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Direct Catalytic Asymmetric Vinylogous Additions of α,β- and β,γ-Butenolides to Polyfluorinated Alkynyl Ketimines

Barry M. Trost,[a] Chao-I (Joey) Hung,[b] and Manuel J. Scharf [b]

Abstract: We report a Zn-ProPhenol catalyzed asymmetric Mannich reaction between butenolides and polyfluorinated alkynyl ketimines to obtain vinylogous products featuring two contiguous tetrasubstituted stereogenic centers. Notably, this is the first successful use of ketimines in the ProPhenol Mannich process, and the reaction offers a new approach for the preparation of pharmaceutically relevant products possessing trifluoromethylated tetrasubstituted alkylamines. The reaction can be performed on large scale with reduced catalyst loading without impacting its efficiency. Moreover, the acetylene moiety can be further elaborated using various methods.

Fluorinated functional groups have become ubiquitous among agrochemicals and pharmaceuticals.[1] The incorporation of such motifs into biologically active molecules can modulate properties including metabolic stability, binding affinity, solubility, lipophilicity, and basicity/acidity of the neighboring groups.[2] Therefore, installing fluorinated functional groups in drug candidates is an important objective in the pharmaceutical industry.[3] Among these fluorinated compounds, chiral trifluoromethylated tetrasubstituted alkylamines are privileged structural motifs found in numerous bioactive molecules (Figure 1).[4-5] As a result, developing a direct catalytic asymmetric pathway to compounds featuring this moiety is of prime importance.

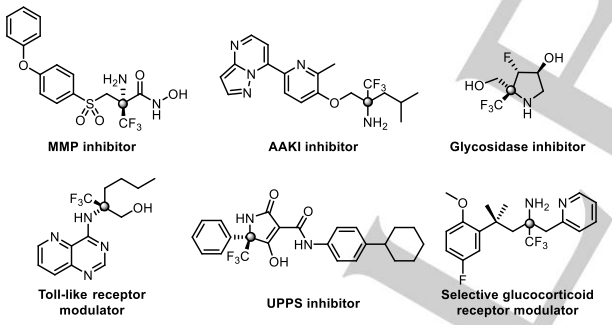
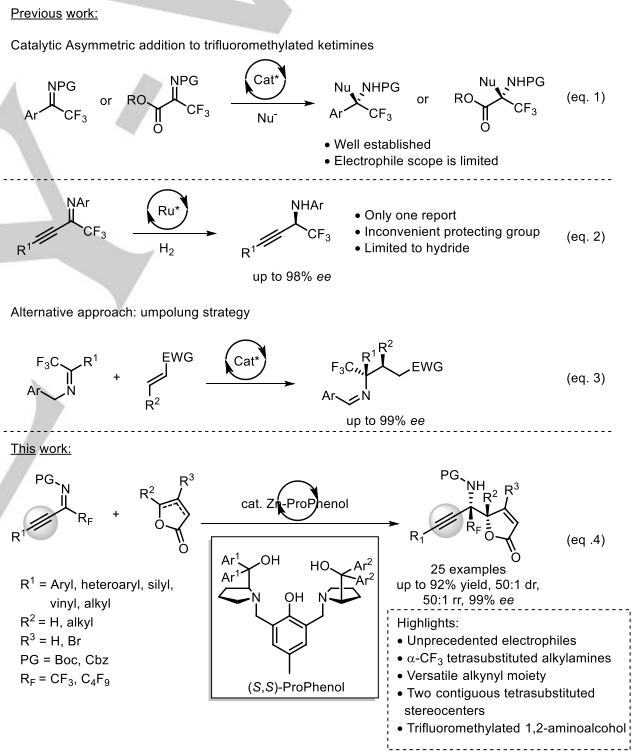


Figure 1. Selected biologically active products featuring a trifluoromethylated tetrasubstituted alkylamino motif.

