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Dynamic kinetic resolution of transient hemiketals: a strategy for the desymmetrisation of prochiral oxetanols†

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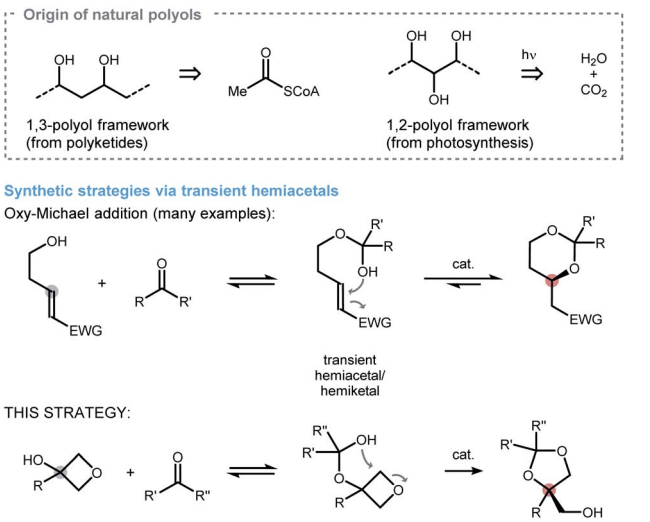
Identification of an electron poor trifluoroacetophenone allows the formation of uniquely stable hemiketals from prochiral oxetanols. When exposed to a cobalt(II) catalyst, efficient ring-opening to densely functionalized dioxolanes is observed. Mechanistic studies suggest an unprecedented redox process between the cobalt(II) catalyst and the hemiketal that initiates the oxetane-opening. Based on this observation, a dynamic kinetic resolution of the transient hemiketals is explored that uses a Katsuki-type ligand for stereoinduction (up to 99 : 1 dr and 96 : 4 er) and allows a variety of 1,3-dioxolanes to be accessed (20 examples up to 98% yield).

Introduction

The stereoselective synthesis of polyols has been a cornerstone of organic chemistry due to the prevalence of this structural motif in biologically important molecules such as polyketides or carbohydrates (Scheme 1, top). As a result, continuous effort is devoted to the development of new methods that establish C–O bonds with high levels of stereocontrol. One possibility to accomplish such an endeavor invokes the application of a transient hemiacetal as an intramolecular nucleophile and was introduced by Evans and coworkers in 1993.[1] Since this early example, many diastereoselective[2] and enantioselective[3] variants have been developed on the basis of Brønsted acid, as well as Lewis acid, catalysis (Scheme 1, middle). Recent extensions regarding the alkene-electrophile[4] as well as applications in the synthesis of natural products[5] have renewed the interest in hemiacetals as a platform for reaction development. However, nucleophilic attack of a transient hemiacetal to other groups than activated alkenes are rare,[6] even though this would allow a much broader range of polyolic targets to be accessed.

To address this limitation, we hypothesized that when adequately activated a transient hemiacetal would be able to undergo ring-opening at a strained heterocyclic core. Based on our laboratory's interest in desymmetrisation of prochiral four-membered rings,[7] we considered 3-oxetanols as promising candidates to test this hypothesis (Scheme 1, bottom). Here, the preformed hemiacetal attacks the oxetane ring to form a dioxolane, which is energetically favourable due to the ~20 kcal mol^{-1} of strain release, and opens the possibility to forge two new stereogenic centres along the way. According to literature precedent, a number of catalysts qualify to activate oxetanes towards desymmetrisation.[8] Among them, Co^{III}·salen[9] as well as chiral phosphoric acids[10] are worth mentioning because they proved viable for the synthesis of various oxygen-heterocycles in the past. However, no synthetic strategy towards the formation of 1,3-dioxolanes was reported so far,



Scheme 1 Overview of asymmetric strategies using hemiacetals to forge new C–O bonds. CoA = coenzyme A; EWG = electron withdrawing group.

