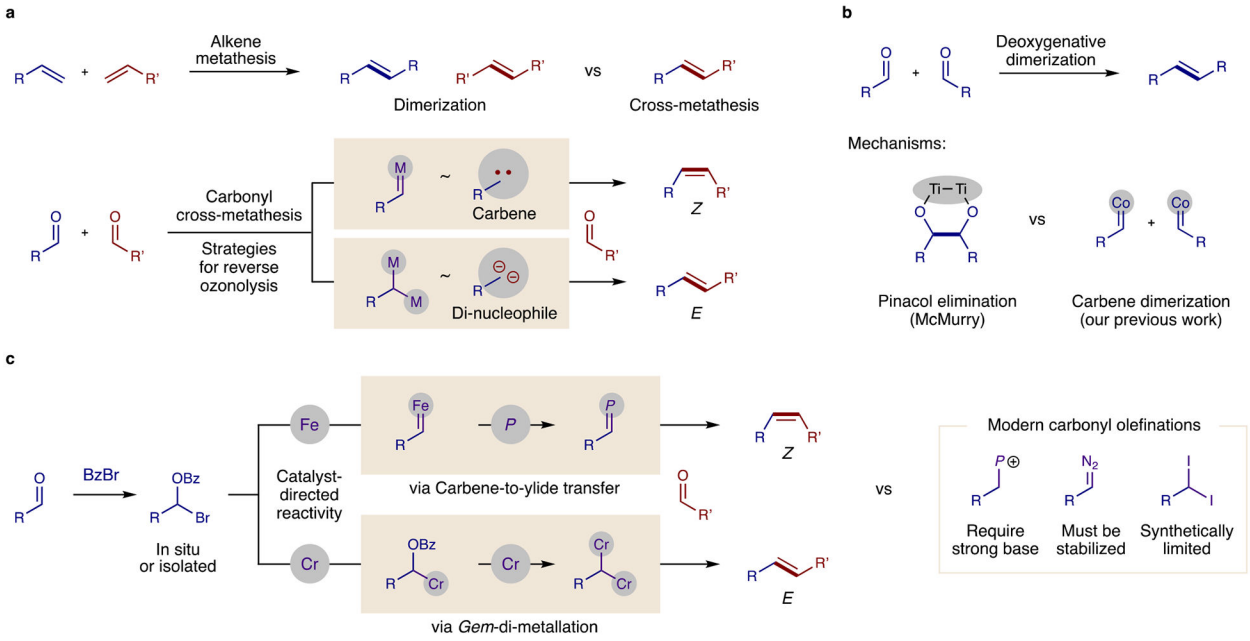


Fig. 1: Carbonyl metathesis strategies are rare and cross-selectivity mechanisms must be developed.

a, Reactivity and selectivity challenges are shown. Cross-selective, alkene metathesis is rare, yet synthetically valuable. Carbonyl cross-metathesis (a reverse ozonolysis of an unsymmetric alkene) is unknown. **b**, State of the art methods for deoxygenative olefination of carbonyls only yield dimeric products. **c**, Two complementary strategies to access cross-selective reactivity are presented via either (1) Fe-catalyzed carbene/ylide or (2) Cr-catalyzed *gem*-di-metal mechanisms. Synthetic advantages of these approaches include mild (base-, diazo-, and dihalo- free) conditions that employ unbiased, enolizable aldehydes and yield robust, divergent (*Z* or *E*) stereoselectivity.

