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Cycloaddition

Diastereo- and Enantioselective Inverse-Electron-Demand Diels–Alder Cycloaddition between 2-Pyrones and Acyclic Enol Ethers

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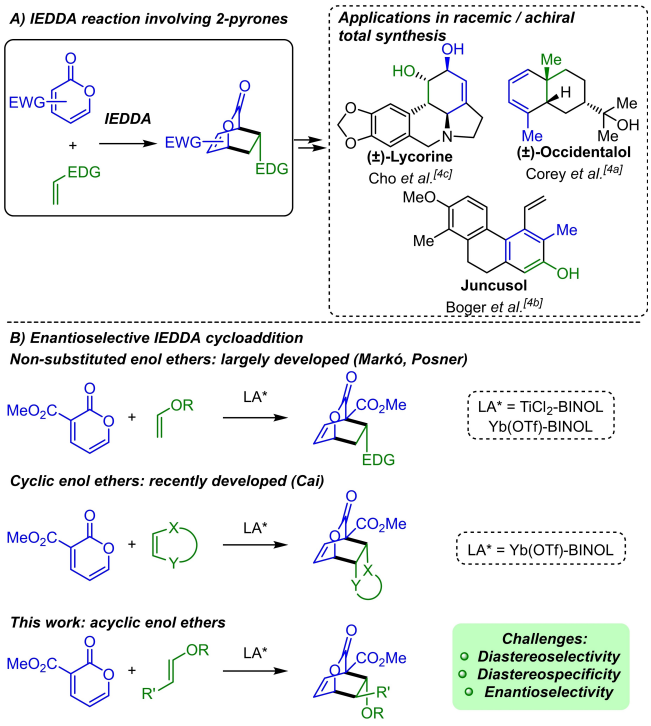
In memory of Professor Yves Langlois.

Abstract: A broadly applicable diastereo- and enantioselective inverse-electron-demand Diels–Alder reaction of 2-pyrones and acyclic enol ethers is reported herein. Using a copper(II)-BOX catalytic system, bridged bicyclic lactones are obtained in very high yields (up to 99 % yield) and enantioselectivities (up to 99 % ee) from diversely substituted 2-pyrones and acyclic enol ethers. Mechanistic experiments as well as DFT calculations indicate the occurrence of a stepwise mechanism. The synthetic potential of the bridged bicyclic lactones is showcased by the enantioselective synthesis of polyfunctional cyclohexenes and cyclohexadienes, as well as a carbasugar unit.

Introduction

The Diels–Alder cycloaddition is a classical textbook reaction ubiquitous in organic synthesis, with broad applications from natural product synthesis to polymer chemistry.[1] While the chemist's attention has been focused on "normal electron demand" Diels–Alder cycloadditions, inverse-electron-demand Diels–Alder (IEDDA) reactions—featuring an electron-enriched dienophile and an electron-deficient diene—have been largely overlooked, despite the promising opportunities they offer for the synthesis of 6-membered carbocycles and bridged structures.[2]

Electron-deficient 2-pyrone derivatives are notoriously good partners for IEDDA reactions, affording bridged lactone structures. These versatile intermediates offer many possibilities for further functionalization, including CO_2 extrusion, ring opening or aromatization. Thus, this reaction was featured in various natural product syntheses, although largely limited to racemic form or the synthesis of achiral natural products (Scheme 1A).[3,4] Asymmetric IEDDA reactions involving 2-pyrone derivatives were developed in the 1990s by the groups of Posner and Markó, using chiral Lewis acid catalysis (Scheme 1B).[5] However, until recently these reactions were limited to non-substituted enol ethers. A huge step forward was taken when the group of Cai reported the enantioselective IEDDA reaction of 2-pyrone and cyclic dienophiles using a combination of $Yb(OTf)_3$ and a modified BINOL ligand.[6,7] However, the enantioselective



Scheme 1. Applications of racemic IEDDA reactions of 2 pyrones and challenges of their enantioselective version.

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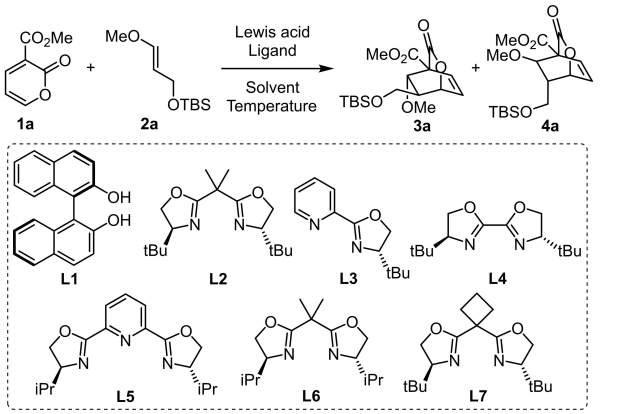
IEDDA reaction of 2-pyrones with acyclic 1,2-disubstituted dienophiles remains elusive. Only one example was reported by Gademann and co-workers, where an alkenyl selenide undergoes an IEDDA reaction with a 2-pyrone derivative, affording the corresponding bridged bicyclic lactone with 84% ee.[8] Unlike cyclic dienophiles, the use of acyclic 1,2-disubstituted dienophiles presents additional challenges of diastereoselectivity (*endo* or *exo*) and diastereospecificity (*cis* or *trans* product for *Z* or *E* substrates), in addition to the enantioselectivity issue. Counterintuitively, IEDDA reactions of 2-pyrone are not always diastereospecific, as both pericyclic and stepwise mechanisms can occur.[9] Attracted by the potential of this reaction—highlighted by the many possible applications in total synthesis[3,4]—we decided to tackle this important issue. Herein, we propose a broadly applicable method for enantio- and diastereoselective IEDDA cycloaddition involving 2-pyrones and acyclic 1,2-disubstituted dienophiles.

