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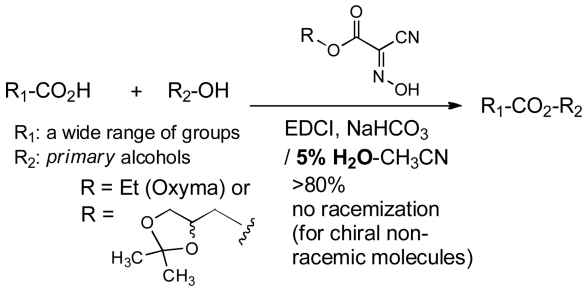
Selective Esterifications of Primary Alcohols in a Water-Containing Solvent

Yong Wang, **Bilal A. Aleiwi**, **Qinghui Wang**, and **Michio Kurosu**
Department of Pharmaceutical Sciences, College of Pharmacy, University of Tennessee Health Science Center, 881 Madison Avenue, Memphis, TN 38163-0001

Michio Kurosu: mkurosu@uthsc.edu

Abstract



Oxyma and an oxyma derivative, (2,2-dimethyl-1,3-dioxolan-4-yl)methyl 2-cyano-2-(hydroxyimino)acetate (5b), displayed remarkable effect on selective esterifications of *primary* alcohols. A wide range of carboxylic acids could be esterified with *primary* alcohols by using EDCI, $NaHCO_3$, and Oxyma or an Oxyma derivative 5b in 5% H_2O-CH_3CN. An Oxyma derivative 5b is particularly useful since it could be removed after the reaction via a simple basic or an acidic aqueous work-up procedure.

In our efforts on total synthesis of muraymycins A_1 (**1**) and D_1 (**2**), and their analogs for structure-activity relationship studies against Gram-positive bacteria including *M. tuberculosis*, it is crucial to develop an efficient synthesis of the dipeptide **3a** and **3b** (Figure 1).[1] We have recently reported an efficient synthesis of the ureido-muraymycidine derivatives (the partial structure highlighted in a box in Figure 1).[1b] In the synthesis of muraymycin A_1 selective acetylation of the *primary* alcohol is necessary to accomplish an efficient synthesis of the left half of **1**. We have screened reported esterification conditions for **4a** to form the mono-acetate **3a**. Although several acetylation conditions with the controlled amounts of reagents and at lowered temperatures provided the mono-acetate at the *primary* alcohol, the selectivity of mono- and di-acetate was not satisfactory. For example, acetylation of **4a** with Ac_2O (5 equiv) and pyridine (10 equiv) in CH_2Cl_2 at 0 °C gave a mixture of **3a** and the di-acetate (3/1) in less than 40% yield. DCC-mediated acetylations under anhydrous conditions yielded the diacetate as a major product. Thus, we commenced optimizing esterification conditions that protect the *primary* alcohol of **4a** with AcOH to yield **3a** exclusively.

Correspondence to: Michio Kurosu, mkurosu@uthsc.edu.

Supporting Information Available Experimental procedures and copies of NMRs. This is available free of charge via the Internet at http://pubs.acs.org.

In our recent finding of amide-forming reactions with the ethyl 2-cyano-2-(hydroxyimino)acetate (Oxyma)[2] derivative (glyceroacetonide-Oxyma, **5b** in Table 1) in water media, it was observed that the **5b**-esters of amino acids (e.g. **9**) are stable during amide-forming reactions in water. Typically, glyceroacetonide-Oxyma catalyzed amide-forming reactions could be achieved with EDCI (1.5 equiv), $NaHCO_3$ (3–6 equiv) in water (0.2–0.3 M) to yield the corresponding peptides in greater than 90% without detectable diastereomers.[3] It has been reported that nucleophilicity of the oxygen atom of alcohols is slightly stronger than that of water.[4] Thus, we expected that selective coupling of the oxime-esters **9** (Table 1) with alcohols could be achieved in water media in the presence of a weak base. Gratifyingly, acetylation of **4a** with excess AcOH (10 equiv), glyceroacetonide-Oxyma **5b** (5 equiv), $NaHCO_3$ (10 equiv) in water (0.2 M) provided the mono-acetate **3a** in 85% yield without the formation of the diacetate (R_2 = OAc in **3a** in Figure 1). Herein, we report the optimization of selective esterifications of *primary* alcohols with Oxyma **5a** or glyceroacetonide-Oxyma **5b**, EDCI, and $NaHCO_3$ in water-containing solvent systems.

