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Letter

Enabling Cyclization Strategies through Carbonyl-Ylide-Mediated Synthesis of Malonate Enol Ethers

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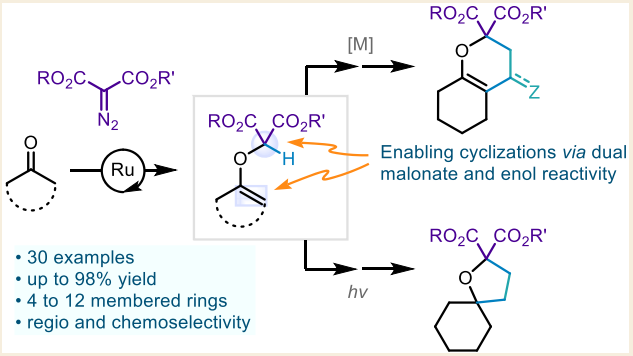
ABSTRACT: Malonate enol ethers are afforded in one step by condensation of cyclic ketones with α-diazomalonates under $[CpRu(CH_3CN)_3][BAr_F]$ catalysis. The dual reactivity of these 2-vinyloxymalonates can be used to expand the classical range of cyclizations derived from carbonyl ylide intermediates.



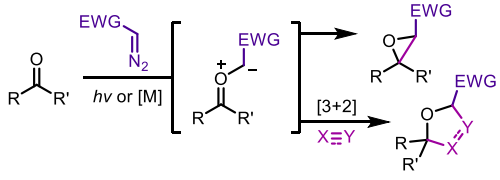
KEYWORDS: *Carbonyl ylide reactivity, CpRu catalysis, Diazo decomposition, Enol ethers, Malonate*

Decompositions of diazo derivatives in the presence of *Lewis* bases is a recognized strategy to generate ylides efficiently.[1−9] With aldehydes and ketones, carbonyl ylides are formed, usually under light irradiation or metal-catalyzed conditions.[6,10−26] Traditionally, these reactive intermediates condense to form epoxides or act as 1,3-dipoles in intra- and intermolecular cycloadditions that form five and sometimes larger oxacycles (Scheme 1, top). These (cascade) cyclizations constitute useful and practical synthetic strategies for making (poly)heterocycles.[11] Herein, in a new development in the field of carbonyl ylides, we report the general reactivity of ketones **1** and α-diazodiesters **2** to generate 2-vinyloxymalonates **3** (Scheme 1, bottom). The condensation is general and uses principally the complex $[CpRu(CH_3CN)_3][BAr_F]$ (BAr_F: tetrakis[3,5-bis(trifluoromethyl)phenyl]borate, [**4**][BAr_F]) as the catalyst. Malonate enol ethers **3** of different ring sizes and geometries are obtained (30 examples), often as single regioisomers, and their mechanism of formation is elucidated based on density functional theory (DFT) calculations. In terms of applications, these compounds behave as versatile three- or four-atom building blocks for annulations under Lewis-acid-mediated conditions or visible-light photoredox catalysis. Several fused and spiro-heterocycles were generated to demonstrate the potential of derivatives **3** as synthetic intermediates. This type of reactivity can be used to expand the classical range of cyclizations derived from carbonyl ylide intermediates.

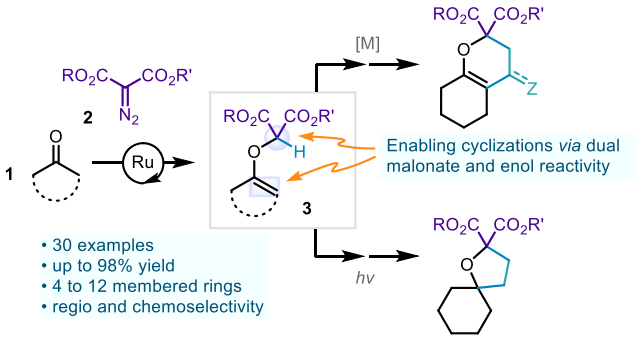
The direct formation of enol ethers from ketones and diazo reagents has been previously reported in only a few instances

Scheme 1

Usual Diazo Decomposition / Carbonyl Ylide Formation and Reactivity



This Study: Carbonyl Ylide Mediated Synthesis of Malonate Enol Ethers for Subsequent Orthogonal Annulation Strategies



