The Efficient Desymmetrization of Glycerol using Scaffolding Catalysis[#]

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Abstract

Glycerol is an ideal building block for the synthesis of complex molecules, because it is inexpensive and highly functionalized. We report the desymmetrization of glycerol through silyl transfer, using a chiral organic catalyst in high yield and enantioselectivity.

There are an abundance of natural products and biologically active compounds that can be derived from glycerol (Figure 1).[1] Although glycerol is an achiral compound, the majority of natural products derived from glycerol are chiral. This fact has led many research groups to investigate reaction sequences that efficiently access a desymmetrized variant of glycerol. One of the most successful methods for accessing these compounds is a multiple step sequence that uses mannitol, a chiral pool material.[2] Because glycerol is a commodity chemical (a by-product of biodiesel production), it would be desirable to develop methods that can directly convert glycerol into chiral building blocks. Enzymatic esterases have been shown to selectively hydrolyse the meso diester of glycerol;[3] however, there are a limited number of methods that can directly desymmetrize glycerol in a single step with high enantioselectivity. The most successful desymmetrizations are in the area of enzymatic reactions,[4] and the only reported synthetic catalysts for the desymmetrization of glycerol use derivatives that are functionalized at the C2-hydroxyl.[5] In this communication, we report an organic catalyst that directly desymmetrizes glycerol in a single step through silylation with state-of-the-art yield and enantioselectivity (>99:1 er, Table 1).

Previous work in our laboratories[6] has shown that catalyst **4** is effective at the desymmetrization and kinetic resolution of 1,2-diols via silyl transfer.[7,8,9,10] Glycerol poses a more challenging substrate class because it contains two reactive primary alcohols, such that suppression of over-addition is critical to obtain high yield and enantioselectivity of the monofunctionalized product. Catalyst **4** has a unique mode of action in which it covalently bonds to alcohol-based substrates and then, through either intramolecular general base catalysis or electrophile transfer, functionalizes the unbound alcohol. We have termed this mode of action scaffolding catalysis,[11] because a primary function of the catalyst is to hold several reacting partners in close proximity to one another. The intramolecular nature of the

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catalyst activation encouraged us to test glycerol as a substrate as a means of suppressing over-silylation. Implementing catalyst **4a** with TBSCl as the electrophile yields the desired silylated product in in 68% yield by ^{1}H NMR and 97:3 er with 14% of bis-silylated product **3** also forming (Table 1, entry 1). Upon optimizing the R group proximal to the imidazole, catalyst **4c** was found to deliver (*R*)-**2** in 78% yield and >99:1 er (Table 1, entry 3). The bis-silylated product **3** also forms in the reaction in 12% yield. The origin of **3** is believed to be a catalysed process rather than background reaction (*vida infra*). Reducing the catalyst loading to 5 mol% results in only a small decrease in yield and er (er = 96:4, Table 1, entry 5). As a control reaction, catalyst **5**, which does not have a covalent substrate-binding site, was employed affording **2** in 52% yield as a racemic mixture (Table 1, entry 6). An additional control experiment with 2-methyl-1,3-propanediol, which lacks a secondary hydroxyl, also resulted in low yield and enantioselectivity of the mono-silylated product (eq 1). These results are consistent with covalent bonding between the secondary hydroxyl of the substrate and catalyst being essential for enantioselectivity.
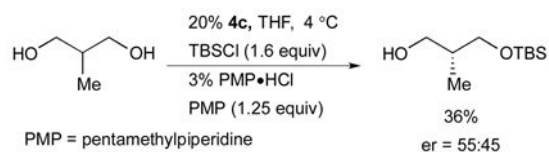
$$(1)$$

With the optimal conditions in hand we investigated the range of silyl chlorides that can be employed in the reaction. Both TIPSCl and TBDPSCl provide the mono-silylated product in high yield and enantioselectivity (eq 2). These silylating reagents generally require extended reaction times (24 h) in order to achieve high conversions. Employing the more reactive TESCl results in a complex mixture of products. In this case, both the bis-silylated product, in which the secondary hydroxyl is protected, and the secondary hydroxyl mono-silylated product are observed.[‡]
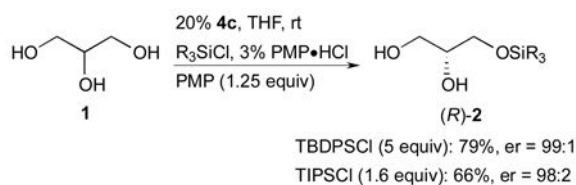
$$(2)$$

The formation of **3** with TBSCl was unusual for catalyst **4** since in the desymmetrization of *cis*-1,2-diols bis-silylated products were not observed in significant quantities.[6b] To determine the origin of the over-silylation the yield and enantioselectivity were monitored as