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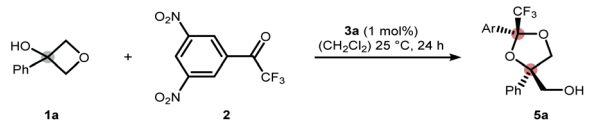
which we now wish to report on along with our efforts identifying a suitable catalyst system for a highly selective desymmetrisation process.[11]

Results and discussion

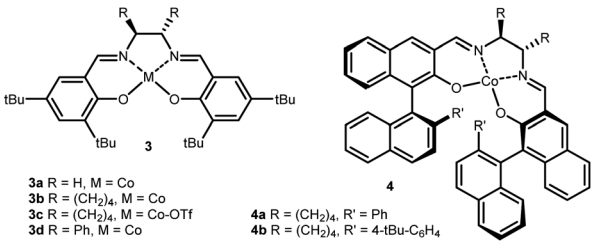
We commenced our study by exploring the ring-opening of 3-phenyloxetanol (**1a**) with simple aldehydes in the presence of a range of Brønsted acids as well as Lewis acids (see ESI† for further details). However, these attempts were met with limited success, presumably due to the low stability of the transient hemiacetal. We addressed this problem by installing electron withdrawing groups at the carbonyl core to increase the stability of the hemiacetal moiety.[12] After exploring a range of electron withdrawing groups, we identified 3,5-dinitrotrifluoroacetophone **2** as a suitable candidate for the envisioned transformation.[13] In the presence of 1 mol% of Co^{II}·salen **3a**, oxetanol **1a** underwent cyclization to dioxolane **5a** in 95% yield and in a diastereomeric ratio (dr) of 76 : 24 (Table 1, entry 1). As expected, no ring-opening was observed without the catalyst (Table 1, entry 2). Interestingly, when the parent trifluoroacetophenone was used instead of **2**, no conversion to the respective dioxolane was detected (entry 3). The reaction was also found to be highly water-sensitive, which lends credibility to a transient hemiketal being a crucial reaction intermediate (Table 1, entry 4).

Table 1 Reaction optimization for the desymmetrization of oxetanol **1a**[a]



1a 2 5a

Entry	Changes from std. conditions	Yield **5a**[b]	dr[c]	er[d]
1	—	95%	76 : 24	—
2	No catalyst added	—	—	—
3	$BzCF_3$ instead of **2**	—[e]	—	—
4	1 equiv. H_2O added	7%	n.d.	—
5	Catalyst **3b** instead of **3a**	92%	79 : 21	60 : 40
6	Co^{III}-catalyst **3c** instead of **3a**	<5%	n.d.	n.d.
7	Catalyst **3d** instead of **3a**	48%	78 : 22	60 : 40
8	Katsuki-type cat **4a** instead of **3a**	90%	90 : 10	75 : 25
9	Katsuki-type cat **4b** instead of **3a**	86%	96 : 4	86 : 14



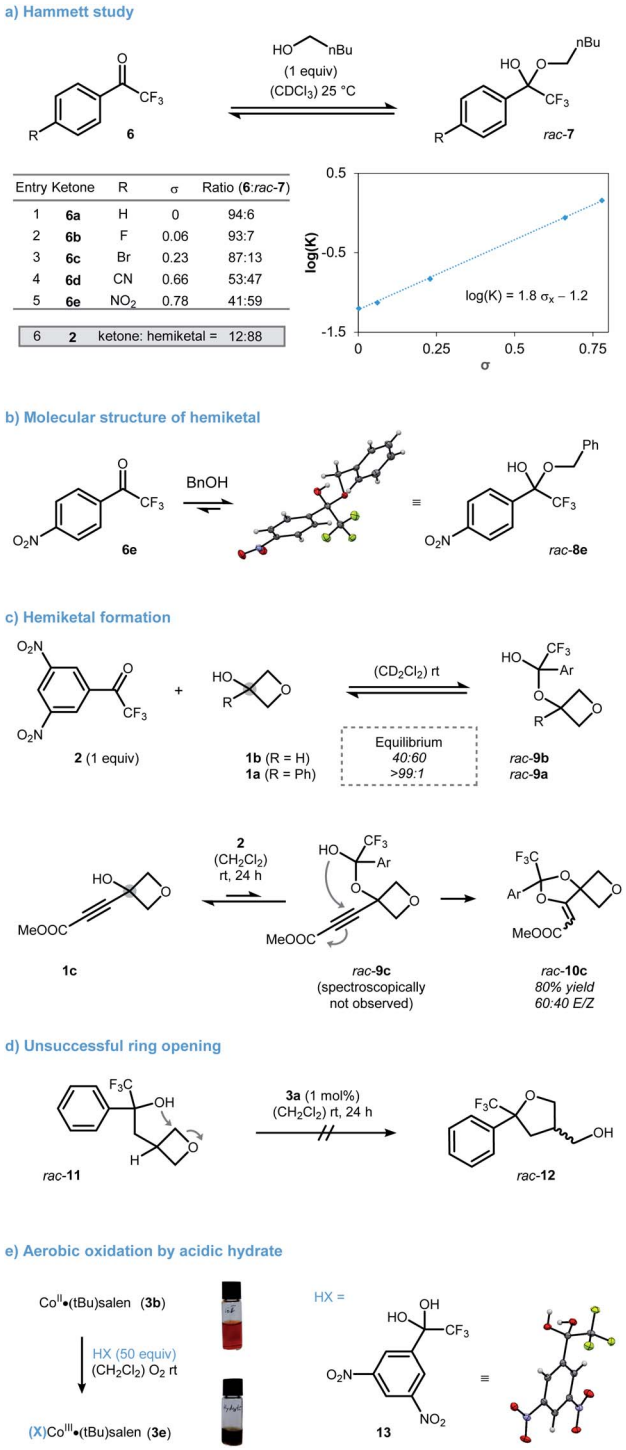
3a R = H, M = Co
3b R = $(CH_2)_4$, M = Co
3c R = $(CH_2)_4$, M = Co-OTf
3d R = Ph, M = Co