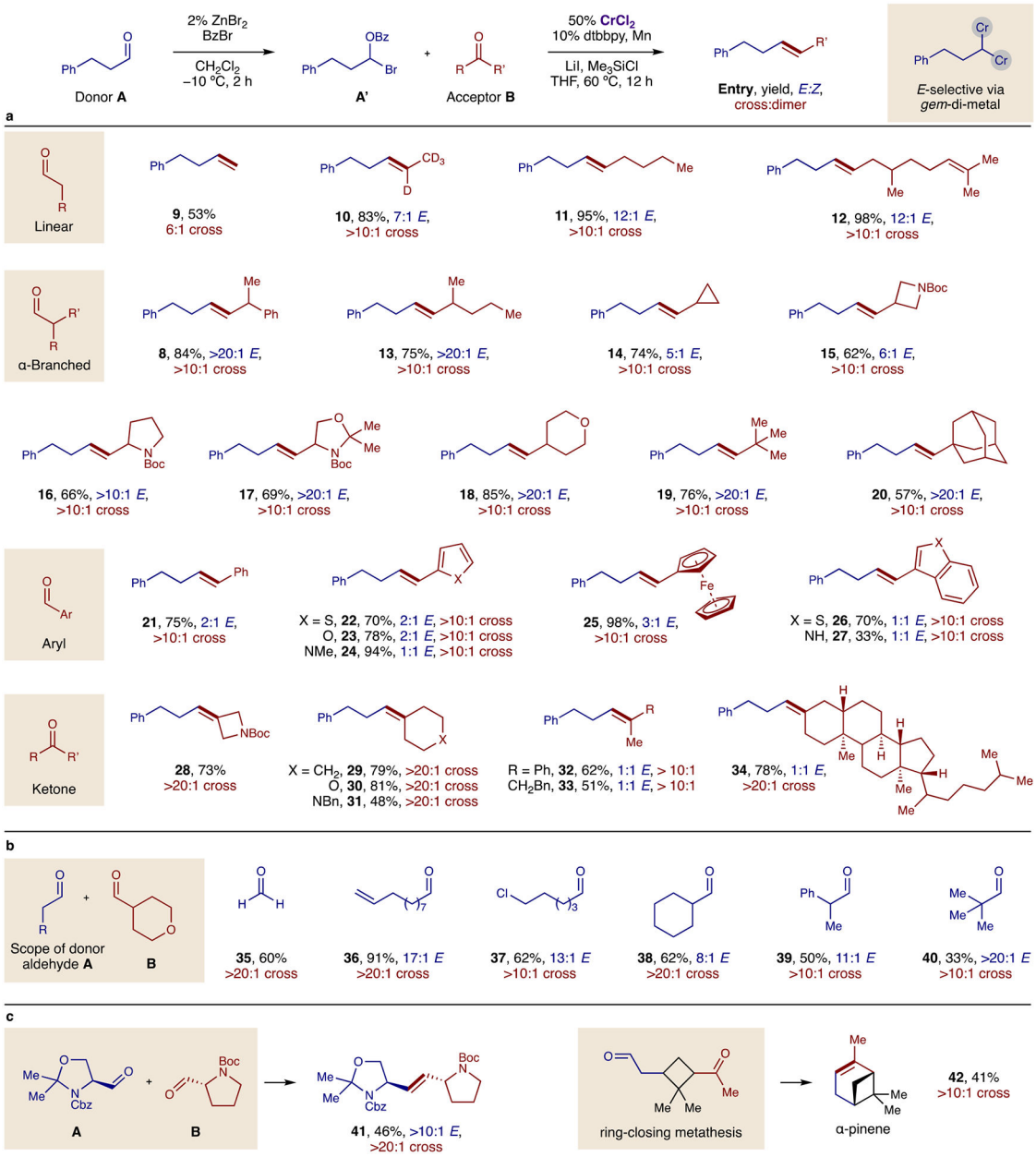


Fig. 2: The Cr-catalyzed carbonyl metathesis has wide scope with robust *E*- and cross-selectivity.
a, Acceptor **B** may be a linear or branched, alkyl or aryl aldehyde, as well as a ketone. **b**, Donor **A** may be a wide range of aldehydes, including the smallest formaldehyde or most hindered, pivaldehyde. **c**, Complex molecule applications show the utility of this olefination. See Table 2 for conditions.