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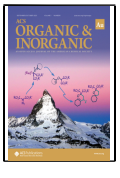
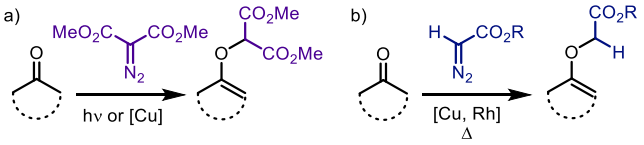


(Scheme 2). Jones and collaborators demonstrated that α-diazodiesters react under photoirradiation with cyclopentanone or acetone to generate the corresponding malonate enol ethers (two examples, 18−22%).[27] Synthesis of compounds **3** under Cu(II) catalysis has also been reported, with the yields of products being however unknown.[28] With monofunctionalized diazoacetates, enol derivatives can be isolated from the reactions with ketones under copper or dirhodium catalysis.[29−33] We decided to focus our attention on malonate **3** as diazo reagents substituted with two electron-withdrawing groups (EWGs) such as diazomalonates are among the most stable diazo derivatives[34] yet are amenable to decomposition reactions that form very reactive electrophilic carbenes.[35]

Scheme 2

Previous studies: *Jones, Talinli, Kharasch, Langrebe, Corey* (refs. 27-33)

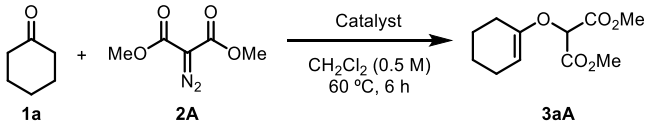


In the context of acceptor−acceptor diazo reagent decompositions, combinations of CpRu [**4**] salts and diimine ligands can be used as catalysts, and original reactivities are then afforded for the resulting metal carbenes.[36] For instance, α-diazo-β-ketoesters react with aldehydes and ketones but also lactones and cyclic carbonates to yield stable dioxolene adducts exclusively.[37,38] With α-diazodiesters **2**, such a dioxolene reactivity had not been characterized. We decided to study the reactions of compounds **1** and **2** and harness the potential of either intermediates or products.

Initial experiments were performed by adding dimethyl diazomalonate **2A** (3 equiv) to a solution of cyclohexanone **1a** (0.3 mmol) in CH_2Cl_2 in the presence of CuI (10 mol %) (Table 1, entry 1). After 6 h at 100 °C, almost full conversion of ketone **1a** was achieved and enol ether **3aA** was identified as the major product of a complex crude reaction mixture (^{1}H NMR yield, 27%). With dirhodium catalysts, $Rh_2(oct)_4$ and $Rh_2(TFA)_4$, enol ether **3aA** was formed in 23 and 63% NMR yields, respectively (entries 2 and 3), with the products of double carbene additions being nevertheless observed in the crude mixtures, sometimes as major adducts (eq S1).[39] Based on previous studies,[36−38,40−42] combinations (1:1) of [CpRu-$(CH_3CN)_3$][X] or [**4**][X] salts and 1,10-phenanthroline were tested as decomposition catalysts. Both [**4**][PF_6] and [**4**]-[BAr_F] complexes afforded, under these conditions, **3aA** in 41 and 58% yields, respectively (entries 4 and 5);[43,44] salt [**4**][BAr_F] was preferred for further studies due to its bench stability. With other diimine ligands, significantly lower yields were obtained (45 and 18%, entries 6 and 7). Full conversion of **1a** and higher yields of **3aA** were achieved in the absence of the phenanthroline ligand (66%, entry 8). Using the tris(benzonitrile)ruthenium(II) complex or increasing sterics and electronics around the cyclopentadienyl ring led to lower yields (entries 9 and 10). Reaction time and stoichiometry were further studied (Tables S1−S3), with 4 h and 1.5 equiv of **2A** being optimal to afford **3aA** in 65% isolated yield. These conditions (entry 11) were selected for the remainder of the studies.