4a R = $(CH_2)_4$, R' = Ph
4b R = $(CH_2)_4$, R' = 4-tBu-C_6H_4

[a] Reactions were run on a 0.1 mmol scale using 1 equivalent of ketone **2** in 0.5 mL of dry solvent (0.2 M). [b] Yield of **5a** (Ar = 3,5-$(NO_2)_2$-C_6H_3) determined by ^{19}F NMR using trifluorotoluene as an internal standard. [c] Determined by ^{19}F NMR from the crude reaction mixture. [d] Enantiomeric ratio of the major diastereomer was determined by HPLC analysis using a chiral stationary phase. [e] In this case, the expected product Ar = Ph was not detected. n.d. = not determined; Bz = benzoyl; OTf = trifluoromethanesulfonate.

To develop an asymmetric variant, commercially available complex **3b** was tested in the reaction sequence. To our delight, product **5a** was obtained in a small but detectable enantiomeric ratio (er) of 60 : 40 (Table 1, entry 5). It was surprising that the oxidized form (TfO)Co^{III}·salen **3c**, a privileged catalyst for the ring-opening of strained cyclic ethers, resulted in only traces of product (Table 1, entry 6).[9] When replacing the cyclohexyl backbone with the sterically more demanding phenyl groups, no notable improvement in enantioselectivity was observed, but the overall yield dropped to 48% (Table 1, entry 7). Following that, we considered a distal group for stereoinduction and were attracted by Katsuki-type ligands **4**.[14] With ligand **4a** an increase in selectivity to 90 : 10 dr and 75 : 25 er was detected (Table 1, entry 8). Finally, the overall performance of the ligand was further improved by the installation of pendant *tert*-butyl groups (complex **4b**) providing dioxolane **5a** in good yield and selectivity (Table 1, entry 9).

While some of the results from the optimization were in accordance with what we had envisioned, some were not and prompted us to conduct further mechanistic investigations. In particular, the origin of the unique activity of dinitrotrifluoroacetophenone **2** compared to trifluoroacetophenone remained unclear. First, we studied hemiketal formation using a range of *para*-substituted trifluoroacetophenones **6** (Scheme 2a). To quantify the electronic effect on hemiketal stability, a Hammett study was performed. A linear correlation between log(K) and the Hammett constant σ was found (Scheme 2a, entries 1–5).[15] The sensitivity constant ρ was determined to be 1.8 highlighting the crucial role of the aryl-substitution on hemiketal stability. As a consequence, ketone **2** pushes the equilibrium far to the hemiketal side. Validation for the proposed structures was provided by X-ray diffraction of compound **8e**, a stable hemiketal deriving from 4-nitroacetophenone **6e** and benzyl alcohol (Scheme 2b). Next, we studied hemiketal formation of **2** with different oxetanols (Scheme 2c). Sterically accessible 3-oxetanol (**1b**) reversibly formed the expected hemiketal *rac*-**9b**, which could be monitored by NMR spectroscopy. Tertiary oxetanols such as **1a** on the other hand, did not form detectible amounts of the respective hemiketal *rac*-**9a**. However, the formation of oxy-Michael product *rac*-**10c** from oxetanol **1c** still points towards the transient formation of tertiary hemiketal *rac*-**9c**, albeit in low concentration. While these results show the steric and electronic contributions to hemiketal formation, they do not account for the relative reactivity towards ring-opening. To investigate the opening without having a pre-equilibrium step present, we designed substrate *rac*-**11** (Scheme 2d). Surprisingly, *rac*-**11** underwent no cyclization to oxolane *rac*-**12** under the optimized conditions. While this may be explained by the reduced electrophilicity of *rac*-**11** due to its lack of an oxygen atom at the 3-position, an insufficient activation of the oxygen nucleophile by the catalyst seems also reasonable. We hypothesized that an *in situ* aerobic Co^{II}·salen oxidation initiated only by acidic hemiketals takes place increasing their inherent

