Cross-Coupling

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Iron-Catalyzed Stereoselective Cross-Coupling Reactions of Stereodefined Enol Carbamates with Grignard Reagents

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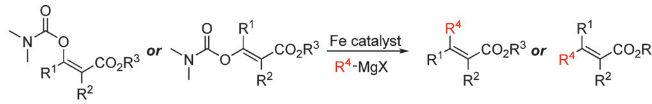
Abstract: *A practical and highly stereoselective iron-catalyzed cross-coupling reaction of stereodefined enol carbamates and Grignard reagents to yield tri- and tetrasubstituted acrylates is reported. A facile method for the stereoselective generation of these enol carbamates has also been developed.*

Alkenes and their functionalized derivatives represent one of the most fundamental classes of building blocks in all of organic synthesis. As such, their synthesis has sparked the curiosity and creativity of synthetic chemists for over a century.[1] This intense effort has led to some of the most well-known transformations in the field, including the Wittig olefination, the Peterson olefination, the Horner–Wadsworth–Emmons reaction, the Heck reaction, and olefin metathesis. Yet despite the undeniable synthetic utility of these methods and others, each one has recognized limitations that continue to inspire new approaches to address these deficiencies. This is especially the case when it comes to the challenging stereoselective synthesis of tri- and tetrasubstituted functionalized olefins.

One approach that has shown promise, however, is the use of metal-catalyzed cross-coupling reactions. In this regard, both palladium and nickel have been the catalysts of choice given their overwhelming success in catalytic C−C bond construction.[2] While these endeavors have been fruitful, the continued evolution of what defines reaction efficiency and sustainability has resulted in the pursuit of more earth-abundant metals to promote these catalytic processes. Thanks to the pioneering studies of Kharasch[3] and Kochi[4] and subsequent work by the groups of Molander,[5] Cahiez,[6] Fürstner,[7] and others, iron-based catalysts have emerged as an attractive alternative for catalytic cross-coupling reactions between alkenyl electrophiles and Grignard reagents.[8] Whereas much of the early work focused on alkenyl halides as substrates, recent methods have utilized oxygen-based electrophiles (pseudohalides) that are easily accessible from carbonyl precursors.[9] For example, success has been had with various cross-coupling partners, including enol triflates,[7] tosylates,[10] phosphates,[11] pivalates,[12] and, most recently, acetates.[13] Nonetheless, very few of these studies have specifically focused on the retention of the geometry of the acyclic olefin across a broad range of substrates in the final substituted alkene products. In some cases, this may be directly attributed to the lack of methods that control the acyclic double bond geometry in the starting electrophiles. Enol triflates and tosylates are the exception.[14] Highly stereoselective syntheses have been reported for these electrophiles, and translation of the stereochemistry in these substrates to the final olefin geometry in the resulting substituted acrylates has been demonstrated in iron-catalyzed cross-coupling reactions with Grignard reagents.[7,10] However, the high cost, environmental impact, and/or low atom efficiency of these sulfonate electrophiles counterbalances the advantages of iron catalysis.

Surprisingly, enol carbamates have yet to be fully exploited in Fe-catalyzed cross-coupling reactions despite the fact that aryl carbamates have been shown to be excellent substrates in these reactions.[15] Specifically, N,N-dimethyl-substituted enol carbamates could have distinct advantages in Fe-catalyzed cross-coupling reactions over their oxygen-based electrophilic counterparts (Scheme 1). Herein, we report a practical and highly stereoselective Fe-catalyzed cross-coupling reaction between readily available stereodefined *N*,*N*-dimethyl enol carbamates and Grignard reagents yielding tri- and tetrasubstituted acrylates.

To develop this approach effectively, we first needed to devise a simple method that would allow us to easily access either the (*E*)- or (*Z*)-enol carbamates ideally from a common precursor. Based on our previous experience using acetoacetate derivatives for the synthesis of stereodefined enol triflates,[14a] we felt that these substrates would also be ideal for the stereoselective synthesis of enol carbamates. Separate reports have appeared for the synthesis of either (*E*)- or (*Z*)-enol carbamates from acetoacetate derivatives but we found that these methods were either not highly stereoselective or completely failed to generate the requisite fully substituted enol carbamates that we wished to pursue.[16] Therefore, we quickly discovered a new general approach to (*E*)-enol carbamates and developed a slightly modified procedure for the synthesis of (*Z*)-enol carbamates based on previous



Advantages:
- Stereoselective synthesis of both (*E*)- and (*Z*)-enol carbamates now available (part of this work)
- Gaseous byproducts (CO_2 and Me_2NH) minimize purification burden and reduce waste volume
- Low costs, good atom economy, and low environmental impact

Scheme 1. Stereodefined enol carbamates as attractive oxygen-based electrophiles for iron-catalyzed cross-coupling reactions with Grignard reagents.