One effective strategy to generate these chiral tetrasubstituted alkylamines is to perform an asymmetric C-C bond formation between a carbon nucleophile and a polyfluorinated alkyl ketimine. Despite advances in catalytic asymmetric Mannich reactions,[6] ketimines are generally more challenging electrophiles than the corresponding aldimines. The catalytic system must not only overcome the steric hindrance due to having two substituents at the electrophilic center, but also differentiate them for high stereoselectivities. Moreover, the use of fluorinated ketimines as electrophiles is generally restricted to substrates derived from trifluoropyruvates[7] or trifluoromethyl arylketones[8] (eq. 1). An alternative strategy for generating chiral trifluoromethyl amines is an umpolung approach pioneered by Deng, in which ketimines act as nucleophiles upon inversion of polarity (eq. 3).[9]



Scheme 1. Catalytic asymmetric synthesis of chiral trifluoromethylated amines from ketimines. EWG = electron withdrawing group, PG = protecting group, Boc = *tert*-butyloxycarbonyl, Cbz = carboxybenzyl.

We envisioned using alkynyl ketimines as electrophiles for several advantages (eq. 4). First, in addition to the electron-withdrawing fluorinated group, the sterically less demanding alkyne and its higher *s*-character should facilitate the desired nucleophilic addition. Moreover, the steric difference between the alkynyl and the fluoroalkyl group would, in principle, allow us to generate ketimines of a single geometry, which has shown to be critical for high stereoselectivities.[7,8,10] Most importantly, the higher degree of unsaturation of alkynes compared to alkenes and alkanes allows a wide range of reactivities leading to various structural motifs.[11] To the best of our knowledge, there is only

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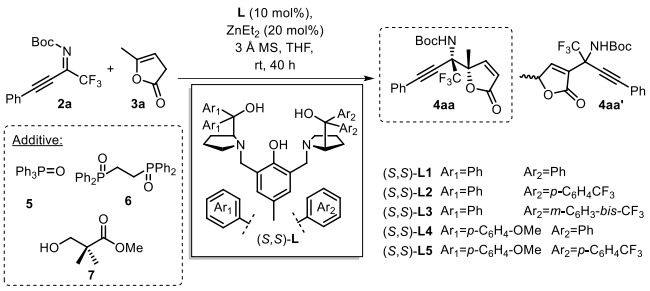
one report using ketimines bearing a *N*-aryl group in asymmetric catalysis, a Ru-catalyzed hydrogenation developed by Zhou (eq. 2).[12] In this context, we sought to develop a process utilizing more complex carbon nucleophiles and incorporating more cleavable protecting groups, such as Boc or Cbz.

Recently, our group has utilized Zn-ProPhenol complexes as effective catalysts in numerous asymmetric Mannich reactions using *N*-carbamoyl aldimines as electrophiles.[13] The excellent coordinating properties of the carbamate protecting groups renders the corresponding aldimines outstanding reaction partners. In this context, we wondered if it was possible to expand the scope of electrophiles to the carbamoyl ketimines.

Table 1. Reaction optimization.[a]

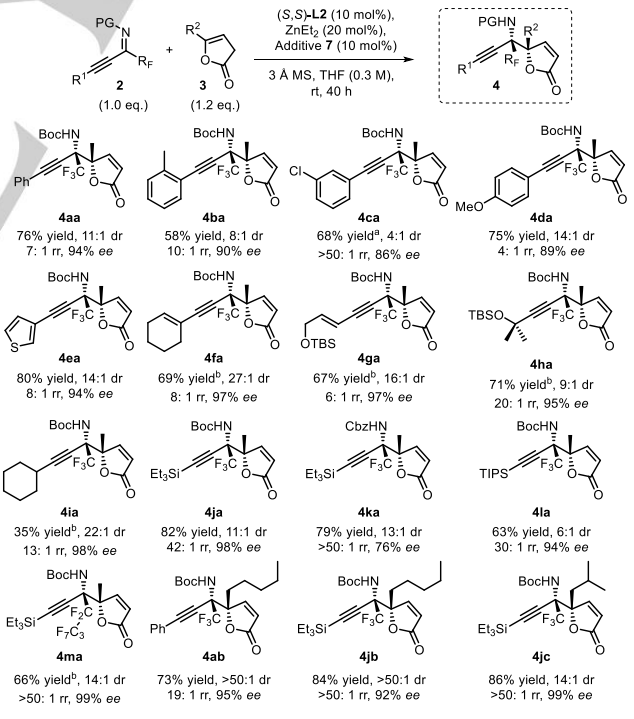


Entry	Ligand	Solvent	Additive	Yield[b]	dr[c]	*ee*[d]	rr[e]
1	**L1**	THF	-	68%	5:1	91%	n.d.
2	**L1**	PhMe	-	48%	3:1	33%	11:1
3	**L1**	Et_2O	-	33%	3:1	33%	5:1
4	**L2**	THF	-	46%	7:1	91%	n.d.
5	**L3**	THF	-	46%	6:1	91%	n.d.
6	**L4**	THF	-	61%	2.5:1	64%	n.d.
7	**L5**	THF	-	61%	5:1	84%	n.d.
8	**L2**	THF	**5**[f]	63%	5:1	87%	7:1
9	**L2**	THF	**6**[g]	78%	6:1	88%	5:1
10	**L2**	THF	**7**[g]	76%	11:1	94%	7:1

