Asymmetric Catalysis

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Palladium-Catalyzed Asymmetric Allylic Alkylation of Cyclic Dienol Carbonates: Efficient Route to Enantioenriched γ-Butenolides Bearing an All-Carbon α-Quaternary Stereogenic Center

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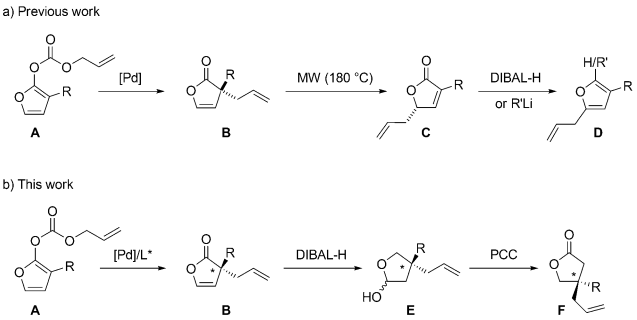
Since its introduction almost simultaneously by Tsuji et al.[1] and Saegusa et al.[2] in the beginning of the 1980s, the palladium-catalyzed decarboxylative allylic alkylation reaction has been the focus of intensive efforts and has become one of the most valuable methods for the construction of C–C bonds.[3] Interestingly however, despite all the developments made during the next two decades, it was only in 2004 that Stoltz et al.,[4] and Burger and Tunge[5] reported the first asymmetric versions of this class of reaction by applying it to cyclic allyl enol carbonates and 1,3-disubstituted allylic β-ketoesters, respectively. Immediately after, Trost et al. reported the use of a new family of ligands derived from 2-diphenylphosphinobenzoic or 1-naphthoic acid and a chiral scalemic diamine enabling the asymmetric synthesis of both cyclic[6] and acyclic[7] ketones bearing either a tertiary or a quaternary α-stereogenic center. Since then, this reaction has been successfully applied to a wide variety of substrates including α-sulfonyl,[8] α-nitro,[9] α-cyano,[10] α-imino,[11] or α-heteroaromatic[12] allyl esters as well as various enol carbonates[13] and silyl enol ethers,[14] thus illustrating its broad functional-group tolerance.

Our work in this field began after observing that cyclic dienol carbonates such as **A** could also serve as valuable substrates for the palladium-catalyzed decarboxylative allylic alkylation (Pd-AA) reaction, thereby affording, predominantly, the α-allylated product **B** (Scheme 1 a). The resulting 1,5-diene could then be engaged in a microwave-mediated Cope rearrangement[15] followed by a nucleophilic addition and a dehydration reaction to afford the corresponding 2,4-disubstituted or 2,3,4-trisubstituted furan **D**.[16] We thus reasoned that by combining a source of Pd^0 with an adequately chosen chiral ligand, this reaction would offer the possibility to access 2(3*H*)-furanones **B** bearing an α-quaternary stereogenic center (α-quaternary butenolides)[17,18] in a highly straightforward and enantioselective fashion. We present here the results of our endeavors (Scheme 1 b).

To test our hypothesis, we decided to initiate our study using the cyclic dienol carbonate **1a** as a model substrate. The



Scheme 1. a) One-pot, four-step, sequence for the synthesis of polysubstituted furans by Pd-AAA. b) Enantioselective synthesis of α-quaternary butenolides and β-quaternary butyrolactones by Pd-AAA. DIBAL-H = diisobutylaluminum hydride, PCC = pyridinium chlorochromate, MW = microwave.

latter, prepared in three steps and 39% overall yield starting from commercially available α-methylene-γ-butyrolactone by cross-metathesis with 3-butenylbenzene,[19] subsequent $RhCl_3$-mediated isomerization,[20] and a final O-acylation, was first engaged in a reactivity and enantioselectivity screen across an array of ligands by performing the reactions in THF at 0 °C. The results of this survey are summarized in Table 1.