With the optimized conditions in hand, using **2A** as the diazo reagent, the reaction was extended to a variety of ketones, leading to enol ethers **3bA**−**3wA** in yields up to 98% (Scheme 3). Satisfactorily, different ring sizes were amenable (4- to 12-membered cycles, 47−79%), including the transformation of cyclobutanone into the strained cyclobutene analogue **3bA** (47%).[45] Overall, the best yields were obtained with 4-substituted cyclohexanones as substrates (**3fA**−**3hA**, 83−98%).[46] Starting from pyranone **2i**, enol ether **3iA** was formed preferentially, indicating the predominant formation of the carbonyl ylide over the oxonium ylide intermediate. α-Indenone and α-tetralone afforded the corresponding aromatic enol ethers **3jA** and **3kA** in moderate yields (59−62%).

Table 1[a]



1a **2A** **3aA**

entry	catalyst (mol %)	conv (%)	yield (%)
1[b]	CuI (10)	97	27
2	$Rh_2(oct)_4$ (1)	99	23
3	$Rh_2(TFA)_4$ (1)	92	63
4	[**4**][PF_6]/Phen (2.5)	86	41
5	[**4**][BAr_F]/Phen (2.5)	79	58
6	[**4**][BAr_F]/BPhen (2.5)	87	45
7	[**4**][BAr_F]/diMeObpy (2.5)	45	18
8	[**4**][BAr_F] (2.5)	100	66
9	[CpRu(**Ph**CN)$_3$][BAr_F] (2.5)	100	54
10	[**Cp***Ru$(CH_3CN)_3$][PF_6] (2.5)	100	47
11[c]	**[4][BAr$_F$] (2.5)**	**97**	**67(65)**
12	no catalyst, no ligand	nr	nr

[a]Reaction conditions: **1a** (0.3 mmol), **2A** (3 equiv), catalyst, CH_2Cl_2 (0.5 M), 60 °C, 6 h. Yields determined by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard. Conversions are based on starting **1a**. Yields of isolated products are given in parentheses. [b]Reaction performed at 100 °C. [c]1.5 equiv of **2A** and 4 h. Cp = cyclopentadienyl, BPhen = 4,7-diphenyl-1,10-phenanthroline, diMeObpy = 4,4′-dimethoxy-2,2′-bipyridine, Cp* = pentamethylcyclopentadienyl, nr = no reaction.

With β-tetralones, moderate to excellent yields were obtained (**3lA**−**3nA**, 51−97%) in favor of the conjugated products predominantly (regioisomeric ratio, rr > 19:1). Excellent regioselectivity was also obtained from 1,3-cyclohexanedione, forming only conjugated **3oA** (53%, rr > 24:1). A series of α-substituted cyclohexanones was also studied, with some of the reactions requiring longer reaction times for full conversion (6−24 h). With α-methyl and α-phenyl groups, trisubstituted enol ethers **3pA** and **3qA** were formed preferentially (rr 9:1, 66−74%).[47] Such regioselectivity forming the so-called kinetic enol geometry[48] was obtained exclusively for bromo derivative **3rA** (47%, rr > 24:1), the structure of which being confirmed by X-ray diffraction analysis (Scheme 3). Interestingly, in the solid state and most probably in solution (^{1}H NMR spectroscopy), the bromine atom assumes a pseudoaxial position due to a minimization of the allylic 1,2-strain.[49,50] Regioselectivity control was not possible with 3-methylcyclohexanone, menthone, and 2-decalone (*cis*/*trans* 1:1) as reactions resulted in inseparable mixtures of regioisomers (**3sA**−**3uA**, 69−97%). In the first two cases, a slight preference was noticed for the formation of the less hindered enol ethers (rr up to 3:1). Using acyclic 4-heptanone, the corresponding enol **3vA** was prepared in 60% yield, presenting a 5:1 *E*/*Z* ratio.[45] Finally, acetylated