Results and Discussion

At the outset of the project, we studied the cycloaddition of electron-deficient pyrone **1a** with enol ether **2a**. The influence of the Lewis acid, ligand and solvent is reported in Table 1 (for detailed optimization see Table S1–S5 in the Supporting Information). A screening of different metals and rare earths showed that copper(II) could catalyze efficiently the reaction (entries 1–4). Among ligands commonly employed with Cu^{II}, BOX ligands gave the best results (entries 4–9). By fine-tuning the BOX ligand, we could identify **L7**, bearing a spiro-cyclobutane motif, as optimal for this cycloaddition (entry 9). Finally, the choice of counterion for the Cu^{II}-BOX complex allowed to reach high yield, dr and ee (entries 10–11).

With these optimal conditions in hand, we started exploring the scope of the reaction (Scheme 2). Various ester moieties were well tolerated in position 3, from non-bulky Me ester to sterically demanding t-Bu ester (**3a**–**3d**), although longer reaction times were needed in the latter case. Benzyl ester, which can be converted to the corresponding carboxylic acid orthogonally to classical saponification conditions, also performed well (**3e**).[10] Testosterone and cholesterol derivatives could also undergo the IEDDA reaction efficiently (**3f**–**3g**), proving its applicability to complex structures. We were disappointed to see that amides were not reactive enough to undergo the cycloaddition. Substitution in position 4 was well tolerated in general, with both alkyl (**3h**) and aryl substituents. Moreover, both electron-enriched (**3j**, **3n**) and electron deficient (**3k**–**3m**) aryl substituents performed well, although with somewhat lower ee in some cases. Substitution was also possible in *ortho* and *meta* position of the C^4 aryl substituent (**3o**–**3p**). C^5-substituted 2-pyrones gave the corresponding bridged bicyclic lactones in very high yields and excellent enantioselectivities, both in the case of alkyl (**3q**–**3s**) and aryl substituents (**3t**–**3w**). However, C^6 substituted 2-pyrones proved unreactive in the reaction conditions. The absolute configuration of the products could be confirmed by single-crystal X-ray analysis of **3r**.[11]

Table 1: Optimization of the reaction conditions.[a]

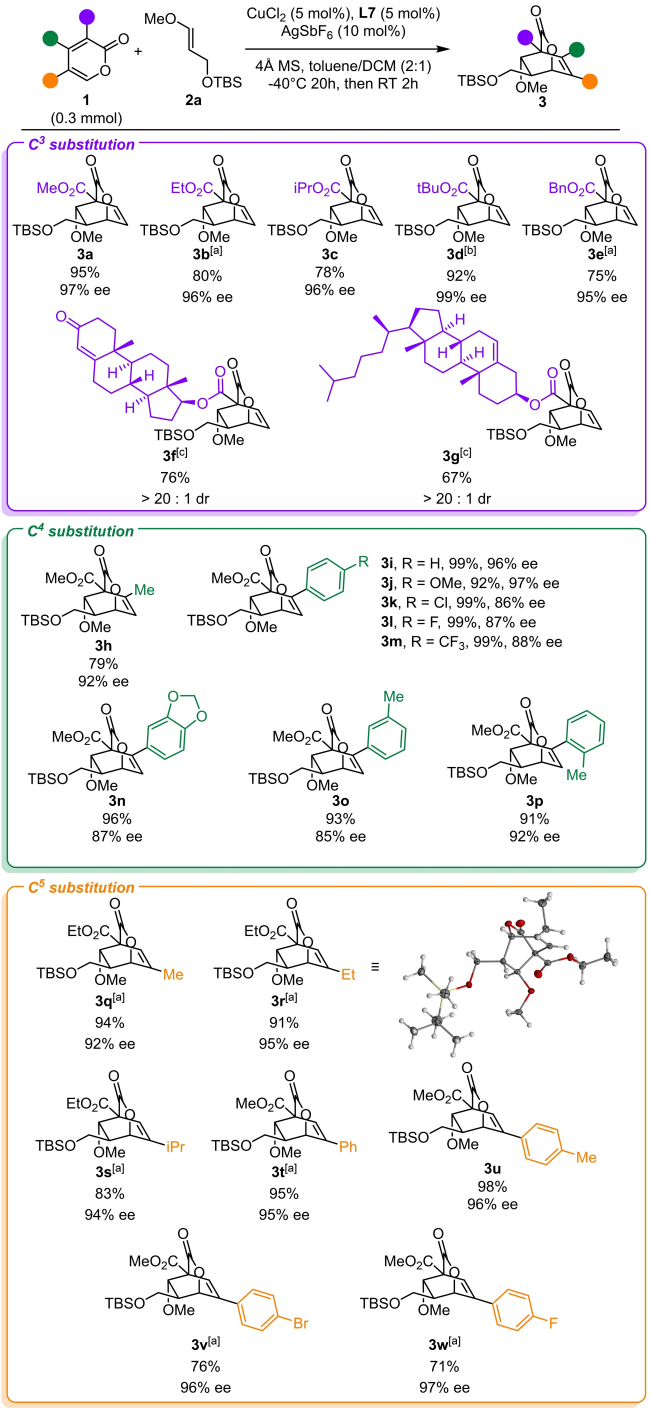


Entry	Lewis acid	Ligand	Yield	*dr* (**3a**/**4a**)	ee
1[b]	$Eu(hfc)_3$	–	65	13:1	8
2[b,c]	$Yb(OTf)_3$	**L1**	83	>20:1	5
3	$Zn(OTf)_2$	**L2**	17	>20:1	25
4	$Cu(OTf)_2$	**L2**	76	>20:1	72
5	$Cu(OTf)_2$	**L3**	10	–	26
6	$Cu(OTf)_2$	**L4**	70	>20:1	44
7	$Cu(OTf)_2$	**L5**	–	–	-
8	$Cu(OTf)_2$	**L6**	76	>20:1	36
9	$Cu(OTf)_2$	**L7**	75	>20:1	73
10[c,d]	$Cu(SbF_6)_2$	**L7**	98	>20:1	87
11[c,d,e]	$Cu(SbF_6)_2$	**L7**	95	>20:1	97

[a] General reaction conditions: **1a** (1 equiv), **2a** (3 equiv), Lewis acid (0.1 equiv), Ligand (0.12 equiv), DCM, RT. [b] The reaction was run at 60 °C. [c] The reaction was run in the presence of 4 Å molecular sieves. [d] The catalyst was pre-formed by mixing $CuCl_2$ with the ligand, adding $AgSbF_6$ and filtrating the silver salts. [e] The reaction was run using 0.05 equiv of $Cu(SbF_6)_2$, 0.05 equiv of ligand, in toluene:DCM (2:1) and at −40 °C.