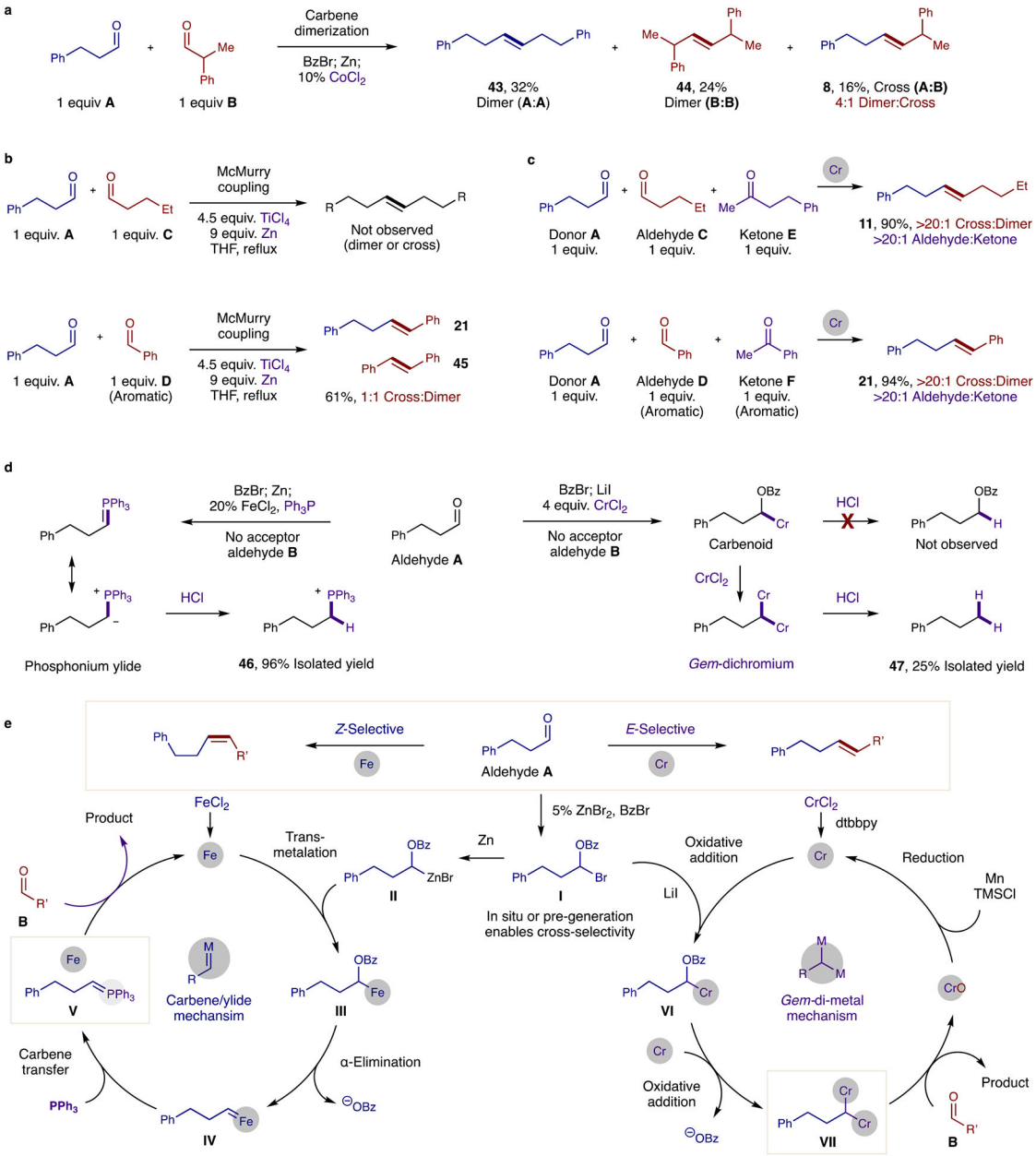


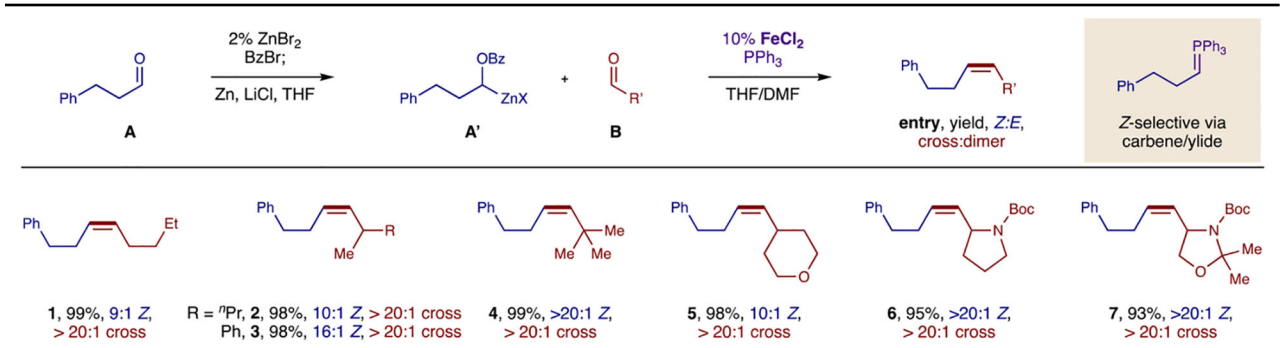
Fig. 3: Cross-metathesis: selectivity probes and mechanism.