As a general trend, with the exception of (*R*)-binaphane (**L7**; Table 1, entry 7), all the reactions proceeded efficiently, independently of the ligand used, to afford predominantly the α-allylated product **2a**. It is worth pointing out however that palladium catalysts derived from C_2-symmetric diphosphines such as **L1**, **L2**, and **L3** displayed higher levels of selectivity (entries 1–3) than the mixed P/N-type ligands such as the phosphine oxazoline (PHOX) ligand **L4**, the axially dissymmetric C_2-chiral diphosphines (*R*)-binap (**L5**; entry 5), biphenyl **L6** (entry 6) and binaphthyl **L7** (entry 7), and the dimethylphospholane-derived ligands (**L8**; entry 8). In the ideal case, the use of the (*R*,*R*)-DACH-phenyl ligand (**L1**, 10 mol%) developed by Trost et al. in conjunction with $[Pd_2(dba)_3{\cdot}CHCl_3]$ (5 mol%) led to the highest level of selectivity, thus affording the α,α-disubstituted 2(3*H*)-furanone in 82% yield and up to 54% *ee* (entry 1).

Encouraged by these preliminary results, we next examined the influence of the solvent. Interestingly, as the solvent system became more polar, a distinct increase in both the regio- and the enantioselectivity was observed. Accordingly, when performing the reaction in *n*-hexnae, we were able to isolate the α,α-disubstituted 2(3*H*)-furanone **2a** in 72% yield (**2a**/**3a** = 3:1) and 16% *ee* (Table 1, entry 9). Solvents such as

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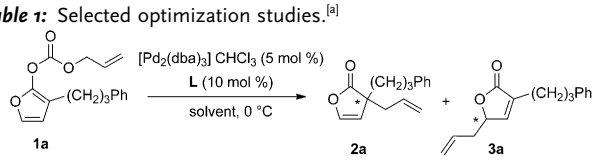
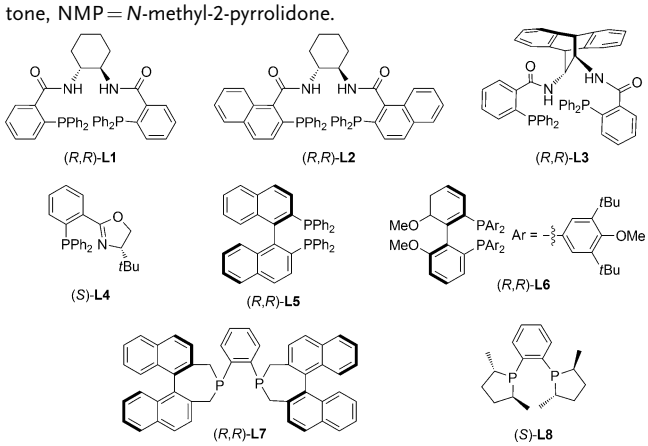
Table 1: Selected optimization studies.[a]