We then studied the applicability of our reaction to different enol ethers (Scheme 3). Various *O*-substituents were well tolerated, with ethyl and isopropyl enol ethers providing the corresponding bridged bicyclic lactones **3x**–**3y** with excellent enantioselectivity. Classical protecting groups such as benzyl, allyl or TBS were also well tolerated (**3z**–**3ad**). Regarding the substitution at position 2, various alkyl substituents were tolerated (**3ab**–**3ad**), including non-bulky Me substituent (**3ab**) or more sterically demanding Bn (**3ad**). Good results were also observed in the presence of protected alcohols (**3af**–**3ai**). Remarkably, a highly sensitive TMS protecting group survived on a primary alcohol in the reaction conditions, underlying the mildness of the reaction conditions.

To test the limits of stereoselection induced by our catalytic system, we evaluated the influence of a mismatched chiral dienophile in the reaction conditions. Thus, (−)-menthyl-enol ether **2n** was subjected to the reaction conditions using an achiral ligand (Scheme 4). Compound **3aj′** was obtained with a 5:1 dr. Conversely, when our catalytic system was employed, the diastereomeric ratio was reversed, and the other diastereoisomer was obtained with a



Scheme 2. Scope of the reaction regarding 2-pyrone derivatives. [a] The reaction was conducted at −40 °C for 40 h then RT for 2 h. [b] The reaction was conducted at −40 °C for 60 h then RT for 2 h. [c] The reaction was conducted at RT for 3 days.

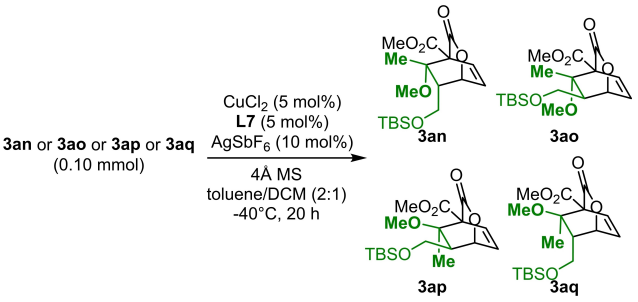
6:1 dr, highlighting the stereoinducing power of our catalytic system.

We were also interested by the diastereospecificity of the reaction. However, a reoptimization was needed for the case of *Z* enol ethers (see Table S6), allowing us to highlight **L9** as the optimal ligand for *Z* enol ethers. When subjecting *Z* enol ethers **2o** and **2p** to the reaction conditions, only *cis*-diastereomers **3ak–3al** were observed (Scheme 5). However, the cycloaddition involving **2q** provided a 28:1 mixture of *cis* and *trans* diastereoisomers. Interestingly, the two diastereomers **3am** and **4a** were isolated with different ee. *Z* to *E* enol ether isomerization cannot be invoked to explain this result, as the minor trans isomer is **4a** and not **3a**. On the other hand, when 1,1′,2-trisubstituted enol ether **2r** reacted with **1a**, 4 diastereoisomers were obtained, with a poor selectivity. Each diastereoisomer could be isolated separately. Remarkably, each pair of epimer **3an–3aq** and **3ao–3ap** had the same ee. These last results are indicative of the occurrence of a stepwise mechanism, although we could not rule out a competing concerted mechanism at this point.

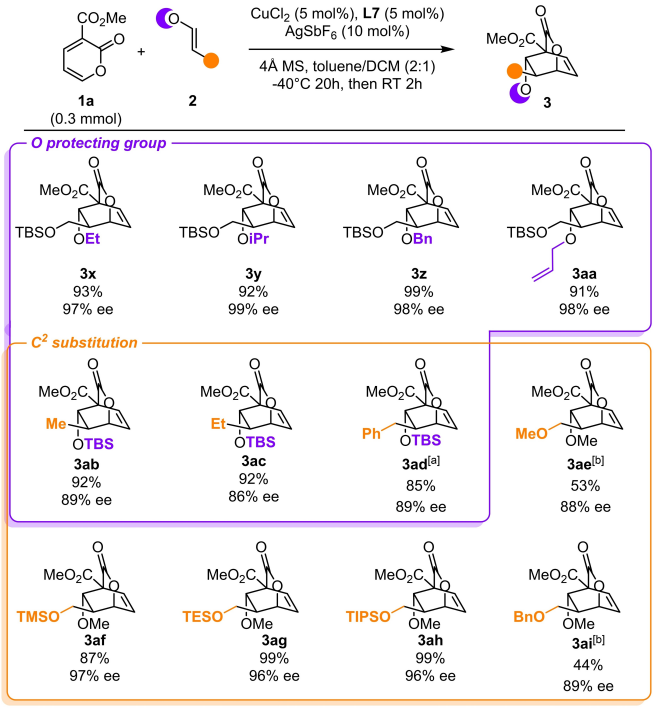
To better understand the last results with *Z*-disubstituted and trisubstituted enol ethers, we re-subjected separately each diastereoisomer **3an–3aq** to the reaction conditions (Table 2). After, 20 h under the reaction conditions, we observed epimerization at ether-bearing stereogenic center, with no significant change in ee. Again, this result points towards a stepwise mechanism, with a reversible cyclization step. The similar ee for each pair of epimers can be explained by the fact that only the cyclization step is effectively reversible in this case. Subjecting **3am** to the reaction conditions led to a similar epimerization, confirming that the presence of **4a** arises from the reversibility of the cyclization step (see Scheme S1). We also performed a kinetic study of the reaction. The results showed that the ratio of each diastereoisomer is constant over the reaction course (Figure 1).