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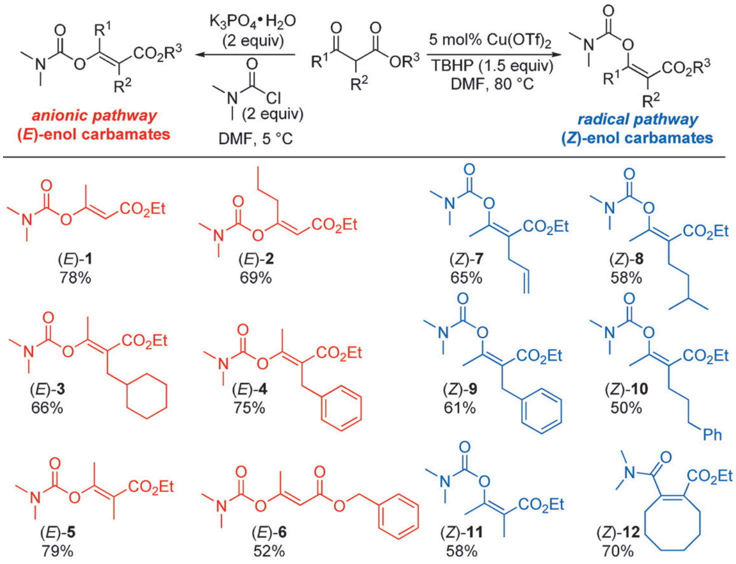
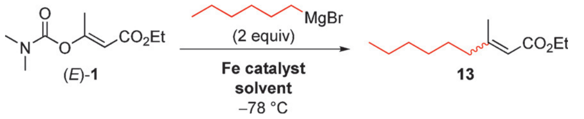


Scheme 2. Selected examples for the stereoselective synthesis of highly substituted (*E*)- and (*Z*)-enol carbamates from readily available acetoacetate derivatives.

work.[16a] A few representative examples are shown in Scheme 2.

With a stereoselective synthesis of enol carbamates in hand, we embarked on a systematic screening approach to identify optimized reaction conditions for the Fe-catalyzed cross-coupling with Grignard reagents. A summary of these efforts using (*E*)-**1** as the model substrate and *n*-hexylmagnesium bromide as the cross-coupling partner is presented in Table 1. We were pleased to find that several Fe^{III} salts were effective in catalyzing the cross-coupling reaction, with the only exception being $FeF_3{\cdot}3H_2O$. Furthermore, as originally discovered by Cahiez and Avedissian,[6] the addition of NMP as a co-solvent provided a noticeable increase in yield and had an even more dramatic positive impact on stereoselectivity. We ultimately elected $FeCl_3$ as our catalyst of choice, a THF/NMP ratio of 7.5:1, and a reaction temperature of −78 °C as our most general reaction conditions to apply to a broad range of (*E*)-enol carbamates. Interestingly, as will be discussed later, we found that NMP was not required as a co-solvent to obtain high yields and stereoselectivities when (*Z*)-enol carbamates were employed.

Table 1: Selected optimization results for the iron-catalyzed cross-coupling between (*E*)-**1** and hexylmagnesium bromide.[a]



Entry	Catalyst	Solvent	Yield [%]	E/Z[d]
1	Fe(acac)$_3$	THF[b]	81	1:1
2	$FeCl_3$	THF[b]	74	2:1
3	Fe(acac)$_3$	THF/NMP[c]	90	15:1
4	$FeBr_3$	THF/NMP[c]	91	45:1
5	$FeF_3{\cdot}3H_2O$	THF/NMP[c]	trace	N/A
6[e]	$FeCl_3$ (99.99 %)	THF/NMP[c]	94	> 50:1
7	**$FeCl_3$**	**THF/NMP**[c]	**96**	**> 50:1**

[a] Reactions were performed at −78 °C with the Fe catalyst (5 mol %), (*E*)-**1** (1 equiv), and *n*-hexylMgBr (2 equiv) unless otherwise stated. [b] Reactions were performed at 0.8 M. [c] Reactions were performed at 0.07 M with a THF/NMP ratio of 7.5:1. [d] Determined by HPLC analysis. [e] The success of high-purity $FeCl_3$ supports the notion that other low-level metal impurities (e.g., Pd) are not responsible for catalysis. acac = acetylacetonate, NMP = *N*-methyl-2-pyrrolidinone.