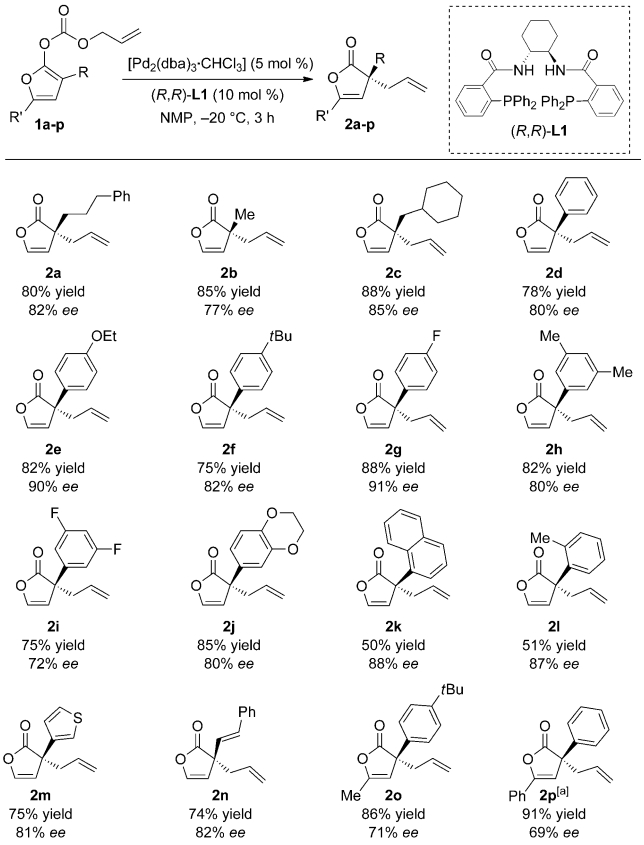


Entry	Solvent	Ligand	**2a**/**3a**[b]	**2a** Yield [%][c]	*ee* [%][d]	**3a** *ee* [%][d]
1	THF	(*R*,*R*)-**L1**	6:1	82	54	92
2	THF	(*R*,*R*)-**L2**	15:1	95	41	–
3	THF	(*R*,*R*)-**L3**	12:1	90	29	40
4	THF	(*S*)-**L4**	12:1	82	4	10
5	THF	(*R*,*R*)-**L5**	4:1	78	7	28
6	THF	(*R*,*R*)-**L6**	7:1	88	4	2
7	THF	(*R*,*R*)-**L7**	6:1	15	10	24
8	THF	(*S*)-**L8**	15:1	80	1	–
9	hexane	(*R*,*R*)-**L1**	3:1	72	16	74
10	toluene	(*R*,*R*)-**L1**	3:1	74	40	98
11	EtOAc	(*R*,*R*)-**L1**	7:1	85	51	95
12	$CHCl_3$	(*R*,*R*)-**L1**	4:1	78	58	90
13	acetone	(*R*,*R*)-**L1**	13:1	82	70	88
14	CH_3CN	(*R*,*R*)-**L1**	16:1	88	72	–
15	DMSO	(*R*,*R*)-**L1**	15:1	90	72	–
16	DMF	(*R*,*R*)-**L1**	15:1	92	75	–
17	NMP	(*R*,*R*)-**L1**	12:1	82	77	90
18	NMP[e]	(*R*,*R*)-**L1**	15:1	84	82	–

[a] All reactions were run on a 0.25 mmol scale. [b] Determined by ^{1}H NMR analysis of the the crude reaction mixture. [c] Yield of isolated **2**. [d] Enantiomeric excess determined by SFC analysis using a chiral stationary phase. [e] Reaction run at −20 °C. dba = dibenzylideneacetone, NMP = *N*-methyl-2-pyrrolidone.



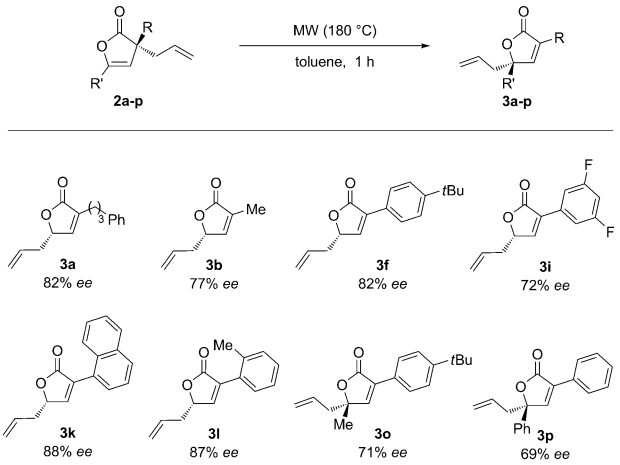
DMSO and DMF led almost exclusively to the α-allylated product in over 90% yield (**2a**/**3a** = 15:1) and with up to 75% *ee* (entries 15 and 16). Ultimately, conducting the experiment in *N*-methyl-2-pyrrolidone (NMP) under otherwise identical reaction conditions offered the best selectivity with an *ee* value of 77% (entry 17), which could be further increased to 82% by running the reaction at −20 °C (entry 18). Additionally, it is worth noting that a difference in selectivity was always observed between the two products **2a** and **3a**, independent of the solvent used. In toluene, for instance, the γ-allylated product was obtained in almost optically pure form (98% *ee*), whereas the α-allylated product was isolated in only 40% *ee* (entry 10), thus confirming our initial assumption[16] that the formation of the γ-monosubstituted 2(5*H*)furanone was solely the result of a competitive γ allylation rather than a [3,3]-sigmatropic Cope rearrangement which could have been triggered during the Pd-AAA process.