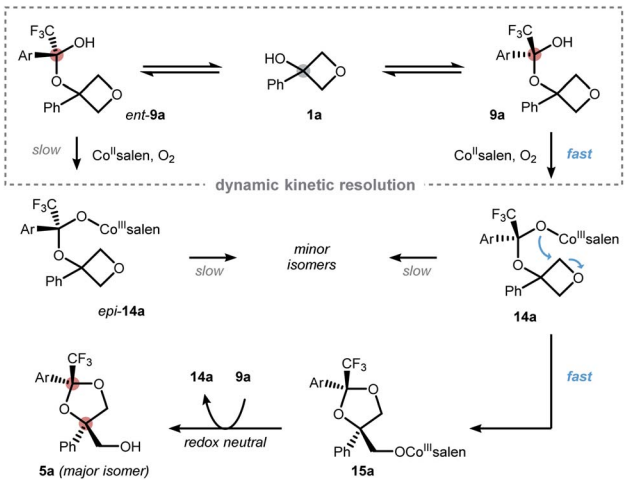


Scheme 2 (a)–(e) Pieces of experimental data highlighting the unique character of ketone **2** for the mechanism. Ar = 3,5-$(NO_2)_2$-C_6H_3. CCDC 2130260 (*rac*-**8e**), CCDC 2130259 (**13**).†

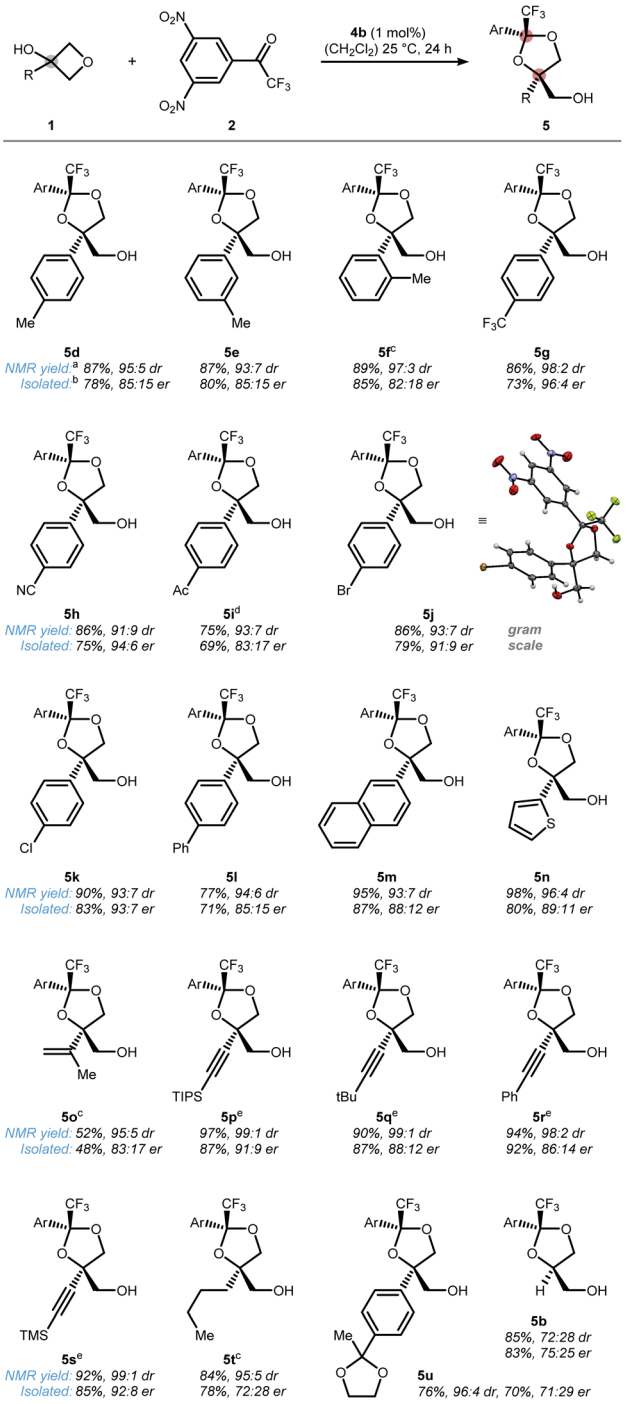
nucleophilicity.[16] In accordance with literature reports, this oxidation process typically requires Brønsted acids with a pK_a below 10.[17] As this coincides well with the expected pK_a for electron deficient hemiketals deriving from **2**, we decided to study such an aerobic oxidation based on easily accessible hydrate **13** as a surrogate (Scheme 2e). When catalyst **3b** was treated with **13** under ambient conditions, cobalt oxidation was observable by the naked eye through a color change from orange to green. UV-vis analysis showed good consistency with related complexes of the general type (X)Co^{III}·salen (see ESI† for further information).[18] By contrast, less acidic trifluoroethanol showed only limited potential in aerobic oxidation of Co^{II}. This not only explains the unsuccessful ring-opening of *rac*-**11** but also underpins the inimitable role of ketone **2** to modulate both the stability and acidity of its respective hemiketals.