We have performed quantum chemical calculations at the density functional theory (DFT) level (see the Supporting Information for details) to shed light on the reaction mechanism and clarify the experimentally observed diastereoselectivity. Figure 2 shows the computed reaction profiles

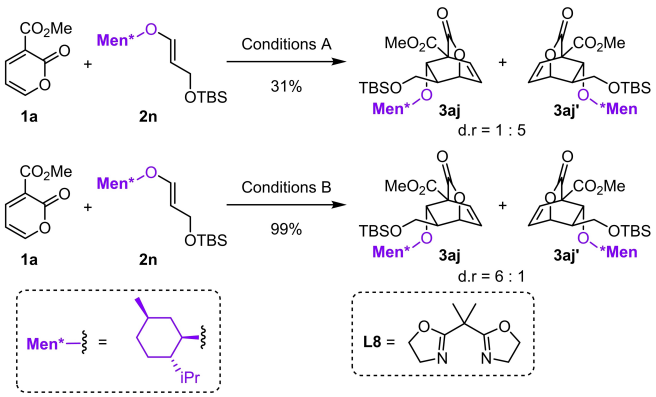
Table 2: Control experiment.



Starting lactone	Resulting lactones			
	3an	**3ao**	**3ap**	**3aq**
3an (90% ee)	22% (90% ee)	–	–	42% (87% ee)
3ao (86% ee)	–	27% (86% ee)	49% (87% ee)	–
3ap (85% ee)	–	25% (86% ee)	64% (85% ee)	–
3aq (90% ee)	22% 90% ee	–	–	70% 91% ee

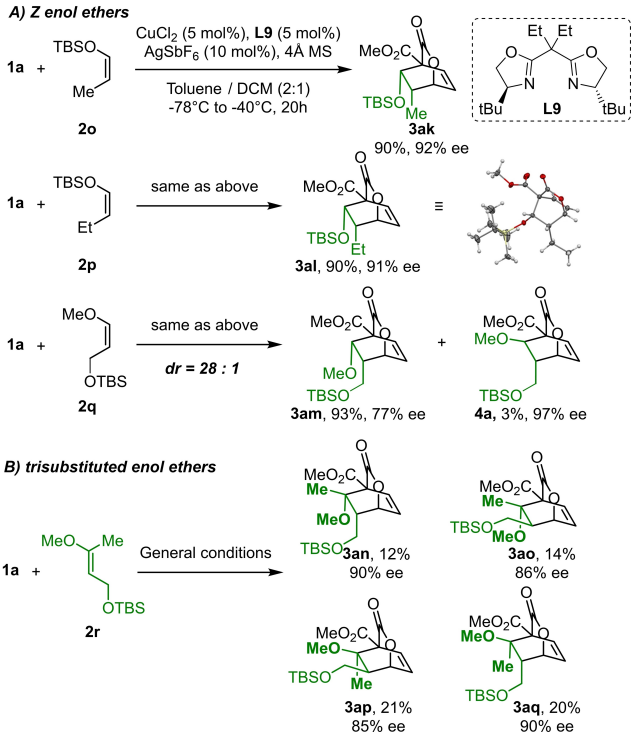


Scheme 3. Scope of the reaction regarding enol ethers. [a] The reaction was conducted at −40 °C for 40 h then at RT for 2 h. [b] The reaction was conducted at −40 °C for 60 h then at RT for 2 h.



Scheme 4. Influence of a mismatched chiral dienophile. Conditions A: **1a** (1 equiv), **2n** (1.5 equiv), $Cu(OTf)_2$ (0.1 equiv), **L8** (0.12 equiv), 4 Å molecular sieves, DCM, −78 °C to RT, 10 h. Conditions B: as in Scheme 2 and 3.

for the reactions of the malonate model complex of the bis(oxazoline) ligand **A-Cu** with the (*E*)-1-methoxyprop-1-ene **B_*E*** (Figure 2A) and (*Z*)-1-methoxyprop-1-ene **B_*Z*** (Figure 2B). The malonate complex **A-Cu** associates with enol ethers **B_*E*** and **B_*Z*** to yield 3.1 and 2.8 kcal mol^{-1} stabilized reactant complexes. The strong intermolecular interaction between the copper and the oxygen atoms of the methoxy groups of enol ethers is the reason for the computed free energy lowering compared to the separately considered reactants. The next step is the attack of the enol ethers. We have explored both concerted and stepwise



Scheme 5. Diastereospecificity of the reaction.

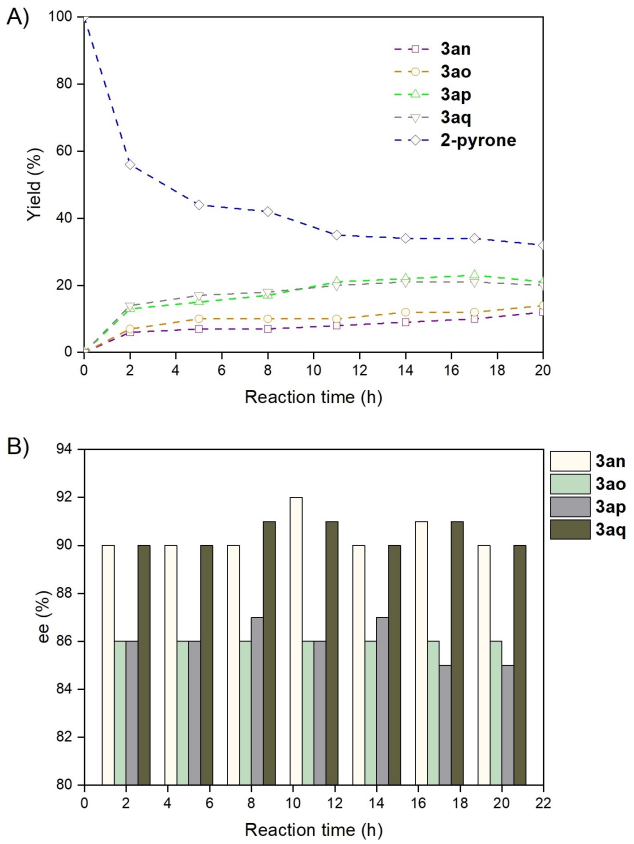


Figure 1. Kinetic experiment.