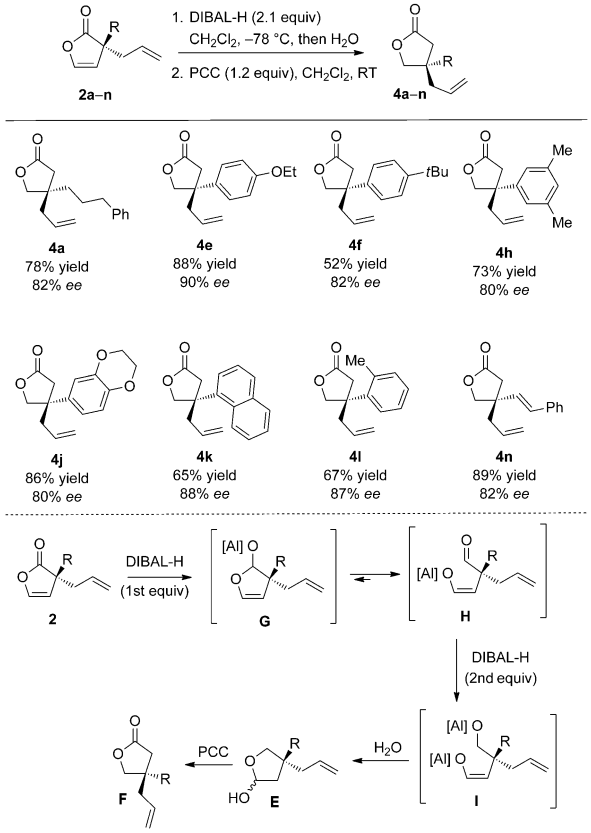
Scheme 2. Scope of the palladium-catalyzed allylic alkylation of allyl dienol carbonates **1a**–**p**. All reactions were run on a 0.25 mmol scale. Enantiomeric excess was determined by SFC analysis using a chiral stationary phase. [a] Reaction run in CH_3CN.

Having identified a useful set of reaction conditions, we next examined the reaction scope by subjecting various alkyl- (**1a**–**c**), aryl- (**1d**–**l**, **1o**–**p**), heteroaryl- (**1m**), and vinyl-substituted (**1n**) dienol carbonates to the Pd-AAA process. The results are summarized in Scheme 2.

Overall, the expected butenolides bearing an α-quaternary stereogenic center (**2a**–**n**) were obtained in high yields (74-88%, α/γ > 10:1) independently of the substitution pattern on the starting allyl dienol carbonate (**1a**–**n**), except perhaps for the two substrates bearing a substitutent at the *ortho* position of the aromatic ring (**1k** and **1l**) for which a lower regioselectivity was observed (α/γ = 3:1) therefore resulting in a slightly lower yield (50–51%). Nonetheless, the enantioselectivities were generally high ranging from 77% to 85% *ee* for the alkyl derivatives (**2a**–**c**), 72% to 91% *ee* for the corresponding aryl derivatives (**2d**–**l**), 80% to 81% *ee* for the heteroaryl- and vinyl-substituted butenolides (**2m**–**n**), and around 70% *ee* for the 1,3-disubstituted allyl dienol carbonates **2o** and **2p**. Finally, to demonstrate the practicality and scalability of the method, a test reaction was performed on a gram scale using the allyl dienol carbonate **1b** as a model substrate. Unsurprisingly, the corresponding α,α-disubsti-



Scheme 3. Microwave-assisted Cope rearrangement of α-quaternary butenolides: a straightforward access to γ-tertiary and γ-quaternary 2(5*H*)furanones. All reactions were run on a 0.2 mmol scale. Enantiomeric excess was determined by SFC analysis using a chiral stationary phase.



Scheme 4. Asymmetric synthesis of β-quaternary butyrolactones. All reactions were run on a 0.25 mmol scale. Yield is that of product isolated after two steps. Enantiomeric excess was determined by SFC analysis using a chiral stationary phase.