Based on the collected data, a mechanistic picture for the desymmetrization of oxetanols is proposed in Scheme 3.[19] Reversible formation of the hemiketals **9a** and *ent*-**9a** is facilitated by the electron deficient nature of ketone **2** and can occur without a catalyst as suggested by the findings from Scheme 2a. However, an influence of the catalyst on the underlying equilibrium can neither be excluded nor confirmed at this point. The enhanced acidity of the hemiketals triggers aerobic oxidation to furnish Co^{III} intermediates **14a** and *epi*-**14a**, respectively. Cobalt-hemiketalate **14a** exhibits an enhanced nucleophilicity triggering efficient ring-opening to furnish intermediate **15a**. Catalyst turn-over can be explained by proton transfer from hemiketal **9a** to **15a** regenerating hemiketalate **14a** and releasing the dioxolane product **5a**. The overall high yield and selectivity can be rationalized by a dynamic kinetic resolution (DKR) of the racemic hemiketals.[20] This implies that hemiketal *ent*-**9a** reacts much slower than its enantiomer **9a** while the rate of racemization remains relatively fast. About a dual role of the catalyst can only be speculated based on our current data, but it seems reasonable that the catalyst also acts as an inter- or intramolecular Lewis acid further facilitating oxetane-opening.

With a reasonable mechanistic picture in hand, we started exploring the scope of the oxetane desymmetrization (Scheme 4). Steric substitution at the *ortho*, *meta*, and *para* position of the phenyl core was well tolerated furnishing tolyl-dioxolanes **5d**, **5e**, and **5f**. Electronic perturbations resulted in an overall improved enantioselectivity of up to 96 : 4 er for the corresponding electron-deficient dioxolanes **5g–5k**. Moreover, gram-

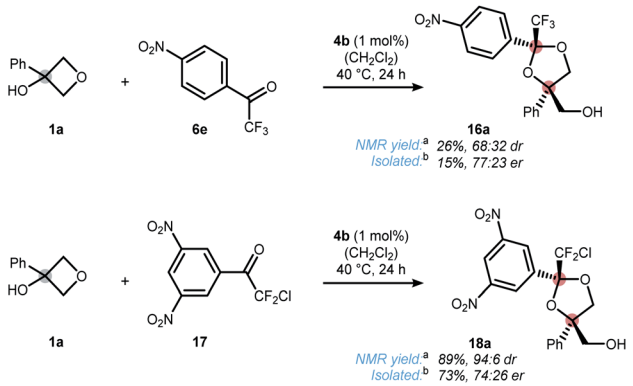


Scheme 3 Mechanistic picture of the desymmetrization *via* a dynamic kinetic resolution of a transient hemiketal in best accordance with the findings from Scheme 2. Ar = 3,5-$(NO_2)_2$-C_6H_3.



Scheme 4 Scope of the desymmetrization of prochiral oxetanols **1** *via* a DKR of the respective transient hemiketals. [a]Determined by ^{19}F NMR using trifluorotoluene as an internal standard. [b]Isolated yield and enantiomeric ratio correspond to the major isomer only. [c]Reactions were run at 40 °C instead of 25 °C. [d]Fluorobenzene was used instead of trifluorotoluene as the internal standard. [e]Reactions run with catalyst **4a** instead of **4b**. Ar = 3,5-$(NO_2)_2$-C_6H_3. CCDC 2141905 (**5j**).†