Although an acetylation of **4a** to form **3a** could be achieved in water with excess reagents, high-yielding esterifications of alcohols using limited amount of carboxylic acids or alcohols are considered to be challenging transformations in aqueous media. Uronium-based reagents have previously been applied to introduce esters on *primary* alcohols under non-aqueous conditions.[5] To the best of our knowledge, no practical esterification reaction has been developed in water-containing solvent systems. We have observed that glyceroacetonide-Oxyma **5b** is beneficial in high-yielding amide-forming reactions in water with wide range of amino acid derivatives.[3] Reactivity difference between Oxyma **5a** and **5b** in amide-forming reactions in water is attributed to the fact that water solubility of **5b** is improved 2.1 times greater than that of **5a** at pH 8.3 (entries 1 and 2 in Table 1).[6] The esterification reactions of Boc-L-Phe-OH (**6**, 1 equiv) with alcohols (2 equiv), **5a** or **5b** (1.5 equiv), EDCI (1.5 equiv), and $NaHCO_3$ (6 equiv) were examined in water and water-containing solvent systems, and these data are summarized in Table 1. Esterification of **6** with MeOH in water furnished Boc-L-Phe-OMe (**11a**) in 45% yield in 2 h (entry 3). This low-yielding reaction in entry 3 was attributed to a slower reaction rate of the esterification compared to the amide-forming reaction in entry 1. In addition, it was realized that the oxime-ester intermediate **9** has a half-life of approximately 6 h in water at pH 8.3.[7] Thus, we examined the effect of a co-solvent to increase nucleophilicity of alcohol and a half-life of **9**. The same reaction in H_2O-CH_3CN (1/1) improved the isolated yield of **11a** to 55% after 2 h (entry 4). Significant improvement of methyl esterification of **6** was observed when the reaction was performed in 5% H_2O-CH_3CN (entry 5); the isolated yield of **11a** was greater than 95%. Oxyma **5a** could effectively serve as a coupling additive for an esterification reaction in the solvent system (5% H_2O-CH_3CN) (entry 6). Thus, further studies of selective esterifications of *primary* alcohols were performed using Oxyma **5a**. Although several solvents such as 5% H_2O-dioxane and 5% H_2O-acetone could be utilized for effective methyl esterification of **6** (entries 7 and 8), the esterifications in 5% H_2O-CH_3CN were superior to those in the other solvent system tested. Under the optimized conditions [acid (1 equiv), alcohol (2 equiv), **5a** or **5b** (1.5 equiv), EDCI (1.5 equiv), and $NaHCO_3$ (6 equiv)], isopropanol and *tert*-butanol did not form the corresponding esters with **6** even after a prolonged reaction time.[8]

In order to understand the scope and limitations of the selective esterification reactions of *primary* alcohols with EDCI, Oxyma **5a**, and $NaHCO_3$ in 5% H_2O-CH_3CN, these conditions were applied to esterifications of a wide variety of acids with alcohols. Selected examples are summarized in Table 2. Esterifications of **6** with methanol, *primary* alcohols and phenols furnished the corresponding esters in greater than 90% yield without detectable racemization (entries 1–7). Significantly, allyl alcohol could be esterified to provide **23c** in 98% yield. It is worth pointing out that esterifications of carboxylic acid with allyl alcohols have never