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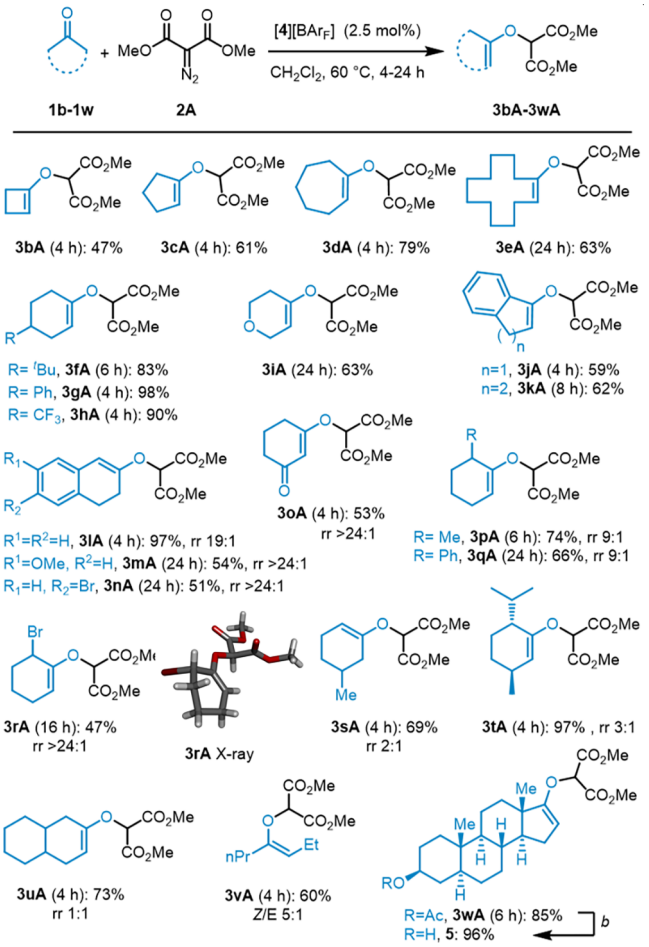
Scheme 3[a]



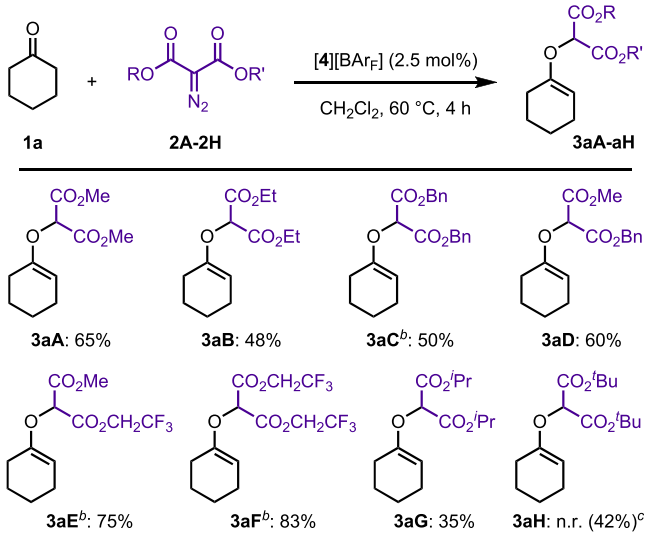
[a]Reaction conditions: **1b−1w** (0.3 mmol), **2A** (1.5 equiv), [**4**][BAr_F] (2.5 mol %), CH_2Cl_2 (0.5 M), 60 °C, 4−24 h. [b]K_2CO_3 (1.3 equiv), MeOH/THF (80/20), 25 °C, 1 h. Major regioisomers or geometrical isomers are drawn.

epiandrosterone reacted chemoselectively on the ketone rather than the ester group[38] to form **3wA** (85%) and without perturbation from the steric hindrance and rigid conformation of the steroid D ring, with the acetate group carried on the A ring being furthermore easily saponified to afford **5** (96%) in the presence of the malonate moiety.[51]

Then, several diazomalonates were investigated (reactants **2B−2H**, Scheme 4). With cyclohexanone **1a** as the substrate, yields ranged from 48 to 65% for **3aA** to **3aD**. With fluorinated **2E** and **2F**, the presence of the electron-withdrawing side chain(s) was beneficial in relation, probably, with a higher reactivity of the electrophilic carbenes (**3aE−3aF**, 75−83%). With [**4**][BAr_F] as a catalyst, a sensitivity to steric hindrance[41] was noticed as diisopropyl product **3aG** was isolated in 35% yield only, and enol ether **3aH** (^{t}Bu) could not be formed. In the latter case, to ensure reactivity, the reaction was performed with $Rh_2(TFA)_4$ to afford the targeted enol ether in 42% isolated yield.