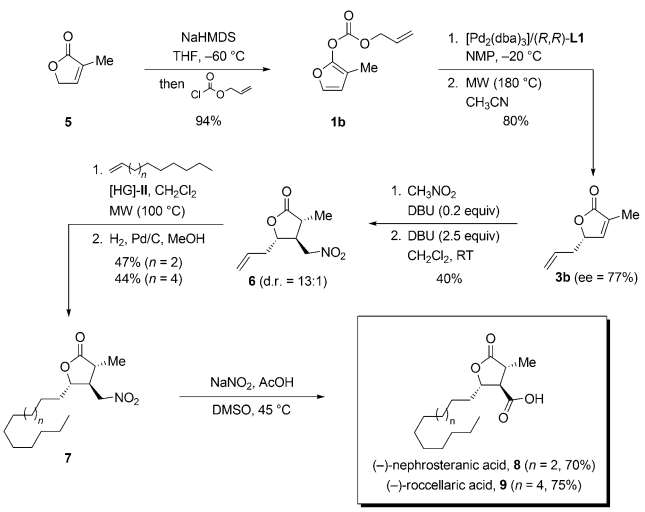
tuted 2(3*H*)-furanone **2b** was isolated in 84% yield and 77% *ee*, which compared favorably with the result obtained on a smaller scale.

With an enantioselective route to enantioenriched butenolides bearing an α-quaternary stereogenic center in hand, we next wanted to illustrate their synthetic utility in the preparation of useful heterocyclic intermediates.[21] In this context, we subjected several α,α-disubstituted butenolides obtained through our catalytic asymmetric alkylation chemistry to a microwave-assisted Cope rearrangement.[22] Indeed, we reasoned that the stereospecificity of this [3,3]-sigmatropic-type transposition would offer straightforward access to enantioenriched 2(5*H*)furanones bearing either a γ-tertiary (**3a–l**) or a γ-quaternary (**3o–p**) stereogenic center (Scheme 3). To our delight, the microwave irradiation of a solution of the α-quaternary butenolides **2a–p** in toluene (closed vessel, 400 W, 180 °C, 1 h) cleanly afforded the desired products **3a–p** in quantitative yield and, most importantly, with no erosion of their optical purity.

Following these results, and with the idea of developing a straightforward and enantioselective route to butyrolactones bearing a β-quaternary stereogenic center, we next decided to subject our α,α-disubstituted butenolides to a two-step sequence featuring a DIBAL-H reduction and a PCC-mediated oxidation. Indeed, we reasoned that in the presence of a hydride source, the α-quaternary butenolides could be readily reduced to the corresponding aluminoxy acetal intermediates **G**, which would be in equilibrium with the aldehyde aluminium enolate species **H** (Scheme 4). Further reduction with a second equivalent of DIBAL-H could then afford the related aluminium alkoxide enolate intermediates **I** which would in turn be converted into the corresponding lactol **E** upon aqueous work-up. Finally, a PCC-mediated oxidation should ultimately afford the desired butyrolactone **F** bearing a β-quaternary stereogenic center (β-quaternary butyrolactone). If successful, this three-step sequence starting from readily available prochiral allyl dienol carbonates would provide a remarkably efficient tool for the synthesis of enantioenriched β-quaternary butyrolactones. To our delight, treating a solution of the α-quaternary butenolides **2a–n** with 2.1 equivalents of DIBAL-H (CH_2Cl_2, −78 °C) and oxidation of the resulting lactol afforded the corresponding β-quaternary butyrolactones **4a–n** in high yields and, once again, with no erosion of their optical purity (Scheme 4).

To determine the absolute configuration of the α-quaternary stereogenic center formed during the palladium-catalyzed allylic alkylation process and also demonstrate the synthetic utility of our method, we undertook the total synthesis of two members of the paraconic acid family[23] of natural products, namely (−)-nephrosteranic acid **8**[24] and (−)-roccellaric acid **9**,[25] both of which exhibit interesting antifungal, antibiotic, antitumor, and antibacterial properties (Scheme 5).

The synthesis of the two natural products began by first converting commercially available 3-methyl-2(5*H*)-furanone **5** into the corresponding ally dienol carbonate **1b** by treatment with NaHMDS and then allyl chloroformate (THF, −60 °C). The resulting allyl dienol carbonate species was then subjected to our optimized Pd-AAA conditions using the (*R*,*R*)-DACH-phenyl Trost ligand in conjunction with [$Pd_2(dba)_3{\cdot}CHCl_3$] (NMP, −20 °C) to afford the α-quaternary butenolide **2b** in 80% yield and 77% *ee*. The latter was then converted into the corresponding γ-tertiary furanone **3b** by



Scheme 5. Application of the palladium-catalyzed allylic alkylation to the synthesis of **8** and **9**. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, DMSO = dimethylsulfoxide, [HG]-II = Hoveyda–Grubbs second generation catalyst, HMDS = hexamethyldisilazide.