been successfully performed using carbodiimide-mediated reaction conditions (entry 3).[9] Unlike 4-(dialkylamino)pyridine-catalyzed DCC-mediated esterification conditions, the Fmoc-group was not cleaved during the benzyl esterifications of the Fmoc-protected amino acids, **12** and **13** (entries 8 and 9).[10] Esterifications of *N*-sulfonylated α-amino acids using carbodiimide coupling reagents often result in low conversion with significant racemization. However, under the conditions in Table 2, the benzyl esterification of **14** furnished **26** in 98% yield with >99% *ee* (entry 10). The chiral carboxylic acids possessing *secondary* alcohols, **15**, **16**, and **17** could be esterified efficiently with the *primary* alcohols. Benzyl esterifications of (*S*)-mandelic acid (**15**) and 3-hydroxybutanoic acid (**16**) furnished the corresponding benzyl esters **27** and **28** in 98% and 99% yields, respectively (entries 11 and 12). Methyl esterification of Boc-L-Thr-OH (**17**) gave rise to Boc-L-Thr-OMe (**29**) in 95% yield (entry 13). Benzoylation, acetylation, and formylation reactions of DL-1,2-isopropylideneglycerol (**18**) provided the corresponding esters **30a**-**c** in greater than 95% yields (entries 14–16). It should be noted that (2,2-dimethyl-1,3-dioxolan-4-yl)methyl formate (**30c**) was not stable to silica gel, thus, its yield was determined based on ^{1}H-NMR analysis of the crude product. On the other hand, formylation of (3,5-bis(benzyloxy)phenyl)methanol (**19**) afforded **31** in 95% yield after silica gel chromatography (entry 17). Selective esterifications of diols were also demonstrated, and selected examples are summarized in Table 2. The *primary* alcohol of butane-1,3-diol (**20**) was selectively benzoylated to afford **32** in 80% yield. Esterifications of glycerol (**21**) with benzoic acid and *n*-hexanoic acid furnished the corresponding diesters **33a** and **33b** in 85% and 90% yield, respectively (entries 19 and 20). Benzoylation of benzyl 2-(acetylamino)-2-deoxy-α-D-glucopyranoside (**22**) was achieved selectively at the C6-position to afford the mono-benzoate **34** in 90% yield (entry 21).

Finally, acylations of the diol of a complex muramic acid derivative **35** were demonstrated as selective esterifications of *primary* alcohols (Scheme 1).[11] Acetylation and benzoylation of **35** using **5b** (1.5 equiv), acid (2 equiv), EDCI (1.5 equiv), and $NaHCO_3$ (6 equiv) at 0 °C gave rise to the *primary* acetate **36a** and benzoate **36b** in greater than 95% without the formation of diacylated product. In the reactions summarized in Scheme 1, it is a significant benefit to use glyceroacetonide-Oxyma **5b**. Although the same reaction with Oxyma **5a** gave equal conversion yield as observed in Scheme 1, separation of **5a** from the product was extremely difficult via silica gel chromatography. On the other hand, **5b** could be removed completely via standard acidic and basic work-ups.

In conclusion, we have optimized selective esterifications of *primary* alcohols using Oxyma **5a** or glyceroacetonide-Oxyma **5b**, EDCI, and $NaHCO_3$ in 5% H_2O-CH_3CN. The selective esterification conditions described here do not require the strict anhydrous condition necessary for ordinal esterification reactions. The coupling additive **5b** can be removed easily after the reactions via acidic and basic work-ups. The new esterification conditions reported here should be a valuable asset in organic synthesis and for selective modifications of polyol molecules.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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References

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5. (a) Twibanire JK, Grindley TB. Org. Lett. 2011; 13:2988–2991. [PubMed: 21591807] (b) Twibanire JK, Omran RP, Grindley TB. Org. Lett. 2012; 14:3909–3911. [PubMed: 22784298]
6. Six equivalents of $NaHCO_3$ in water (0.2 M) shows pH of 8.3.
7. The acetate and benzoate of **5b** have a half-life of over 12 h.
8. Esterifications of **6** with (+)-menthol and cholesterol also did not provide the corresponding esters.
9. (a) Monagle JJ. J. Org. Chem. 1962; 27:3851–3855.(b) Steglich W, Höfle G. Angew. Chem. Int. Ed. Engl. 1969; 8:981.(c) Boden EP, Keck GE. J. Org. Chem. 1985; 50:2394–2395.
10. Spivey AC, Arseniyadis S. Angew. Chem. Int. Ed. 2004; 43:5436–5441.
11. Under the optimized conditions, acetylation of **4a** furnished **3a** in greater than 95% without the formation of the diacetate (Figure 1)