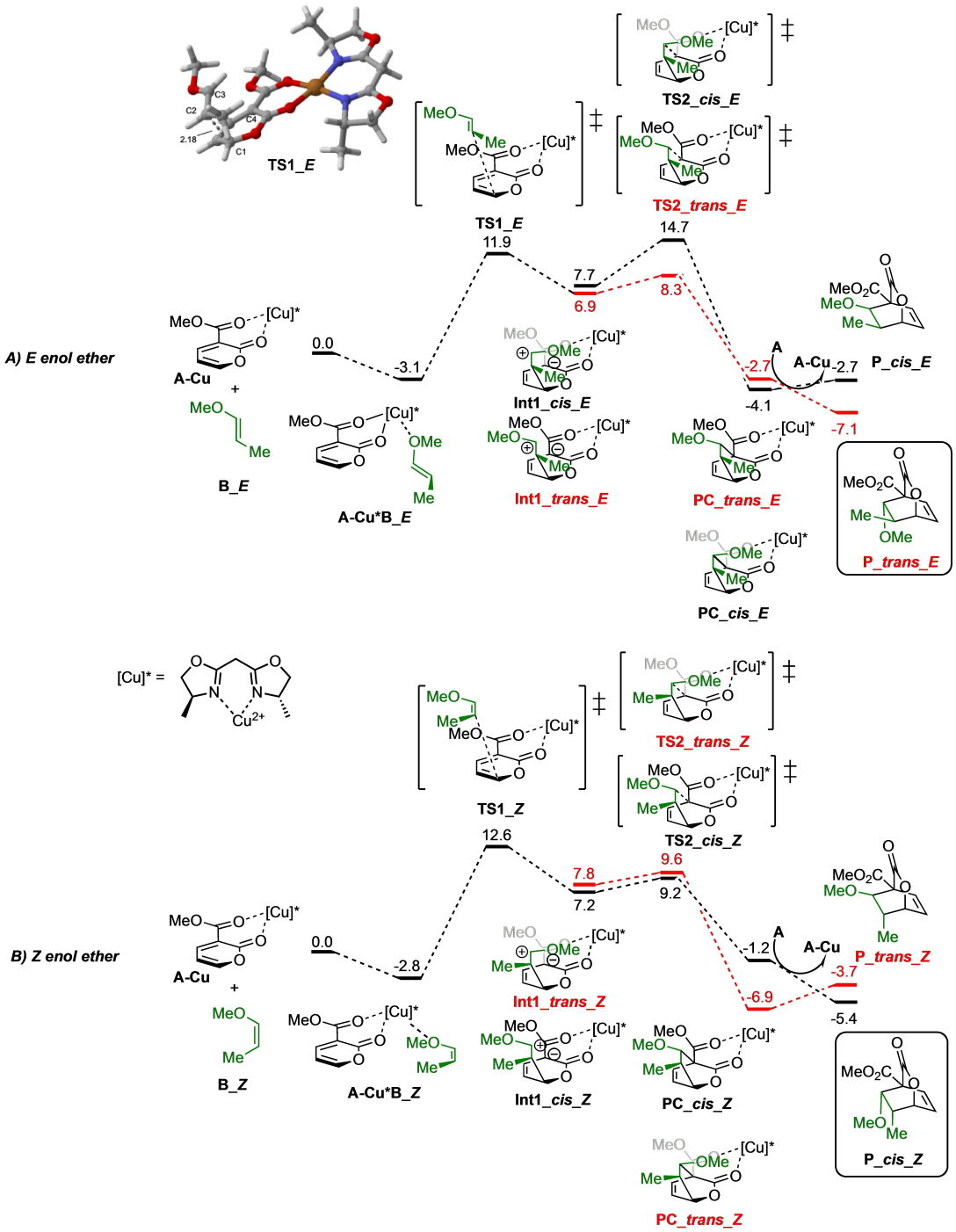


Figure 2. Computed reaction profiles (ωB97X-D/def2-TZVP//ωB97X-D/6-31G(d),LanL2DZ, $\Delta G_{298,\text{toluene}}$, kcal mol^{-1}) for the reaction with the *E* and *Z* enol ethers.

mechanisms for this event, and the calculations strongly deny the concerted mechanism. The *endo* attack of the enol ethers leads to the formation of the **Int1_*E*** and **Int1_*Z*** via low barrier transition states **TS1_*E*** ($\Delta G^{\ddagger} = 15.0$ kcal mol^{-1}, the optimized 3d structure is also shown in Figure 2A) and **TS1_*Z*** ($\Delta G^{\ddagger} = 15.4$ kcal mol^{-1}) respectively. The conformational flexibility of the intermediates **Int1_*E*** and **Int1_*Z*** allows two types of structures regarding Me and OMe groups orientation: **Int1_*trans*** and **Int1_*cis*.** As shown in Figure 2 the *trans* form of the intermediate **Int1** is more stabilized than the cis form in the case of the *E* enol ether, while vice versa the *cis* form is thermodynamically more favorable for the *Z* enol ether.

The following step is the exergonic formation of the second C–C bond leading to the product complexes and ultimately to the final products. In good agreement with the experiment the formation of the in vitro observed product **P_*trans_E*** in the case of *E* enol ether substrates is both

kinetically ($\Delta\Delta G^{\ddagger} = \Delta G^{\ddagger}$(**int1_*E*→P_*cis_E*)$-\Delta G^{\ddagger}$(**int1_*E*→P_*trans_E*)$= 14.7-8.3 = 6.4$ kcal mol^{-1}) and thermodynamically ($\Delta\Delta G = G$(**P_*cis_E*)$-G$(**P_*trans_E*)$= -2.7-(-7.1) = 4.4$ kcal mol^{-1}) more favorable as compared to the **P_*cis_E***. Also in the case of *Z* enol ether the calculations agree with the experimental evidence, suggesting that the formation of the *cis* product **P_*cis_Z*** is energetically more probable, $\Delta\Delta G^{\ddagger} = \Delta G^{\ddagger}$(**int1_*Z*→P_*trans_Z*)$-\Delta G^{\ddagger}$(**int1_*Z*→P_*cis_Z*)$= 9.6-9.2 = 0.4$ kcal mol^{-1}, $\Delta\Delta G = G$(**P_*trans_Z*)$-G$(**P_*cis_Z*)$= -3.7-(-5.4) = 1.7$ kcal mol^{-1}. Moreover, the calculations predict a more significant free energy gap between the **TS2** transition states in the case of *E* enol ether: $\Delta\Delta G^{\ddagger} =$ $\Delta G^{\ddagger}$ (**TS2_*cis_E*)**$-\Delta G^{\ddagger}$(**TS2_*trans_E*)$= 6.4$ kcal mol^{-1} as compared to $\Delta\Delta G^{\ddagger} = \Delta G^{\ddagger}$(**TS2_*trans_Z*)**$-\Delta G^{\ddagger}$(**TS2_*cis_Z*)$= 0.4$ kcal mol^{-1}. This result agrees with the experimentally observed higher epimerization probability in the case of the *Z* enol ether. Thus, the computationally revealed stepwise mechanism allows us to clarify the observed diastereoselectivity for the reactions with *Z* and *E* dienophiles.