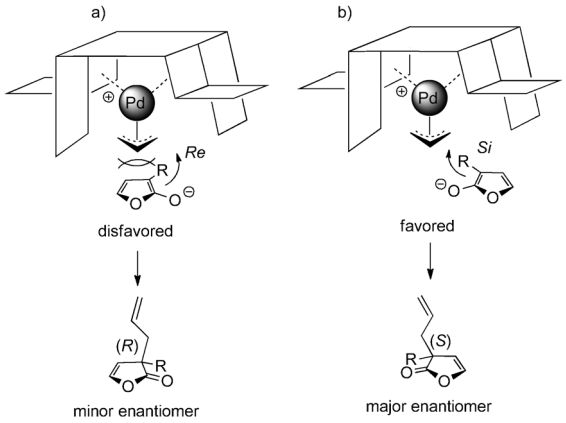


Figure 1. Model for the explanation of the selectivity.

a highly stereospecific microwave-assisted Cope rearrangement (toluene, 180 °C, 1 h, quant.) before a diastereoselective conjugate addition of nitromethane, subsequent cross-metathesis-mediated side-chain elongation, and a final hydrogenation over Pd/C eventually afforded the two natural product precursors in roughly 18 % overall yield. To complete the syntheses, the latter were finally engaged in a modified Kornblum oxidation[26] ($NaNO_2$, AcOH, 45 °C) to afford the desired natural products **8** and **9** in 70 and 75 % yield, respectively.

Gratifyingly, the spectroscopic and physical data of **8** and **9** were consistent with the ones reported in the literature for (−)-nephrosteranic acid {$[\alpha]_D^{20} = -13.8$ ($c = 0.5$, $CHCl_3$); lit.: $[\alpha]_D^{22} = -27.7$ ($c = 0.9$, $CHCl_3$)}[24i] and (−)-roccellaric acid {$[\alpha]_D^{20} = -14.9$ ($c = 0.45$, $CHCl_3$); lit.: $[\alpha]_D^{22} = -26.0$ ($c = 0.5$, $CHCl_3$)},[24i] respectively, thus confirming that the use of the (*R*,*R*)-DACH-phenyl Trost ligand leads preferentially to the formation of the (*S*)-butenolides.

The selectivity of the palladium-catalyzed asymmetric allylic alkylation could have also been predicted using the model proposed by Trost et al. (Figure 1)[7] in which the nucleophile should approach the π-allylpalladium/**L1** complex from its Si face (Figure 1 a) to avoid the disfavored steric interaction between the "wall" of the ligand and the substrate's furan ring (Figure 1 b). Hence, if this assumption is correct, the *S*-configured enantiomer should be formed predominantly during the course of the reaction.

In summary, we have developed an extremely mild and particularly efficient method for the enantioselective synthesis of butenolides bearing an all-carbon α-quaternary stereogenic center. Additionally, we showed that these butenolides could undergo a variety of synthetic transformations and thus serve as valuable intermediates for the synthesis of useful heterocyclic building blocks including β-quaternary butyrolactones, as well as β-quaternary- and γ-tertiary furanones. Finally, we also demonstrated the synthetic utility of our method by applying it as a key step in the total syntheses of (−)-nephrosteranic acid **8** and (−)-roccellaric acid **9**.

Experimental Section

Representative procedure for the palladium-catalyzed decarboxylative asymmetric allylic alkylation of **1a**: to a solution of allyl dienol carbonate **1a** (0.2 mmol) in NMP (1 mL) at −20° was slowly added a premixed solution of $[Pd_2(dba)_3{\cdot}CHCl_3]$ $CHCl_3$ (0.01 mmol, 5 mol %) and (*R*,*R*)-DACH-phenyl Trost ligand (0.02 mmol, 10 mol %) in NMP (1 mL). The resulting reaction mixture was then stirred at the same temperature until complete conversion of the starting material (reaction monitored by TLC analysis). A saturated aqueous solution of brine (20 mL) was then added and the aqueous phase was extracted with AcOEt (3 × 2 mL). The combined organic layers were washed with brine (2 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The crude residue was finally purified by flash column chromatography over silica gel to afford pure furanone **2a** (80 %) as a colorless oil.

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