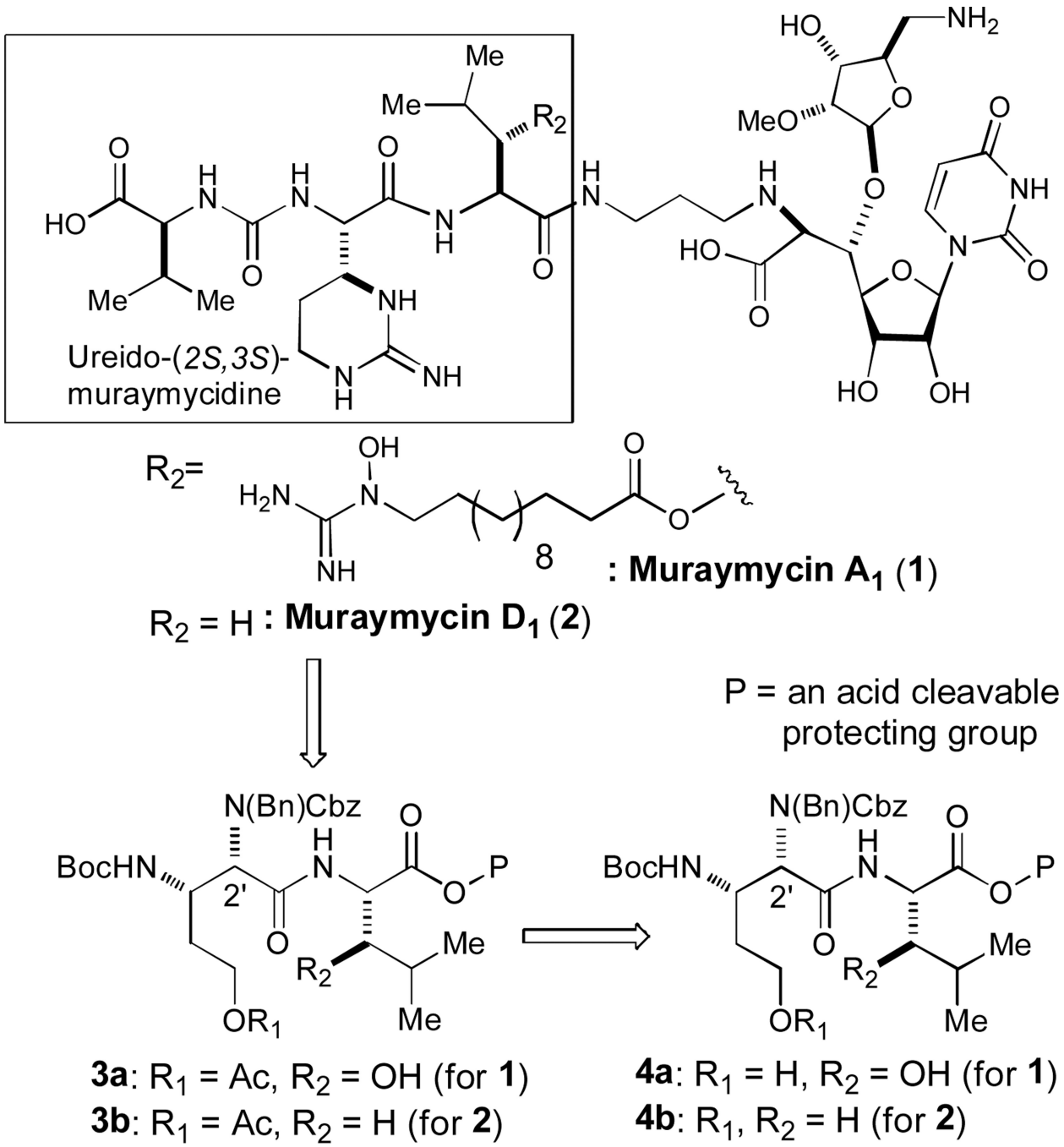
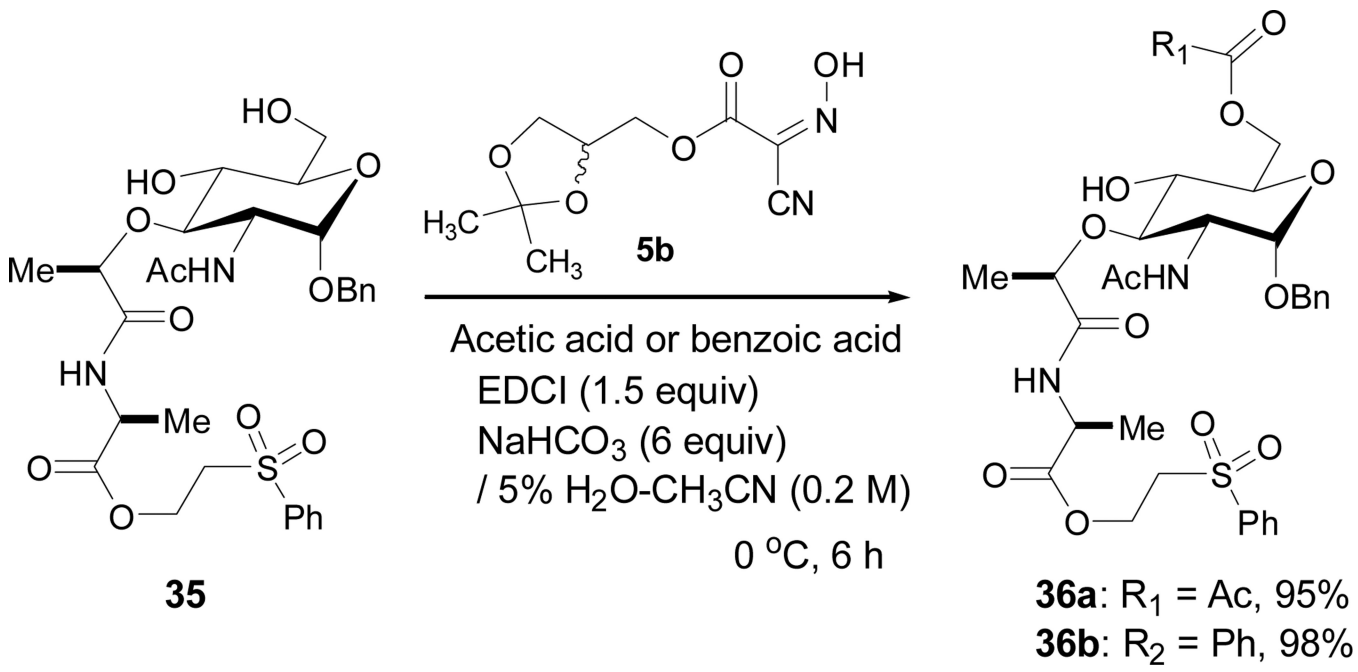