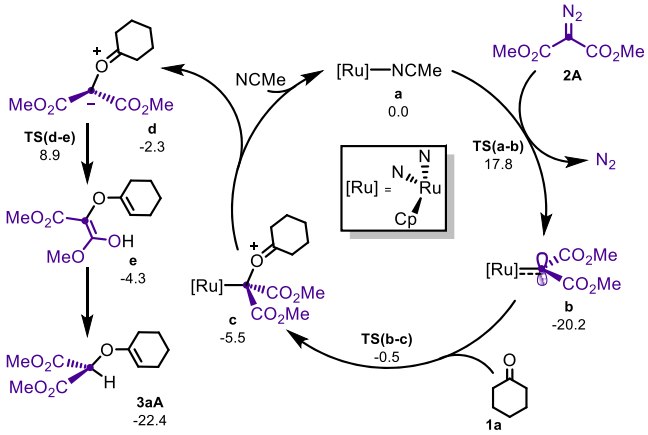
In terms of the mechanism, modeled for the reaction of **2A** to **3aA**, DFT calculations show that the favored pathway starts with the coordination of diazomalonate **2A** to [Ru], as defined in Scheme 5, and its subsequent N_2 extrusion (**TS(a-b)**, $\Delta G^{\ddagger}$ = 17.8 kcal·mol^{-1}). This step yields very stable metal-carbene **b**, lying at −20.2 kcal·mol^{-1}. Intermediate **b** traps cyclohexanone

Scheme 4[a]



[a]Reaction conditions: **1a** (0.3 mmol), **2A−2H** (1.5 equiv), [**4**][BAr_F] (2.5 mol %), CH_2Cl_2 (0.5 M), 60 °C, 4 h. [b]Reaction time 5 h. [c]Reaction performed with $Rh_2(TFA)_4$ (1 mol %) for 6 h at 60 °C.

Scheme 5. Computed Catalytic Cycle[a]



[a]Gibbs energies are given in kcal·mol^{-1}.

1a via **TS(b-c)**, with a relative barrier of 19.7 kcal·mol^{-1}, to achieve the metal-ylide **c**. This rate-determining step is also endergonic by 14.7 kcal·mol^{-1}. This transformation is fortunately upset by the high concentration of **2A** in the media that pushes the process toward the liberation of ylide **d** and initiates a new catalytic cycle (see Figures S7−S12). Free ylide **d** then evolves in an exergonic manner to its enol derivative **e** through a small barrier **TS(d-e)**. For this step **d** → **e**, experimental studies with deuterium-labeled substrates demonstrate the intramolecular nature of the hydrogen transfer (see Schemes S2−S3 and Figures S2−S4). Finally, enol **e** tautomerizes to its diester form, obtaining the final product **3aA**.[52]

With compounds **3** in hand, we realized that the classical scope of carbonyl ylide cyclizations could be expanded remarkably. In fact, we can rely not only on the three atoms constituting the 1,3-dipole but also on both sp^2-carbons of the enol moiety, as well.[53] Malonate enol ethers **3** then provide versatile three- or four-atom building blocks for annulation processes. Both malonate and enol functional groups can be

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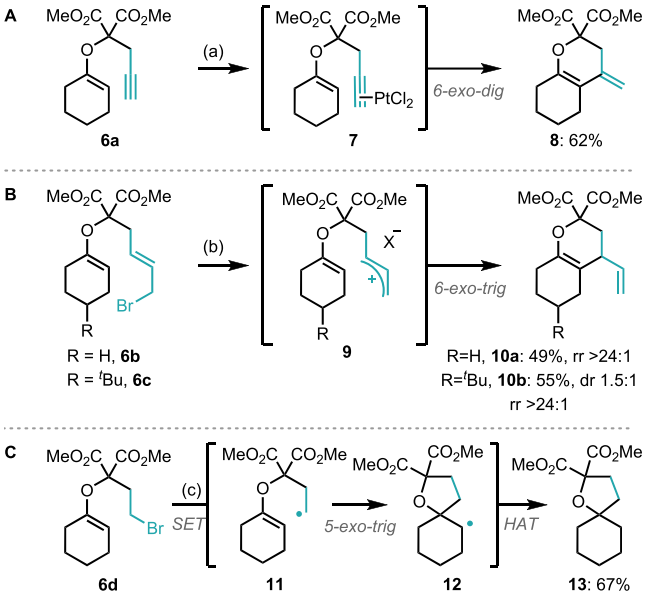
manipulated independently and orthogonally but also in synergy to promote diverse ring formations.