Table 2 summarizes our substrate scope to date with more elaborate (*E*)-enol carbamates and a variety of Grignard reagents. A wide range of functional groups were tolerated, including acetals (**27**), ethers (**37**), silanes (**38**), primary bromides (**39**), terminal alkynes and alkenes (**20**, **40**, **41**), and protected amines (**42**). What perhaps is most important to highlight is that the current method is very amendable to the stereoselective synthesis of acyclic tetrasubstituted acrylates (i.e., **20**–**24**, **31**, **32**) where other Fe-catalyzed methods have yet to show their full potential. Whereas most of the products shown in Table 2 have no precedence in the literature, several of them had been synthesized previously but with very poor stereoselectivity. For example, the synthesis of **13** has previously been achieved in 80 % yield and an *E*/*Z* ratio of 3.8:1 by employing a solvent-free Horner–Wadsworth–Emmons approach.[17] The Fe-catalyzed cross-coupling between (*E*)-**1** and hexylmagnesium bromide, for comparison, gave **13** in an *E*/*Z* ratio of 65:1 and 96 % yield (Table 2). Olefin **26** is an important precursor to the fragrances phenoxanol, citralis, and citralis nitrile, and the starting olefin geometry plays a critical role in the asymmetric synthesis of these chiral fragrant molecules.[18] The highest stereoselectivity for the synthesis of **26** that we could find was achieved by a reductive debromination of the corresponding vicinal dibromide with an *E*/*Z* ratio of 5.25:1 with an overall yield of 65 %.[19] As can be seen in Table 2, the Fe-catalyzed cross-coupling between (*E*)-**1** and phenethylmagnesium chloride gave **26** in an *E*/*Z* ratio of > 50:1 and 82 % yield. Finally, this method is readily scalable, with a 20 mmol scale reaction yielding almost identical yields and stereoselectivities as the same reaction on 1 mmol scale (see compound **18** in Table 2).

Next, we turned our attention to exploring the scope with (*Z*)-enol carbamates. The culmination of our efforts with these substrates is summarized in Table 3. We are pleased to report that all of the fully substituted acyclic (*Z*)-carbamates that we have explored to date reacted with a very high level of stereoselectivity in the Fe-catalyzed cross-coupling reaction with alkyl Grignard reagents. In fact, the reaction is stereospecific for many of the products as we were unable to detect the corresponding *E* isomers by ^{1}H NMR spectroscopy or LC/MS. Furthermore, we observed that NMP is not required to obtain high yields or stereoselectivities for these substrates.[20] We believe that the proximity of the carbonyl oxygen atom in the *Z* stereoisomers plays a similar role as NMP in stabilizing an intermediate organoiron species, thus obviating the need for any co-solvent. As a result, all of the products shown in Table 3 except for **53**, **54**, and **55** did not require any chromatographic purification. At this point, we would also like to highlight several products that demonstrate the