No cross-selectivity is observed via previous methods, including: **a**, Co-catalyzed carbene dimerization, or **b**, Ti-mediated McMurry coupling with either alkyl or aryl aldehyde acceptors. **c**, In contrast, Cr-catalysis affords cross- and chemo- selectivity, even in three-component competitions with aldehyde and ketone acceptors. **d**, In the absence of an aldehyde acceptor, key proposed intermediates were isolated to support each mechanism, including phosphonium **46** by ylide protonation and doubly reduced **47** by *gem*-dichromium protodemetalation. **e**, Proposed mechanisms for each strategy are shown. Cross-selectivity is ensured by transient formation of **I** from aldehyde **A**. *Z*-selectivity (left catalytic cycle) occurs by Zn-insertion of **I** to **II**, followed by transmetallation to an $FeCl_2$ catalyst. Upon α-elimination of **III** to alkyl carbene **IV**, carbene transfer to PPh_3 affords catalyst turnover

and ylide **V**, which enables *Z*-selective olefination of **B**. In contrast, *E*-selectivity (right catalytic cycle) occurs by double Cr-insertions of **I** to **VI** to **VII**. This catalytically generated *gem*-dichromium arises from two oxidative additions of a L·$CrCl_2$ catalyst to the α-oxy carbon of **I**, in a net deoxygenation of carbonyl **A**. Upon *E*-selective olefination of **B** by doubly nucleophilic organometal **VII**, CrO reduction permits catalyst turnover.

Table 1:

Discovery and synthetic scope of an Fe-catalyzed, carbonyl cross-metathesis (*Z*-selective).

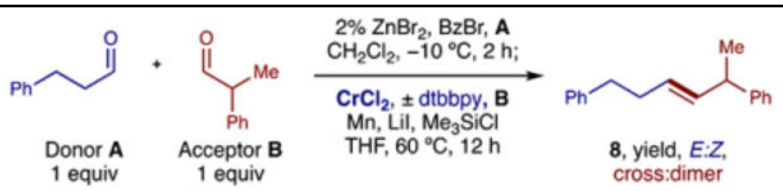


Reaction conditions: Aldehyde **A** (0.2 mmol, 1 equiv), $ZnBr_2$ (2 mol%), BzBr (1.2 equiv) in CH_2Cl_2 (0.6 mL) at −10 °C for 2 h; α-OBzBr of **A** (2 equiv), LiCl (2 equiv), Zn (3 equiv) in THF (1 mL) at r.t. for 8 h; carbenoid **A'** (2 equiv), $FeCl_2$ (10 mol%), Ph_3P (2 equiv), aldehyde **B** (1 equiv) in THF/DMF (2 mL/0.5 mL) at r.t. for 12 h. Isolated yields. Cross- and Stereo- selectivity measured by ^1H NMR.

THF, tetrahydrofuran; DMF, *N,N*-dimethylformamide.

Table 2:

Discovery of a Cr-catalyzed cross-metathesis of aldehydes (*E*-selective).



Entry	CrCl2	dtbbpy	Yield 8	*E:Z*	Cross
1	100%	—	90%	>20:1	>10:1
2	0%	10%	0%	—	—
3	25%	10%	79%	10:1	8:1
4	50%	10%	95%	>20:1	>10:1
5	100%	10%	91%	>20:1	>10:1

Reaction conditions: Aldehyde **A** (0.2 mmol, 1 equiv), $ZnBr_2$ (2 mol%), BzBr (1.2 equiv) in CH_2Cl_2 (0.2 mL) at −10 °C for 2 h; then add to aldehyde **B** (1 equiv), $CrCl_2$ (X mol%), dtbbpy (Y mol%), Mn (2 equiv), LiI (3 equiv), Me_3SiCl (2 equiv) in THF (2.5 mL) at 60 °C for 4–12 h. Isolated yields. Cross- and Stereo- selectivity measured by ^1H NMR. THF, tetrahydrofuran; dtbbpy, 4,4′-di-tert-butyl-2,2′-bipyridyl.