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[‡]The functionalization of the secondary hydroxyl is consistent with previous published results (ref 6a), which demonstrate the regiodivergent resolution of terminal 1,2-diols.

a function of time. As Figure 2 shows, the initial enantioselectivity of the reaction is 90:10 er with 45% yield of **2** after 1 h. Over time the enantioselectivity increases to >99:1 er with concomitant formation of **3**. These results are consistent with a secondary resolution occurring on the mono-silylated product.[12] Rephrasing these results in terms of kinetics, the formation of (*R*)-**2** is approximately 9x faster than (*S*)-**2** ($k_2 > k_1$, Figure 3). Notably, both (*S*)-**2** and (*R*)-**2** can still bind to the catalyst; however, (*S*)-**2** is stereochemically matched to catalyst **4c**. A secondary kinetic resolution occurs in which (*S*)-**2** reacts at a faster rate than (*R*)-**2** ($k_3 > k_4$, Figure 3). Consequently, the formation of **3** is still a scaffold-catalysed process, which helps to increase the enantioselectivity of the desired product (*R*)-**2**.

The desymmetrization of glycerol has proven to be a challenging problem in asymmetric catalysis. By employing a catalyst that uses reversible covalent bonding, a highly efficient desymmetrization is achieved. In this case, the power of intramolecularity helps to avoid intermolecular processes that lead to undesired by-product formation. We are continuing to explore modifications of the catalyst structure to improve catalyst activity, and we are investigating the expansion of the scope of the reaction to other electrophiles.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Notes and references

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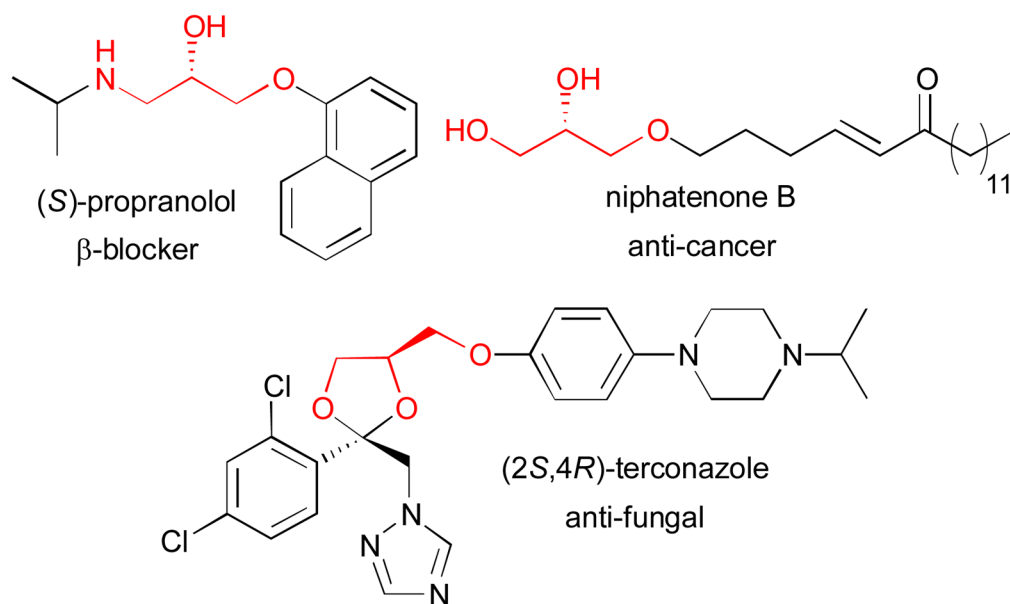**Figure 1.**
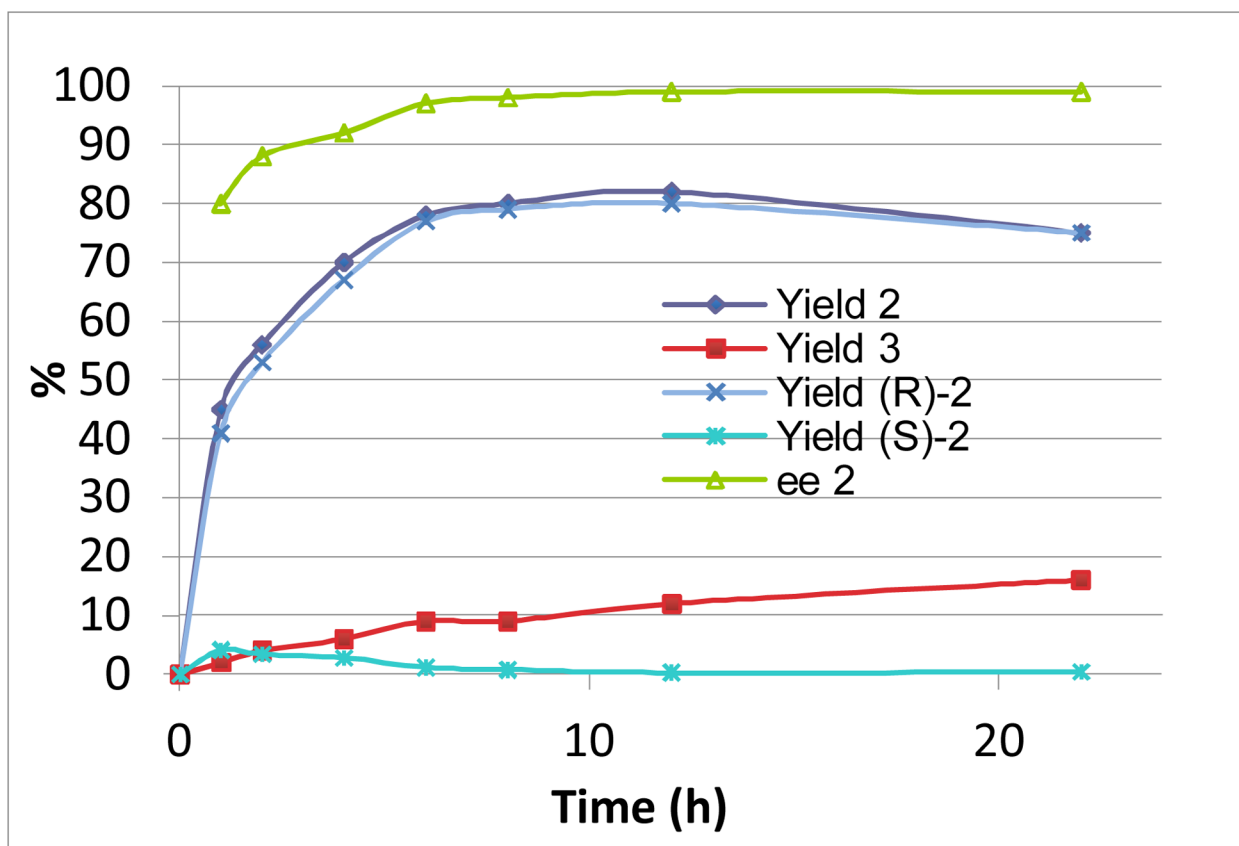Biologically Active Glycerol Derived Products