[a] Reaction conditions: 1 eq. of **2a**, 1.2 eq. of **3a,** 10 mol% of **L,** 20 mol% Et_2Zn (1 M in hexanes) at rt in solvent (0.3 M) for 40 h. [b] Isolated yield. [c] Determined by ^1H and ^{19}F NMR. [d] Determined by chiral HPLC. [e] rr = regio-ratio between **4aa** and **4aa'** determined by ^{19}F NMR. [f] 20 mol% was used. [g] 10 mol% was used. MS = molecular sieve, THF = tetrahydrofuran.

Having settled on fluorinated alkynyl ketimines as electrophiles due to the structural versatility of subsequent elaboration of the alkyne, we chose to use butenolides as nucleophiles for several reasons (eq. 4). First, nitrogen-containing butenolides are common bioactive motifs and our approach would offer access to fluorinated analogs.[14] Furthermore, the butenolides could be unmasked to give access to 1,2-aminoalcohols, another pharmaceutically and synthetically relevant motif.[15] In addition, our recent success shows that Zn-ProPhenol can activate butenolides of various substitutions for reaction with aldimines[13c]; whereas other Mannich methods mainly restricted to α-angelica lactone[16] or 2(*5H*)-furanone[17], or require pre-activation to the siloxyfurans.[18] However, our process must overcome the potential 1,4-addition onto the alkynyl ketimines as well as the steric hindrance during the construction of two contiguous tetrasubstituted stereocenters, which remains rare and difficult in modern asymmetric catalysis.[19]

We initiated our studies using ketimine **2a** and α-angelica lactone **2a** (Table 1). Ketimines **2** can be easily prepared from the readily available ketones **1** (see SI). One geometric isomer was observed for all cases, presumably due to the steric difference between the fluoroalkyl and alkynyl substituents.[20] In the presence of 10 mol% catalyst using commercially available **L1** in THF, the desired Mannich adduct **4aa** was obtained in 68% yield and 91% *ee* (entry 1). This result shows that our catalyst is indeed sufficiently reactive to generate two contiguous tetrasubstituted stereocenters. Switching the solvent to either toluene or Et_2O decreased the yield and *ee* (entry 2 & 3). To improve the diastereoselectivity, we examined non-C_2 symmetric ligands. Using ligand **L2**, the diastereoselectivity was increased to 7:1 without reducing the enantioselectivity (entry 4), whereas other electronically differentiating ligands **L3-5** generally gave inferior results (entry 5-7). Although using phosphine oxides as additives (**5** and **6**) did not alter the stereoselectivities, less decomposition of the starting materials was observed, allowing us to better identify and monitor the formation of regioisomer **4aa'** (entry 8 & 9). Using alcohol **7** as the additive gave the best result (76% yield, 11:1 dr, 94% *ee*, 7:1 rr) and these conditions were applied for all subsequent reactions (entry 10).



a. Reaction performed at 4°C. b. 20 mol% catalyst was used.

Scheme 2. Scope of ketimines with β,γ-butenolides. TIPS = triisoppropylsilyl, TBS = *tert*-butyldimethylsilyl

With optimized conditions in hand, a variety of fluorinated ketimines were evaluated using β,γ-butenolides (Scheme 2).