At the next stage of the computational study, we explored the reaction of the malonate model complex of the bis(oxazoline) ligand **A-Cu** with the trisubstituted dienophile (*E*)-2-methoxybut-2-ene **C** (Figure 3). Both *exo* and

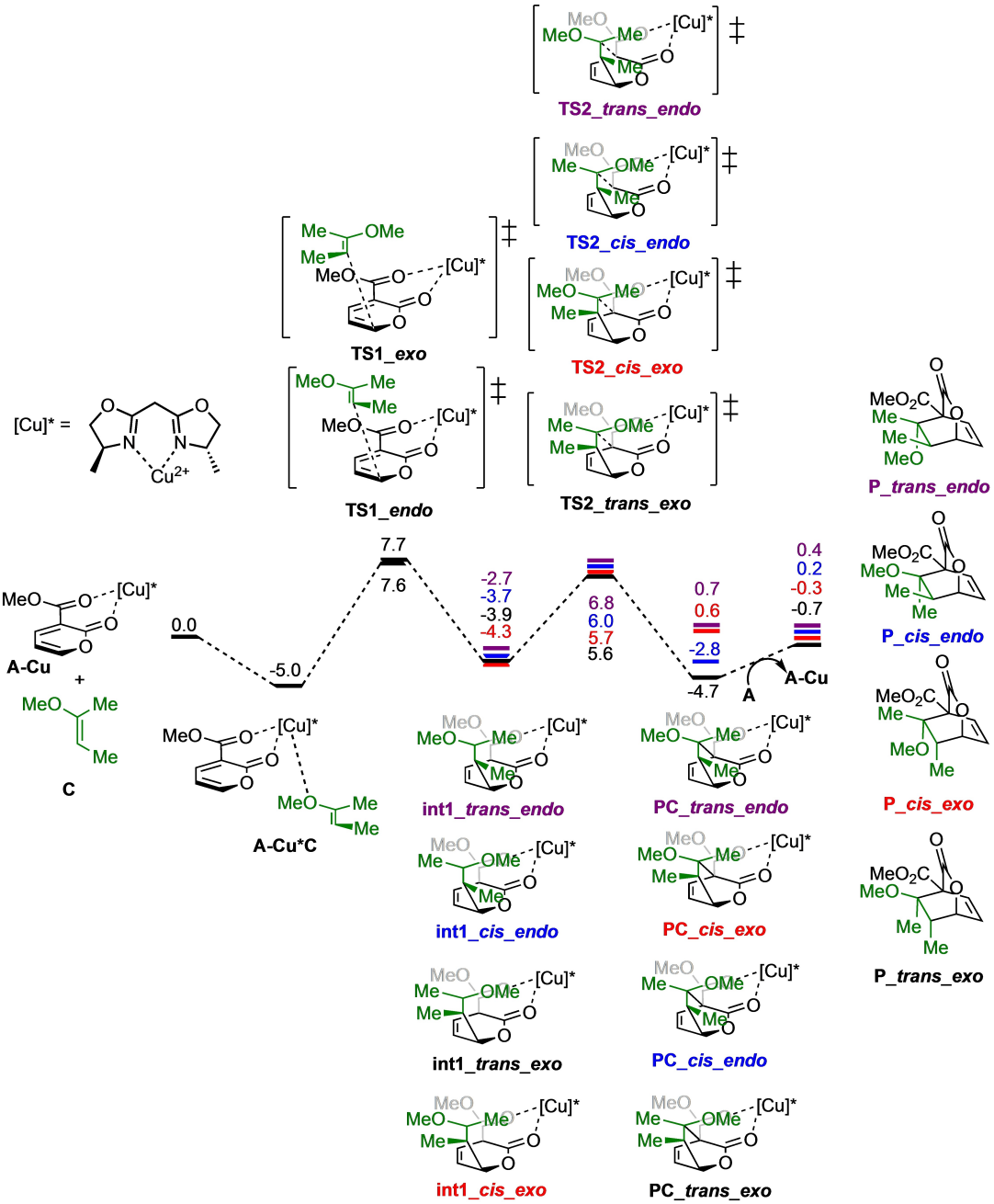


Figure 3. Computed reaction profiles (ωB97X-D/def2-TZVP//ωB97X-D/6-31G(d),LanL2DZ, $\Delta G_{298,\text{toluene}}$, kcal mol^{-1}) for the reaction with the trisubstituted dienophile.

endo pathways have been computed and found to be kinetically equivalent. Indeed, the barrier of the *exo* attack is $\Delta G^{\ddagger}$(**A-Cu*C→int1_*exo***) = 12.6 kcal mol^{-1}, while of the *endo* attack, it is $\Delta G^{\ddagger}$(**A-Cu*C→int1_*endo***) = 12.7 kcal mol^{-1}.