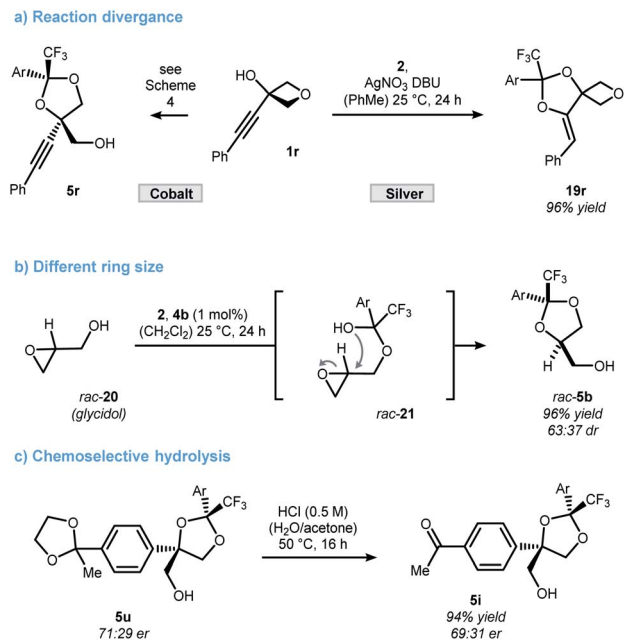
scale reaction was feasible with no loss in selectivity as indicated by bromophenyl dioxolane **5j.** The very same dioxolane was also suitable for growing single crystals to determine the absolute configuration. Extended π-systems such as naphthyl and diphenylyl as well as heterocycles such as thiophene



Scheme 5 Ketone scope. [a]Determined by ^{19}F NMR using trifluorotoluene as an internal standard. [b]Isolated yield and enantiomeric ratio correspond to the major isomer only.

revealed good efficiency in the cyclization event (**5l–5n**). In addition, alkenyl as well as alkynyl substitution was tolerated (**5o–5s**). Replacing the aryl group with an *n*-butyl group resulted in a substantial decrease in enantioselectivity (**5t**). Furthermore, sterically encumbered aryl **1u** as well as unsubstituted oxetanol (**1b**) successfully underwent ring-opening to the corresponding alcohols **5u** and **5b**, albeit in significantly lower diastereo- and enantioselectivity. These results suggest that some sort of π-interaction between the catalyst and substrate is crucial for a successful DKR.

In contrast to the quite general scope of the oxetanol precursor, alterations at the ketone scaffold were less fruitful (Scheme 5). Changing from two to one nitro-groups (ketone **6e**) significantly reduced the reaction rate and only 15% yield of



Scheme 6 Reactions using hemiketal formation as a platform for reaction development (a and b). Chemical stability of ketals deriving from ketone **2** (c). Ar = 3,5-$(NO_2)_2$-C_6H_3.

dioxolane **16a** were obtained after 24 h. On the other hand, replacing the CF_3 by a CF_2Cl group (ketone **17**) allowed the synthesis of dioxolane **18a** in reasonable yield and moderate selectivity. More drastic changes to the scaffold of ketone **2** completely shut down the reaction (for details see the ESI†). Altogether, these results underline the unique character of ketone **2**, which was further elaborated upon in Scheme 6. First, a stereodivergent synthesis of dioxolanes **5r** and **19r** from phenylacetylated oxetanol **1r** was achieved by switching the metal catalyst (Scheme 6a).[6b,c] Ring-opening at other strained rings such as epoxides was also feasible. This was showcased by the reaction of glycidol (*rac*-**20**) to dioxolane **5b** using 1 mol% of cobalt catalyst **4b** (Scheme 5b).[21] It should be noted that for this epoxide-opening no signs of kinetic resolution were observed, presumably because the reaction is too fast. Nonetheless, no reaction was observed in the absence of catalyst **4b**. Unlike 1,2-diol protecting groups such as acetonide or benzylidene, attempts to cleave the ketal group deriving from trifluoroacetophenone **2** were unsuccessful (see ESI† for a table of all tested conditions). While this currently limits the applicability of the presented method, there were some interesting observations made during the attempted cleavage. The complementary nature of electron deficient ketals allows a chemoselective deprotection indicated by the conversion of dioxolane **5u** to ketone **5i** upon treatment with hydrochloric acid (Scheme 6c). The unexpected stability towards acids might qualify trifluoromethyl-dioxolanes as a rare acetal motif suitable for (oral) drug discovery, an important property as elucidated by Yu and Meanwell in a recent review.[22] Further studies to successfully cleave the trifluoroketal-motif and access the free triol motif are currently underway in our laboratory.