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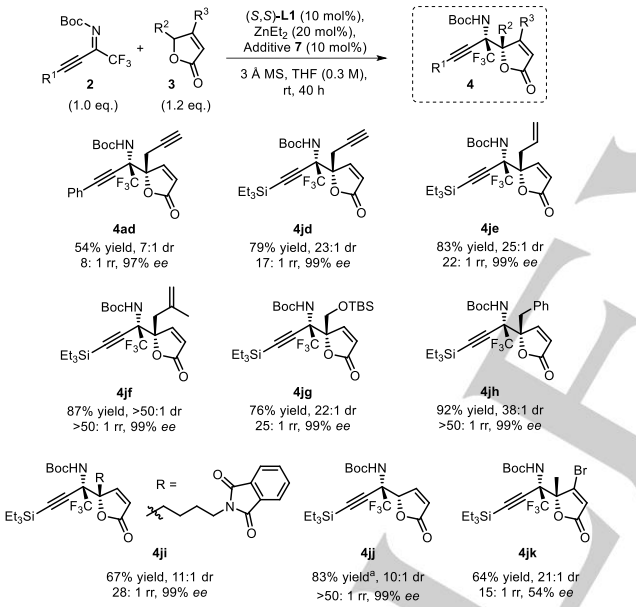
Substitution at the *ortho*-, *meta*-, or *para*-position of aryl-bearing ketimines is well tolerated, affording adduct **4ba**, **4ca**, and **4da** in up to 76% yield and 94% *ee*. Notably, heteroaryl ketimine **2e** also gave good results, affording **4ea** in 80% yield, 14:1 dr, and 94% *ee*. Using vinyl-substituted ketimines, adducts **4fa** and **4ga** were obtained in excellent diastereo- and enantioselectivity. Aliphatic substituents are also tolerated despite having lower reactivity. Pleasingly, the low reactivity can be remedied by increasing the catalyst loading, affording **4ha** and **4ia** in 95% *ee* and 98% *ee*, respectively. Using TES-protected ketimine **2j**, product **4ja** was obtained in 82% yield, 11:1 dr, and excellent regio- and enantioselectivity. This result is particularly attractive since the silyl group can be cleaved to release the terminal alkyne for further structural manipulations. *N*-Cbz ketimine **2k** was also successfully employed. Despite a moderate *ee* of 76%, **4ka** was obtained as a single regioisomer in 79% yield. Importantly, the reaction is not restricted to CF_3-substituents. With nonafluoroalkyl ketimine **2m**, **4ma** was obtained as a single regioisomer in 66% yield and excellent 99% *ee*. Finally, larger substituents than methyl at the 5-position of β,γ-butenolides are well tolerated, affording **4ab**, **4jb**, and **4jc** with excellent regio-, diastereo-, and enantioselectivity.

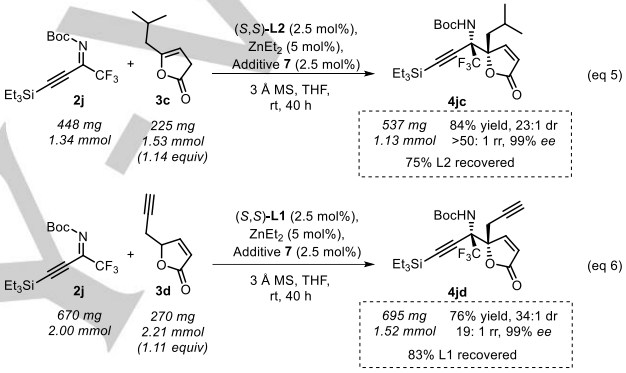


a. Reaction performed at -10°C for 24 h using **L2** as ligand.

Scheme 3. Scope of α,β-butenolides.

Under similar reaction conditions with commercially available **L1**, we are pleased to report that a variety of α,β-butenolides can be utilized (Scheme 3). Propargyl butenolide **3d** reacted with both phenyl **2a** and silyl **2j** ketimines, generating **4ad** and **4jd** in good yields and excellent *ee*'s. The adducts contain two chemically distinguished alkynes, which can be selectively functionalized. Allyl substrate **3e** also gave competent results, affording **4je** in 83% yield and 99% *ee*. Introducing a bulky isobutenyl group had no effect on the course of the reaction, yielding **4jf** as a single diastereo- and regioisomer with 99% *ee*. Protected alcohol and amine are also tolerated, affording **4jg** and **4ji** with 99% *ee*. Additionally, using **L2** at -10 °C, commercially available furanone **3j** successfully reacted with **2j** to afford **4jj** as a single regioisomer with 99% *ee*. A good dr of 10:1 was observed despite the presence of a highly epimerizable α-proton. Introducing a bromo substituent adjacent to the nucleophilic site offered **4jk** in 64% yield, 21:1 dr, and moderate 54% *ee*, which can be used for cross coupling reactions.