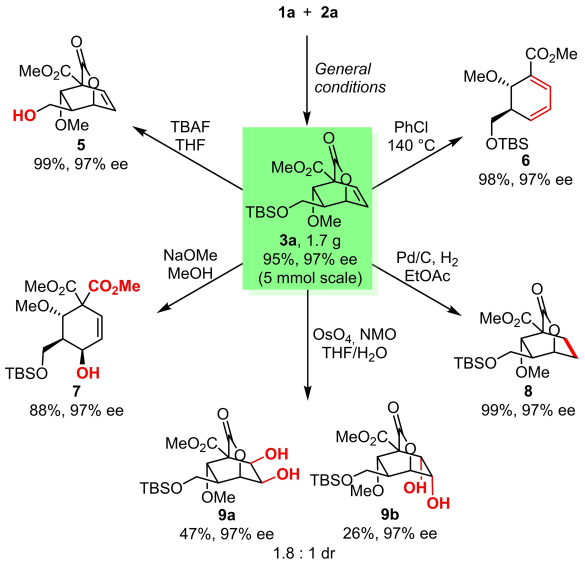
The conformational flexibility of the intermediates **Int1_*exo*** and **Int1_*endo*** allows four possible further pathways (*trans* and *cis* pathways for *endo* and *exo* attacks), finally leading to the four products. These four products are very close thermodynamically and kinetically. Indeed, the energy range as the difference between the most stable **P_*trans_exo*** and the least stable **P_*trans_endo*** products is only $\Delta\Delta G = G$(**P_*trans_endo***) − G(**P_*trans_exo***) = 0.4 − (−0.7) = 1.1 kcal mol^{-1}. Which is smaller compared to the case of 1-methoxyprop-1-ene. Thus, the calculations suggest that all four products can be formed. The latter strongly supports the experimental evidence. Moreover, the calculations also clarify the in vitro observation of the reaction reversibility in the case of trisubstituted dienophile. Indeed, the thermodynamic gain of this reaction is almost zero in contrast to the clearly exergonic reactions with 1-methoxyprop-1-ene. Overall, the calculations 1) suggest stepwise mechanism of the considered reactions and deny the possibility of concerted mechanism, 2) reveal the reason for the experimentally observed diastereoselectivity, and 3) explain the reversibility of the reaction with the trisubstituted dienophile.

We decided to show the broad applicability of the resulting bicyclic lactones by performing a gram-scale reaction and post functionalization (Scheme 6). The TBS protecting group could be removed without altering the integrity of the bridged lactone. Bicyclic lactone **3a** could be thermically decarboxylated through a retro-[4+2] reaction. It should be noted that the resulting cyclohexadiene **6** cannot be prepared enantioselectively by any other method to the best of our knowledge. On the other hand, bridged bicyclic lactone **3a** could be ring-opened by transesterification, affording polysubstituted cyclohexene **7**. Remarkably, both IEDDA/CO_2 extrusion and IEDDA/lactone opening sequences were key points in the synthesis of various calcitriol analogs and pseudo disaccharides.[12] However, as no enantioselective method for the IEDDA reaction of 2-pyrones with acyclic 1,2-disubstituted enol ethers existed at the time, these syntheses had to rely on the chiral pool. The olefin could be hydrogenated, furnishing bicyclic compound **8** quantitatively. Finally, dihydroxylation could lead to diols **9a** and **9b**, albeit with poor diastereoselectivity (1.8:1).

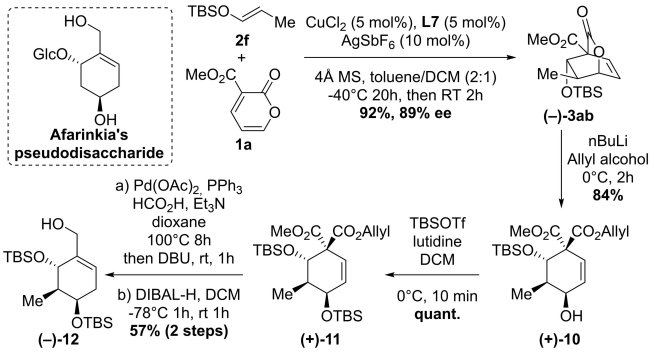
Carbasugars are carbohydrate-like structures where the ring oxygen is replaced by a methylene unit. This structural change provides carbasugar analogs with increased stability and different biological properties.[13] Thus, the synthesis of carbasugar units is of utmost importance as new, non-natural carbasugars could open the door to new bioactive molecules. Inspired by the work of Afarinkia,[12c] we decided to apply our reaction to the enantioselective synthesis of a new carbasugar analog. Starting from 2-pyrone **1a** and enol ether **2f**, the IEDDA reaction afforded **(−)-3ab** in high yield and good ee (Scheme 7). Ring-opening through transesterification led to cyclohexene derivative **(+)-10**, on which the free alcohol was protected as a TBS ether. From the resulting intermediate **(+)-11**, we performed a Pd-mediated decarboxylative deallylation. A mixture of olefin isomers was obtained, and therefore the mixture was treated with DBU at the end of the reaction to obtain the conjugated alkene. Finally, ester reduction led to the formation of **(−)-12**, a protected carbasugar unit which is a methyl analog of Afarinkia's carbasugar.[12c]

Conclusion

To conclude, we have developed a broadly applicable, diastereo- and enantioselective IEDDA reaction between 2-pyrones and 1,2-disubstituted acyclic enol ethers. The reaction could support various substituted 2-pyrones as well as dienophiles. Mechanistic experiments suggested that the reaction proceeds at least partially through a stepwise mechanism. DFT calculations supported the proposed stepwise mechanism, explaining the observed diastereoselectivity. Given the numerous uses of the racemic version of this reaction in natural product synthesis, we are convinced



Scheme 6. Post-functionalization of the bicyclic lactone.



Scheme 7. Synthesis of a carbasugar unit.

that this method will become an important tool in total synthesis in the future.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: Asymmetric Catalysis · Copper · Cycloaddition · Diastereoselectivity · Enantioselectivity

[1] a) J.-A. Funel, S. Abele, *Angew. Chem. Int. Ed.* **2013**, *52*, 3822–3863; *Angew. Chem.* **2013**, *125*, 3912–3955; b) V. Eschenbrenner-Lux, K. Kumar, H. Waldmann, *Angew. Chem. Int. Ed.* **2014**, *53*, 11146–11157; *Angew. Chem.* **2014**, *126*, 11326–11337; c) K. Houk, F. Liu, Z. Yang, J. Seeman, *Angew. Chem. Int. Ed.* **2021**, *60*, 12660–12681; *Angew. Chem.* **2021**, *133*, 12768–12790; d) B. Briou, B. Améduri, B. Boutevin, *Chem. Soc. Rev.* **2021**, *50*, 11055–11097.