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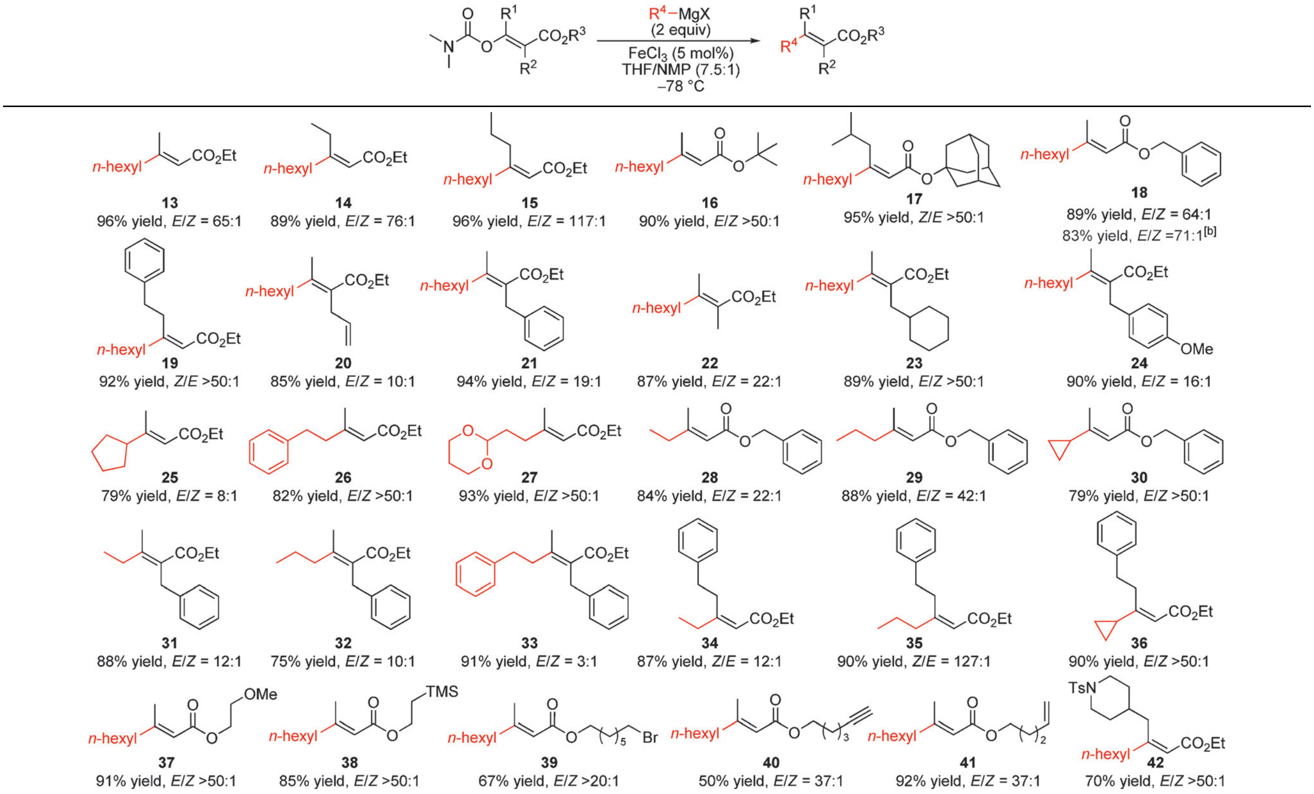
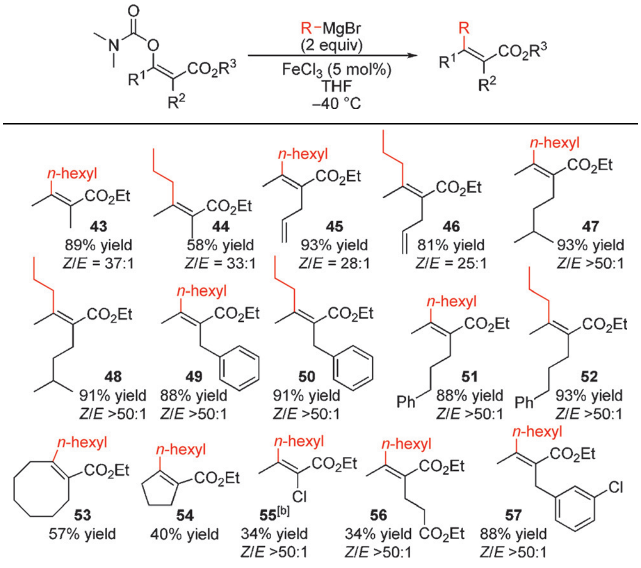
Table 2: Preliminary substrate scope for the iron-catalyzed cross-coupling of (*E*)-enol carbamates and Grignard reagents.[a]



[a] Reactions were performed at a concentration of 0.06 M with the reaction times ranging from 4–24 h. The yields reported are isolated yields with the isomeric ratios determined by either LC/MS or ^{1}H NMR analysis. [b] On 20 mmol scale.