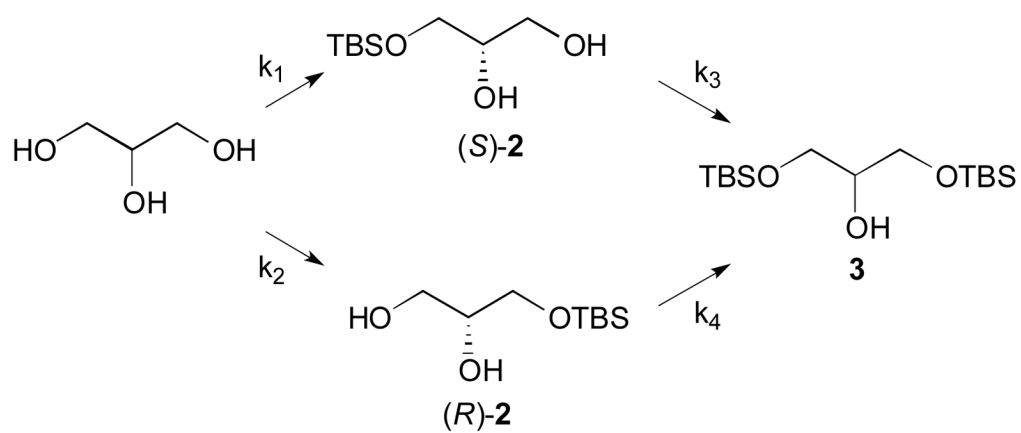**Figure 2.**
Time Course of Selectivity and Yield of Desymmetrization

Figure 3.
Mechanism of Secondary Kinetic Resolution

Table 1

Optimization of Glycerol Desymmetrization

entry	catalyst loading (%)	catalyst	yield 2 (%)[a]	yield 3 (%)[a]	er[b]
1[c]	20	4a	68	14	3:97
2[c]	20	4b	74	12	98:2
3[c]	20	4c	82 (78)[e]	12	>99:1 (>99:1)[e]
4[d]	10	4c	66	20	99:1
5[d]	5	4c	66 (65)[e]	10	99:1 (96:4)[e]
6[c]	20	5	52	8	50:50

[a] yields determined by ^{1}H NMR by comparison to internal standard 1,3,5-trimethoxybenzene.

[b] er's determined by HPLC analysis after derivatization with 1-naphthoyl chloride.

[c] reaction time 12 h.

[d] reaction time 26 h.

[e] isolated yield and er of product on 1 mmol scale and an average of two runs.