[2] a) X. Jiang, R. Wang, *Chem. Rev.* **2013**, *113*, 5515–5546; b) R. A. A. Foster, M. C. Willis, *Chem. Soc. Rev.* **2013**, *42*, 63–76; c) A. C. Knall, C. Slugovc, *Chem. Soc. Rev.* **2013**, *42*, 5131–5142; d) B. L. Oliveira, Z. Guo, G. J. L. Bernardes, *Chem. Soc. Rev.* **2017**, *46*, 4895–4950; e) J. Zhang, V. Shukla, D. L. Boger, *J. Org. Chem.* **2019**, *84*, 9397–9445.

[3] For reviews, see: a) Q. Cai, *Chin. J. Chem.* **2019**, *37*, 946–976; b) G. Huang, C. Kouklovsky, A. de la Torre, *Chem. Eur. J.* **2021**, *27*, 4760–4788; c) X.-G. Si, Z.-M. Zhang, Q. Cai, *Synlett* **2021**, *32*, 947–954.

[4] For selected exampes, see: a) D. S. Watt, E. J. Corey, *Tetrahedron Lett.* **1972**, *13*, 4651–4654; b) D. L. Boger, M. D. Mullican, *J. Org. Chem.* **1984**, *49*, 4045–4050; c) H.-S. Shin, Y.-G. Jung, H.-K. Cho, Y.-G. Park, C.-G. Cho, *Org. Lett.* **2014**, *16*, 5718–5720.

[5] a) I. E. Markó, G. R. Evans, J. P. Declerq, *Tetrahedron* **1994**, *50*, 4557–4574; b) I. E. Markó, G. R. Evans, *Tetrahedron Lett.* **1994**, *35*, 2771–2774; c) G. H. Posner, J. C. Carry, J. K. Lee, D. S. Bull, H. Dai, *Tetrahedron Lett.* **1994**, *35*, 1321–1324; d) G. H. Posner, F. Eydoux, J. K. Lee, D. S. Bull, *Tetrahedron Lett.* **1994**, *35*, 7541–7544; e) G. H. Posner, H. Dai, D. S. Bull, J. K. Lee, F. Eydoux, Y. Ishihara, W. Welsh, N. Pryor, S. Petr, *J. Org. Chem.* **1996**, *61*, 671–676; f) I. E. Markó, I. Chellé-Regnaut, B. Leroy, S. L. Warriner, *Tetrahedron Lett.* **1997**, *38*, 4269–4272.

[6] a) X.-W. Liang, Y. Zhao, X.-G. Si, M.-M. Xu, J.-H. Tan, Z.-M. Zhang, C.-G. Zheng, C. Zheng, Q. Cai, *Angew. Chem. Int. Ed.* **2019**, *58*, 14562–14567; *Angew. Chem.* **2019**, *131*, 14704–14709; b) X.-G. Si, Z.-M. Zhang, C.-G. Zheng, Z.-T. Li, Q. Cai, *Angew. Chem. Int. Ed.* **2020**, *59*, 18412–18417; *Angew. Chem.* **2020**, *132*, 18570–18575; c) M.-M. Xu, X.-Y. You, Y.-Z. Zhang, Y. Lu, K. Tan, L. Yang, Q. Cai, *J. Am. Chem. Soc.* **2021**, *143*, 8993–9001; d) M.-M. Xu, L. Yang, K. Tan, X. Chen, Q.-T. Lu, K. N. Houk, Q. Cai, *Nat. Catal.* **2021**, *4*, 892–900; e) Y. Lu, M.-M. Xu, Z.-M. Zhang, J. Zhang, Q. Cai, *Angew. Chem. Int. Ed.* **2021**, *60*, 26610–26615; *Angew. Chem.* **2021**, *133*, 26814–26819.

[7] During the publication process of our manuscript, a new IEDDA reaction of 2-pyrones with cyclic enamines was reported: F. Zhang, B.-T. Ren, Y. Zhou, Y. Liu, X. Feng, *Chem. Sci.* **2022**, *13*, 5562–5567.

[8] Until now only one example was reported, with 84 % ee: P. Burch, M. Binaghi, M. Scherer, C. Wentzel, D. Bossert, L. Eberhardt, M. Neuburger, P. Scheiffele, K. Gademann, *Chem. Eur. J.* **2013**, *19*, 2589–2591.

[9] G. H. Posner, C.-G. Cho, T. E. N. Anjeh, N. Johnson, R. L. Horst, T. Kobayashi, T. Okano, N. Tsugawa, *J. Org. Chem.* **1995**, *60*, 4617–4628.

[10] a) P. K. Mandal, J. S. McMurray, *J. Org. Chem.* **2007**, *72*, 6599–6601; b) J. M. Khurana, R. Arora, *Synthesis* **2009**, 1127–1130; c) F.-X. Felpin, E. Fouquet, *Chem. Eur. J.* **2010**, *16*, 12440–12445.

[11] Deposition Numbers 2160985, 2160986, 2160987 and 2160988 contain the supplementary crystallographic data for this paper (compounds **3r**, **3ac**, **3al** and **4a**). These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service.

[12] a) G. H. Posner, N. Johnson, *J. Org. Chem.* **1994**, *59*, 7855–7861; b) G. H. Posner, B. T. Woodard, K. R. Crawford, S. Peleg, A. J. Brown, P. Dolan, T. W. Kensler, *Bioorg. Med. Chem.* **2002**, *10*, 2353–2365; c) K. Afarinkia, M. H. Abdullahi, I. J. Scowen, *Org. Lett.* **2009**, *11*, 5182–5184; d) K. Afarinkia, M. H. Abdullahi, I. J. Scowen, *Org. Lett.* **2010**, *12*, 5564–5566.

[13] a) O. Arjona, A. M. Gómez, J. C. López, J. Plumet, *Chem. Rev.* **2007**, *107*, 1919–2036; b) S. Jarosz, M. Nowogródzki, M. Magdycz, M. A. Potopnyk, *Carbohydr. Chem.* **2012**, *37*, 303–325; c) R. Lahiri, A. A. Ansari, Y. D. Vankar, *Chem. Soc. Rev.* **2013**, *42*, 5102–5118.

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