Table 3: Preliminary substrate scope for the iron-catalyzed cross-coupling of (*Z*)-enol carbamates and Grignard reagents.[a]

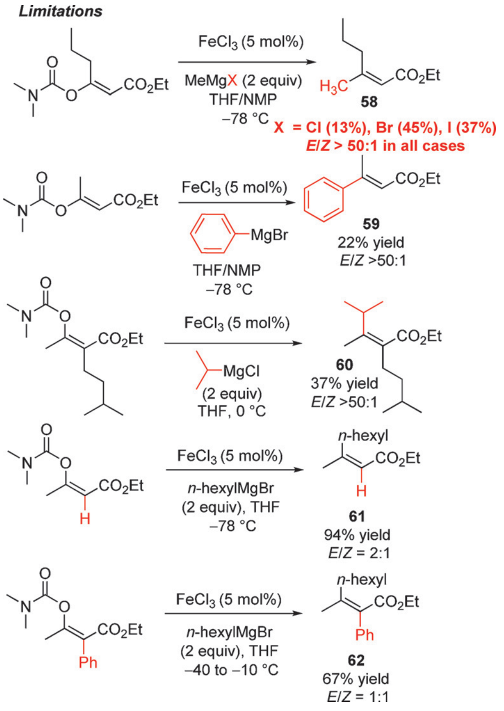


[a] Reactions were performed at a concentration of 0.2 M with reaction times ranging from 2–6 h. The yields reported are isolated yields with the isomeric ratios determined by either LC/MS or ^{1}H NMR analysis.
[b] Reaction performed at 0 °C.

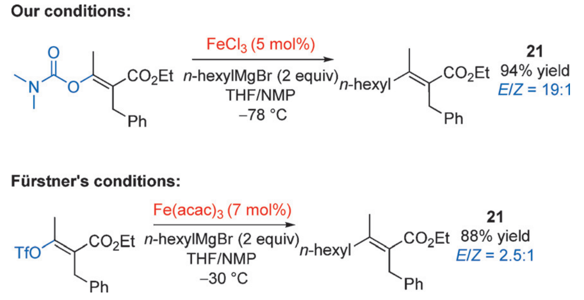
tolerability of this method. As far as we are aware, α-chloroacrylate **55** represents the only example demonstrating the selective Fe-catalyzed cross-coupling of an oxygen-based electrophilic group over a vinylic halide. Furthermore, the high yield obtained with **56** indicates that even functional groups that are highly reactive towards Grignard reagents, in this case alkyl esters, are compatible with this method.

Finally, we would like to highlight the limitations that we have encountered at this stage of development. Although methyl, acyclic secondary, and aryl Grignard reagents provide the corresponding cross-coupled products with high stereoselectivities, the yields are much lower than those with other Grignard reagents (Scheme 3).[21] Furthermore, (*Z*)-enol carbamates lacking substitution at the α-carbon atom participate in the cross-coupling event in high yields but interestingly with very low levels of stereocontrol (Scheme 4). However, one discrete advantage of the current method over the previously reported Fe-catalyzed cross-coupling between enol triflates and Grignard reagents is evident when analyzing the stereochemical fidelity of the resulting fully substituted acrylate **21** obtained by each approach. Whereas both methods provide the product in high yield, the current approach delivers the product in much higher stereochemical purity ($E/Z = 19:1$) than starting with the enol triflate ($E/Z = 2.5:1$; Scheme 4).[22]

In conclusion, we have developed a highly stereoselective iron-catalyzed cross-coupling reaction between stereodefined enol carbamates and Grignard reagents to access tri- and tetrasubstituted acrylates. In turn, these richly functionalized olefins can further be exploited in a multitude of classical and



Scheme 3. Known limitations of the iron-catalyzed cross-coupling reaction between stereodefined enol carbamates and Grignard reagents.



Scheme 4. Comparison of our current approach with enol carbamates with a previously reported method based on enol triflates.

modern transformations that take advantage of the high stereochemical purity afforded by this approach.

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Keywords: acrylates · cross-coupling · enol carbamates · iron catalysis · stereoselective synthesis

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[20] A reviewer suggested the possibility of residual Cu^{II} salts catalyzing the cross-coupling reaction with (*Z*)-enol carbamates as $Cu(OTf)_2$ is used in the synthesis of these substrates. We have attempted several cross-coupling reactions with both (*E*)- and (*Z*)-enol carbamates in the absence of Fe^{III} salts and never observed product formation.

[21] Several attempts to successfully cross-couple benzylic Grignard reagents failed with both (*E*)- and (*Z*)-enol carbamates.

[22] Although $FeCl_3$ is hygroscopic, all of the reactions highlighted in this manuscript used $FeCl_3$, which was weighed out on the benchtop with no special precautions to dry it before use.

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