Conclusions

In this study, electron deficient trifluoroacetophenone **2** was identified to form remarkably stable hemiketals with unique properties. Based on this observation, a novel ring-opening of prochiral oxetanols was pursued, which relies on a dynamic kinetic resolution of transiently formed hemiketals and an *in situ* oxidation of the Co^{II} catalyst. By providing access to a range of complex dioxolanes with good control of selectivity, this study not only widens the reach of hemiketals but also serves as a platform for future reaction development.

Data availability

Crystallographic data for *rac*-**8e**, and **5j** has been deposited at the CCDC and is available under 2130260, 2130259, and 2141905 respectively. Experimental data including detailed procedures, characterisation of new compounds as well as NMR and HPLC spectra is accessible in the ESI.†

Author contributions

A. S. and H. M. conducted and analysed all experiments. C. G. D. and D. S. performed the X-ray analysis. A. S. and J. M. W. conceptualized the experiments and prepared the manuscript.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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References

1 D. A. Evans and J. A. Gauchet-Prunet, *J. Org. Chem.*, 1993, **58**, 2446.
2 (*a*) P. A. Evans, A. Grisin and M. J. Lawler, *J. Am. Chem. Soc.*, 2012, **134**, 2856; (*b*) A. Grisin, S. Oliver, M. D. Ganton, J. Bacsa and P. A. Evans, *Chem. Commun.*, 2015, **51**, 15681; (*c*) K. Murata, K. Sakamoto and H. Fuwa, *Org. Lett.*, 2019, **21**, 3730; (*d*) H. Watanabe, K. Machida, D. Itoh, H. Nagatsuka and T. Kitahara, *Chirality*, 2001, **13**, 379.
3 (*a*) D. M. Rubush, M. A. Morges, B. J. Rose, D. H. Thamm and T. Rovis, *J. Am. Chem. Soc.*, 2012, **134**, 13554; (*b*) A. Matsumoto, K. Asano and S. Matsubara, *Chem. Commun.*, 2015, **51**, 11693; (*c*) K. Asano and S. Matsubara, *Org. Lett.*, 2012, **14**, 1620.
4 (*a*) A. Khan, R. Zheng, Y. Kan, J. Ye, J. Xing and Y. J. Zhang, *Angew. Chem., Int. Ed.*, 2014, **53**, 6439; (*b*) R. Zhang, W. Guo, M. Duan, K. N. Houk and J. Sun, *Angew. Chem., Int. Ed.*, 2019, **58**, 18055; (*c*) L. Wang and D. Menche, *Angew. Chem., Int. Ed.*, 2012, **51**, 9425; (*d*) K. Miura, T. Takahashi, H. Nishikori and A. Hosomi, *Chem. Lett.*, 2001, **30**, 958; (*e*) J. A. Goodwin, C. F. Ballesteros and A. Aponick, *Org. Lett.*, 2015, **17**, 5574; (*f*) S. D. Dreher, K. R. Hornberger, S. T. Sarraf and J. L. Leighton, *Org. Lett.*, 2000, **2**, 3197; (*g*) A. T. Herrmann, T. Saito, C. E. Stivala, J. Tom and A. Zakarian, *J. Am. Chem. Soc.*, 2010, **132**, 5962.
5 (*a*) P. A. Evans, M.-H. Huang, M. J. Lawler and S. Maroto, *Nat. Chem.*, 2012, **4**, 680; (*b*) D. A. Evans, P. J. Coleman and L. C. Dias, *Angew. Chem., Int. Ed. Engl.*, 1997, **36**, 2738; (*c*) N. Yoneda, Y. Fukata, K. Asano and S. Matsubara, *Angew. Chem., Int. Ed.*, 2015, **54**, 15497; (*d*) A. Matsumoto, K. Asano and S. Matsubara, *Asian J. Org. Chem.*, 2019, **8**, 814.
6 (*a*) M. A. Williams, M. J. Miller and N. P. Rath, *J. Org. Chem.*, 1991, **56**, 1293; (*b*) J. Wang, F. Li, H. Xie, M. Xu, X. Zhao, L. Liu and W.-X. Zhao, *Appl. Organomet. Chem.*, 2017, **31**, e3545; (*c*) X.-B. Ding, D. P. Furkert and M. A. Brimble, *Angew. Chem., Int. Ed.*, 2019, **58**, 11830.
7 J. Sietmann, M. Ong, C. Mück-Lichtenfeld, C. G. Daniliuc and J. M. Wahl, *Angew. Chem., Int. Ed.*, 2021, **60**, 9719.
8 (*a*) A. Sandvoß and J. M. Wahl, *Chem.–Eur. J.*, 2021, **27**, 5871; (*b*) Z. Wang, Z. Chen and J. Sun, *Org. Biomol. Chem.*, 2014, **12**, 6028.
9 R. N. Loy and E. N. Jacobsen, *J. Am. Chem. Soc.*, 2009, **131**, 2786.