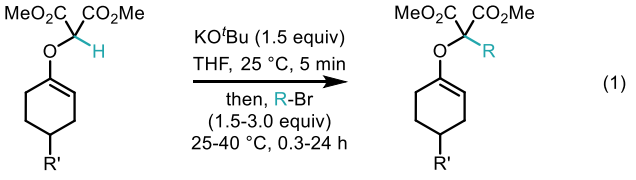
Three different types of transformations are presented, two metal-mediated processes and one photoinduced process, that afford a variety of fused and spiro-heterocycles (Scheme 6). All

Scheme 6[a]



[a]Reaction conditions: (a) $PtCl_2$ (5 mol %), dioxane (0.1 M), 60 °C, 16 h; (b) AgOTf (1.0 equiv), 2,6-di-*tert*-butyl-4-methylpyridine (3.0 equiv), DCM (0.1 M), 25 °C, 2 h; (c) ($Ir(ppy)_3$, 2.5 mol %), blue LEDs irradiation, DIPEA (10 equiv), MeCN (0.1 M), 25 °C, 5 h. SET: single electron transfer. HAT: hydrogen atom transfer.

cyclization sequences benefit from the reactivity of the malonate group with alkyl halides (eq 1). In effect, compounds



(1)

3aA or **3fA** are readily deprotonated in the presence of potassium *tert*-butoxide, and products of C−C bond formation carrying various functional groups are obtained readily (**6a**−**6d**, 60−88%).[54]

Then, using propargyl-substituted **6a**, a $PtCl_2$-catalyzed (5 mol %) reaction was performed (Scheme 6A).[55−61] In the presence of the Lewis acid activating the alkyne (intermediate **7**), a *6-exo-dig* cyclization occurs, and after proton loss that regenerates the enol, formation of the conjugated chromene **8** is afforded as a single regioisomer (62% yield).[62] With **6b** and **6c**, treatment with AgOTf in the presence of 2,6-di-*tert*-butyl-4-methylpyridine yielded bicyclic derivatives **10a** and **10b** in 49 and 55% yields, respectively (Scheme 6B). The reactions proceed most likely via a stabilized allylic cation **9**, and after a 6-*exo-trig* Mukaiyama-type intramolecular alkylation,[63−65] proton loss affords the bicyclic enol products **10a** and **10b** as single regioisomers again. With **6d** in hand, a radical cyclization under visible-light photoredox catalysis was considered alternatively (Scheme 6C).[66−72] Under blue light-emitting diode (LED) irradiation and using tris[2-phenylpyridinato-C^2,*N*]iridium(III) or $Ir(ppy)_3$ as catalyst,[73,74] product **13** was obtained in 67% yield. Compound **6d** led to spiro adduct **13** via a 5-*exo-trig* cyclization, as it is generally observed in radical processes.[75,76] A detailed mechanistic proposal is reported in Scheme S1.

In conclusion, we report the effective formation of malonate enol ethers **3** by condensations of ketones with metal carbenes derived from α-diazomalonates and $[CpRu(CH_3CN)_3][BAr_F]$ as a catalyst. These 2-vinyloxymalonates **3** are obtained in good to excellent yields (up to 98%), and their mechanism of formation was elucidated based on DFT calculations. Furthermore, they are interesting building blocks for annulation strategies as exemplified by the three transformations selected (Scheme 6). In effect, derivatives **3** predispose reactive enol and malonate functional groups at immediate proximity to enable cyclization strategies that would be difficult to consider otherwise.[77]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsorginorgau.1c00006.

Synthetic protocols, experimental conditions, full characterizations of new compounds, computational details. Original data related to this publication can be found under DOI: 10.26037/yareta:xt74kr35jrcgblxomojxsmnd3y. It will be preserved for 10 years (PDF)

Accession Codes

CCDC 2058765 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Author Contributions

§J.V.-L. and G.L. contributed equally to the work.

Notes

The authors declare no competing financial interest.

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(46) The substituents probably induce small but significant changes to the preferred chair conformation of the substrates that favor the (preferentially axial) proton loss and hence the enol formation.
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