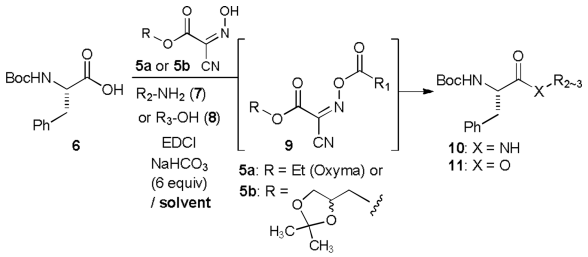
Figure 1.
Syntheses of muraymycins A_1 (**1**) and D_1 (**2**).



Scheme 1.
Selective acylations of **35**.

Table 1

Amide- or ester-forming reactions in water media.



entry	additive / solvent	7 or 8	product (10 or 11)	yield (%)[d]
1[a]	**5b** H_2O	HCl•H-L-Ala-OMe(**7a**)	Boc-Phe-Ala-OMe (**10a**)[c]	93
2[a]	**5a** H_2O	**7a**	**10a**[c]	25
3[b]	**5b** H_2O	MeOH	Boc-Phe-OMe (**11a**)[c]	45
4[b]	**5b** 50% H_2O-CH_3CN	MeOH	**11a**	55
5[b]	**5b** 5%H_2O-CH_3CN	MeOH	**11a**[c]	>95
6[b]	**5a** 5%H_2O-CH_3CN	MeOH	**11a**[c]	>95
7[b]	**5a** 5%H_2O-dioxane	MeOH	**11a**[c]	90
8[b]	**5a** 5%H_2O-acetone	MeOH	**11a**[c]	85
9[b]	**5a** 5%H_2O-CH_3CN	^{i}PrOH	Boc-Phe-O^{i}Pr (**11b**)[c]	0
10[b]	**5a** 5%H_2O-CH_3CN	^{t}BuOH	Boc-Phe-O^{t}Bu (**11c**)[c]	0

[a] **6** (1.0 equiv), **7** (1.5 equiv), additive (1.5 equiv), EDCI (1.5 equiv), $NaHCO_3$ (6 equiv) in H_2O (0.2 M concentrations), 2 h;

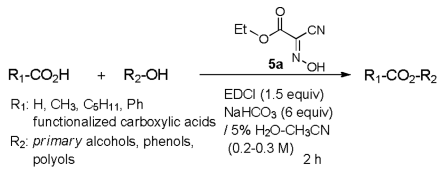
[b] **6** (1.0 equiv), **8** (2.0 equiv), additive (1.5 equiv), EDCI (1.5 equiv), $NaHCO_3$ (6 equiv) (0.2 M concentrations);