In addition to providing valuable products with broad scope and high enantiomeric purity, millimole-scale reactions could be performed utilizing both α,β- and β,γ-butenolides at decreased catalyst loading without impacting yield or selectivity. Using 2.5 mol% Zn-(*S*,*S*)-**L2**, β,γ-butenolide **3c** reacted with ketimine **2j** to afford **4jc** in 84% yield, 23:1 dr, and 99% *ee* (eq. 5). Notably, 75% of ligand **L2** can be recovered via chromatography during product purification, mitigating the relatively high catalyst loading in some examples. On the other hand, α,β-butenolide **3d** reacted with ketimine **2j** to afford **4jd** in 76% yield, 34:1 dr, and 99% *ee* using 2.5 mol% of Zn-(*S*,*S*)-**L1** (eq. 6). After an acid-base extraction, 83% of commercially available **L1** was recovered.[13a]



Scheme 4. Millimole-scale reactions and recovery of ligands.

Highlighting the versatility of the alkyne, the Mannich adducts **4** were converted into various trifluoromethylated tetrasubstituted alkylamines (Scheme 5). Treatment of **4jc** with $NaBH_4$ and $NiCl_2$ selectively reduced the butenolide alkene to afford saturated lactone **8** while leaving the alkynyl group intact. The Boc group was removed with TFA, liberating free amine **9** quantitatively. Treatment of **4jc** with TBAF cleaved the silyl group, generating terminal acetylene **10**, which can serve as an effective handle. For example, a Pd-catalyzed alkyne-alkyne coupling reaction[21] joined **10** with methyl 2-octynoate to afford enyne **11** in 86% yield as a single geometric isomer. A Sonogashira reaction between **10** and 5-iodo-2'-deoxyuridine generated nucleoside derivative **12** in 72% yield with all other functional groups intact. Under hydrogenation conditions, both the alkyne and butenolide olefin were reduced to generate fully saturated **13** in 97% yield.

Diyne **4jd** was also functionalized into various structures. First, a Cu-catalyzed 1,3-dipolar cycloaddition was performed to couple **4jd** with benzyl azide to generate the corresponding triazole **14** in 84% yield. Notably, the reaction proceeded selectively at the terminal acetylene in the presence of two other possible dipolarophiles. In the presence of 2.5 mol% $IPrAuNTf_2$, a *5-exo-dig* cyclization occurred to furnish spiroheterocycle **15** in 98% yield. Upon removal of the silyl group from **4jd**, a Ru-catalyzed [2+2+2] cycloaddition[22] with 1-hexyne generated spirolactone **17** with 3:1 rr, which was further purified via chromatography to afford

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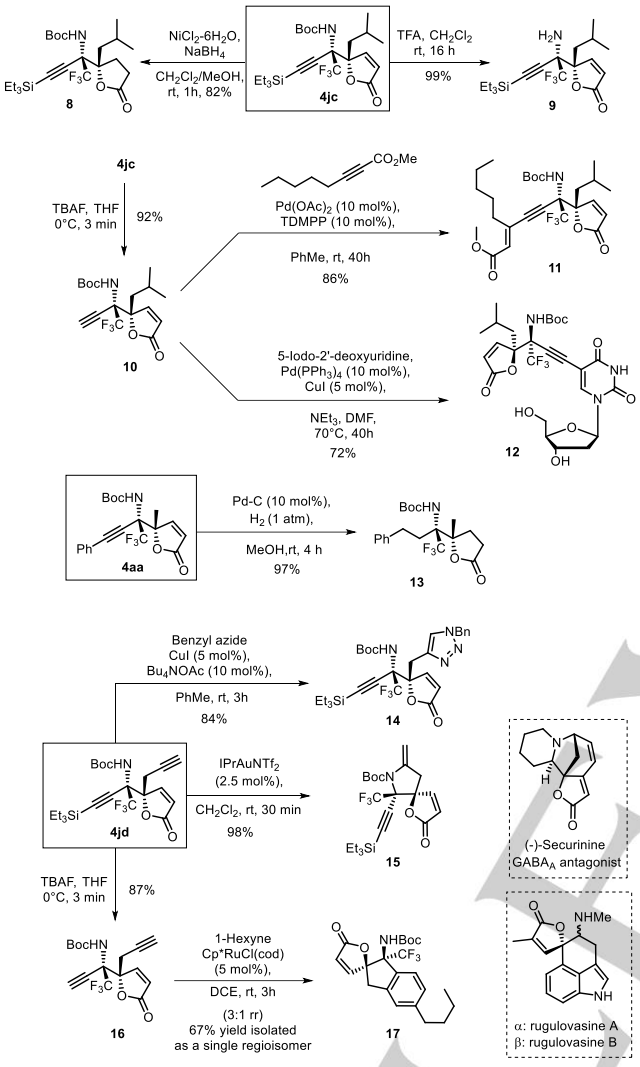
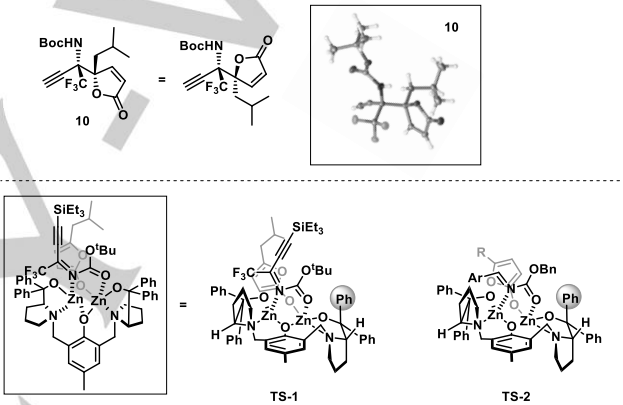
17 in 68% yield as a single isomer. Notably, such spirolactone motifs are ubiquitous in a variety of biologically active and naturally occurring butenolides, and our process can be potentially applied to generate their fluorinated analogs.[14]