10 (*a*) W. Yang and J. Sun, *Angew. Chem., Int. Ed.*, 2016, **55**, 1868; (*b*) X. Zou, G. Sun, H. Huang, J. Wang, W. Yang and J. Sun, *Org. Lett.*, 2020, **22**, 249; (*c*) V. A. Bhosale, M. Nigríni, M. Dračínský, I. Císařová and J. Veselý, *Org. Lett.*, 2021, **23**, 9376.

11 (*a*) Z. X. Giustra and K. L. Tan, *Chem. Commun.*, 2013, **49**, 4370; (*b*) Y. Zhao, A. W. Mitra, A. H. Hoveyda and M. L. Snapper, *Angew. Chem., Int. Ed.*, 2007, **46**, 8471.

12 (*a*) S. Maeda, A. Sudo and T. Endo, *Tetrahedron Lett.*, 2016, **57**, 1061; (*b*) J. F. Miller and A. Spaltenstein, *Tetrahedron Lett.*, 1996, **37**, 2521; (*c*) R. Stewart and J. D. van Dyke, *Can. J. Chem.*, 1970, **48**, 3961.

13 (*a*) R. Stewart and D. G. Lee, *Can. J. Chem.*, 1964, **42**, 439; (*b*) A. Ohno, H. Yamamoto and S. Oka, *J. Am. Chem. Soc.*, 1981, **103**, 2041.

14 R. Irie, T. Uchida and K. Matsumoto, *Chem. Lett.*, 2015, **44**, 1268.

15 C. Hansch, A. Leo and R. W. Taft, *Chem. Rev.*, 1991, **91**, 165.

16 A. Nishinaga, T. Kondo and T. Matsuura, *Chem. Lett.*, 1985, **14**, 905.

17 (*a*) R. Blaauw, I. E. Kingma, J. H. Laan, J. L. van der Baan, S. Balt, M. W. G. de Bolster, G. W. Klumpp, W. J. J. Smeets and A. L. Spek, *J. Chem. Soc., Perkin Trans. 1*, 2000, 1199; (*b*) J. M. Ready and E. N. Jacobsen, *J. Am. Chem. Soc.*, 1999, **121**, 6086.

18 (*a*) S. Kemper, P. Hrobárik, M. Kaupp and N. E. Schlörer, *J. Am. Chem. Soc.*, 2009, **131**, 4172; (*b*) A. Kochem, H. Kanso, B. Baptiste, H. Arora, C. Philouze, O. Jarjayes, H. Vezin, D. Luneau, M. Orio and F. Thomas, *Inorg. Chem.*, 2012, **51**, 10557; (*c*) T. Kurahashi and H. Fujii, *Inorg. Chem.*, 2013, **52**, 3908; (*d*) M. Hatazawa, K. Nakabayashi, S. Ohkoshi and K. Nozaki, *Chem.–Eur. J.*, 2016, **22**, 13677.

19 (*a*) L. P. C. Nielsen, C. P. Stevenson, D. G. Blackmond and E. N. Jacobsen, *J. Am. Chem. Soc.*, 2004, **126**, 1360; (*b*) D. D. Ford, L. P. C. Nielsen, S. J. Zuend and E. N. Jacobsen, *J. Am. Chem. Soc.*, 2013, **135**, 15595.

20 (*a*) B. Ghosh, R. Balhara, G. Jindal and S. Mukherjee, *Angew. Chem., Int. Ed.*, 2021, **60**, 9086; (*b*) S. Müller, M. J. Webber and B. List, *J. Am. Chem. Soc.*, 2011, **133**, 18534; (*c*) K. Murata, K. Sakamoto and H. Fuwa, *Org. Lett.*, 2019, **21**, 3730.

21 (*a*) S. E. Schaus, B. D. Brandes, J. F. Larrow, M. Tokunaga, K. B. Hansen, A. E. Gould, M. E. Furrow and E. N. Jacobsen, *J. Am. Chem. Soc.*, 2002, **124**, 1307; (*b*) M. Tokunaga, J. F. Larrow, F. Kakiuchi and E. N. Jacobsen, *Science*, 1997, **277**, 936.

22 Y.-J. Wu and N. A. Meanwell, *J. Med. Chem.*, 2021, **64**, 9786.