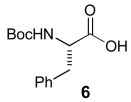
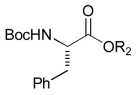
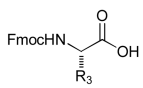
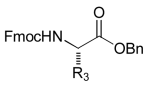
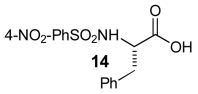
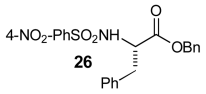
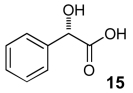
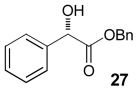
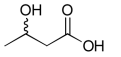
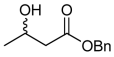
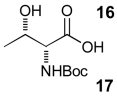
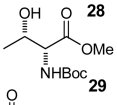
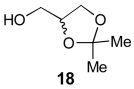
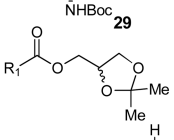
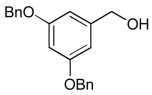
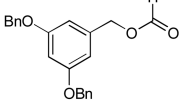
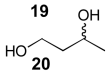
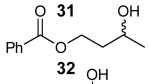
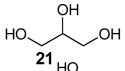
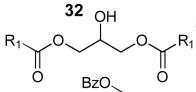
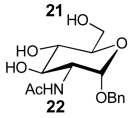
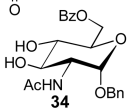
[c] *de* or *ee* was determined to be >99% via HPLC analysis;

[d] isolated yield.

Table 2

Selective esterifications of *primary* alcohols using EDCI, Oxyma **5a**, and $NaHCO_3$ in 5% H_2O-CH_3CN[a]



entry	R_1-CO_2H	R_2-OH	product	yield (%)	*ee* (%)[b]
1[c]	 **6**	EtOH	 **23a**: R_2 = Et	95	>99
2[c]		*n*-hexanol	**23b**: R_2 = C_6H_{13}	97	>99
3[c]		allyl alcohol	**23c**: R_2 = allyl	98	>99
4[c]		BnOH	**23d**: R_2 = Bn	99	>99
5[c]		Phenol	**23e**: R_2 = Ph	95	>99
6[c]		4-chlorophenol	**23f**: R_2 = 4-Cl-Ph	95	>99
7[c]		2,4,6-trichlorophenol	**23g**: R_2 = 2,3,4-tri-Cl-Ph	90	-
8[c]	 **12**: R_3 = 4-(OH) $PhCH_2$	BnOH[g]	 **24**: R_3 = 4-(OH) $PhCH_2$	96	>99
9[c]	**13**: R_3 = ^{i}Pr	BnOH	**25**: R_3 = ^{i}Pr	95	>99
10[c]	 **14**	BnOH	 **26**	98	>99
11[c]	 **15**	BnOH	 **27**	98	>99
12[c]	 **16**	BnOH	 **28**	99	-
13[c]	 **17**	MeOH	 **29**	95	>99
14[d]	R_1 = Ph	 **18**	 **30a**: R_1 = Ph	>95	-
15[d]	R_1 = CH_3		**30b**: R_1 = CH_3	99	-
16[d]	R_1 = H		**30c**: R_1 = H	>95[e]	-
17[d]	R_1 = H	 **19**	 **31**	95	-
18[d]	R_1 = Ph	 **20**	 **32**	80	-
19[d]	R_1 = Ph	 **21**	 **33a**: R_1 = Ph	85	-
20[d]	R_1 = C_5H_{11}		**33b**: R_1 = C_5H_{11}	90	-
21[d,f]	R_1 = Ph	 **22**	 **34**	90	-

[a] All reactions were carried out using **5a** (1.5 equiv) at rt except where noted;

[b] *ee* was determined by HPLC (Daicel Chiralcel OD-Hcolumn);

[c] R_1-CO_2H (1 equiv) and R_2-OH (2 equiv) were used;

[d] R_1-CO_2H (2 equiv) and R_2-OH (1 equiv) were used;

[e] yield was determined *via* ^{1}H-NMR;

[f] the reaction was carried out at 0 °C;

[g] R_1-CO_2H (1 equiv) and R_2-OH (8 equiv) were used.