Scheme 5. Synthetic applications. TFA = trifluoroacetic acid, TDMPP = tris(2,6-dimethoxyphenyl)phosphine, TBAF = tetrabutylammonium fluoride, DMF = Dimethylformamide, DCE = 1,2-dichloroethane.

The absolute configuration of our vinylogous Mannich products was unambiguously determined by the crystal structure of **10 (**Scheme 6**)**.[23] The stereochemistry was assigned to all products by analogy. Interestingly, in contrast to the *syn*-Mannich adducts obtained previously using *N*-Cbz aldimines[13c], an opposite sense of chirality at the butenolide center was observed. To rationalize this, proposed transition states of these two reactions are illustrated (**TS-1** & **-2**). Since the nitrogen-bearing carbon retains the same chirality, we propose identical two-point binding of the imine to the catalyst for both methods. Similar to the orientation adopted by the aryl aldimine, the ketimine favors the conformation shown to minimize steric interactions between the pseudo-axial phenyl unit (highlighted) and the bulky trifluoromethyl group. The butenolide, however, adopts an orientation to avoid the electronic repulsion between the endocyclic oxygen and the trifluoromethyl substituent, which is absent in the aldimine case.

In conclusion, our Zn-ProPhenol system efficiently catalyzes the direct vinylogous addition of various substituted butenolides to a variety of fluorinated alkynyl *N*-carbamoyl ketimines with excellent enantio- (up to 99% *ee*), diastereo- (up to >50:1 dr), and regioselectivity (up to >50:1 rr). This is the first report of the ProPhenol system utilizing ketimines as electrophiles and overcoming the steric repulsion associated with the generation of two contiguous tetrasubstituted stereocenters. This is also the first report utilizing these unprecedented substrates for any type of transformation. A broad range of functionalized α,β- and β,γ-butenolides are viable nucleophiles without any pre-activation. Most importantly, this method generates valuable fluorinated tetrasubstituted alkylamines that are present in numerous bioactive compounds, and the alkynyl moiety can be easily transformed into different skeletal types.



Scheme 6. X-ray crystallography and proposed transition states.

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Keywords: asymmetric catalysis • enantioselectivity • fluorine • chiral butenolides • zinc

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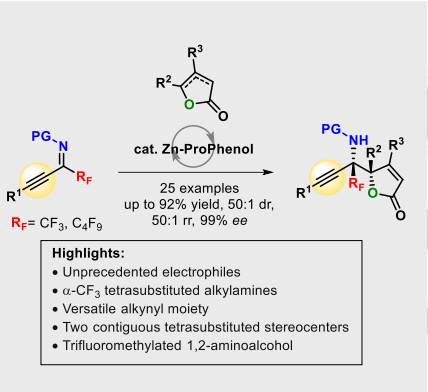

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