Organic LETTERS

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Asymmetric Synthesis of Highly Functionalized Tetrahydropyrans via a One-Pot Organocatalytic Michael/Henry/Ketalization Sequence

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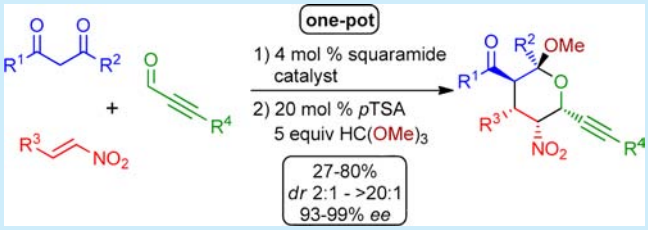
Supporting Information

ABSTRACT: A diastereo- and enantioselective Michael/Henry/ketalization sequence to functionalized tetrahydropyrans is described. The multicomponent cascade reaction uses acetylacetone or β-keto esters, β-nitrostyrenes, and alkynyl aldehydes as substrates affording tetrahydropyrans with five contiguous stereocenters. Employing a bifunctional quinine-based squaramide organocatalyst, the title compounds are obtained in moderate to good yields (27−80%), excellent enantiomeric excesses (93−99% ee), and high diastereomeric ratios (dr > 20:1) after one crystallization.



Over the past years, we have witnessed a strong increase in the number of publications on organocatalysis as the main topic because of their wide applications for the synthesis of valuable chiral entities.[1] Today, numerous groups of organocatalysts are known, with the classes of primary[2] and secondary amines,[3] hydrogen-bonding organocatalysts,[4] chiral phosphoric acids,[5] as well as *N*-heterocyclic carbenes[6] being used preferentially. The catalytic asymmetric synthesis with these small organic molecules under metal-free conditions now constitutes a rapidly growing research area at the frontier of green chemistry.[7] Furthermore, the construction of contiguous stereocenters via cascade reactions from easily available starting materials is one of the main reasons for its exponential increase over the past years.[8] Hayashi and co-workers[9] reported a cross-aldol reaction of alkynyl aldehydes **4** with other simple aliphatic aldehydes to obtain synthetically useful β-alkynyl-β-hydroxy aldehydes. Similar to the cross-aldol reactions, Henry reactions with α-acidic nitro compounds are possible as well.[10] We wanted to combine these methods by incorporating the resulting alcohol functionality in an intramolecular fashion to generate six-membered rings. We envisaged the use of alkynyl aldehydes **4** to facilitate the 1,2-addition to be followed up by a ketalization key step to afford 2-hydroxytetrahydropyrans.[11] To the best of our knowledge, an organocascade Michael/Henry/ketalization[12] sequence to generate densely functionalized tetrahydropyrans bearing five stereogenic centers including one tetrasubstituted carbon is not known. Moreover, the reported organocatalytic asymmetric Michael/Henry/acetalization sequences require additional base to facilitate the formation of tetrahydropyrans.[12b,c] The triple bond is a versatile structural element that can be used for several transformations, e.g., cycloadditions or selective reductions to alkenes and as a precursor of ketones. The 2-hydroxy (or rather alkoxy) tetrahydropyran unit is a characteristic structural feature of a huge number of natural products, besides carbohydrates for instance of spiroketals,[13] in soraphen A[14] and pederin[15] as well as in the class of the bryostatins.[16]

To build up the motif of the tetrahydropyran we planned the addition of a γ-nitro carbonyl compound to an aldehyde.[17] Achiral γ-nitro carbonyl compounds were extensively tested, but no good asymmetric inductions could be achieved. After intensive literature research, a method provided by Rawal et al.[18] was tested. They developed the synthesis of several Michael adducts between 1,3-diketones with β-nitrostyrenes with a novel squaramide organocatalyst based on cinchonine in excellent yields and enantiomeric excesses. Because of the pseudoenantiomeric nature of the cinchona alkaloids, we decided to employ a quinine-based organocatalyst to prove the diversity of this method by synthesizing the corresponding enantiomer.

According to the protocol of the Rawal group, acetylacetone **1a** and β-nitrostyrene **2a** reacted smoothly with catalyst **A** to the Michael adduct **3a**, and in the following new step of the one-pot sequence the aldehyde **4a** was added to form the hemiketal **5a** (Scheme 1). The product was obtained in an excellent enantiomeric excess of 99%, but in a low yield of 30% after column chromatography. To investigate this outcome, we stirred the intermediate Michael product **5a** over silica gel and found out that a retro-aldol reaction between C2/C3 occurred. Addition of a small amount of base during chromatography to neutralize the acidity of silica resulted in a noncharacterizable product. To create a stable compound, we investigated several hydroxyl protecting groups, which all had to react under almost neutral or mild conditions. The best result was obtained with the combination of *p*TSA and $HC(OMe)_3$ in a quantitative yield and with no loss of enantioselectivity. With this knowledge in hand, we added the protecting reagents to the reaction mixture, and thus, we were able to get the desired product in a good yield. Knowing how to overcome the stability problems, we screened for the best reaction conditions. A short temperature screening

Received: April 30, 2014
Published: June 27, 2014

dx.doi.org/10.1021/ol501236a | *Org. Lett.* 2014, 16, 3636−3639

Scheme 1. Initial Outcome of the Envisaged Domino Sequence

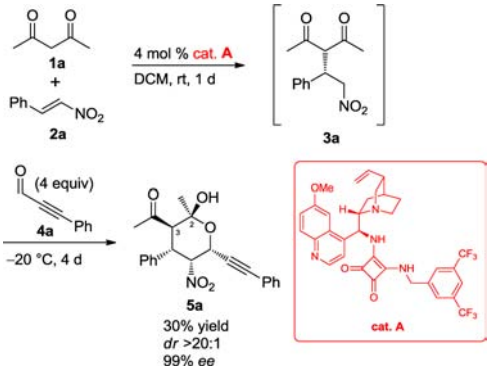
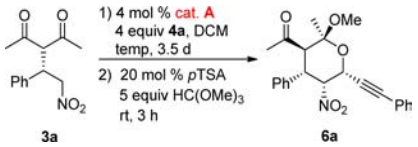


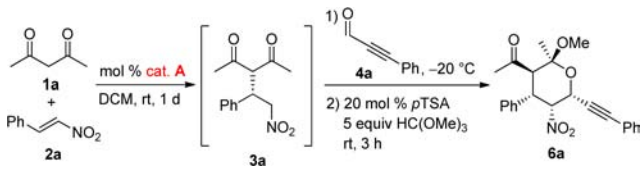
Table 1. Optimizing the Reaction Temperature for the Henry/Ketalization Sequence



entry[a]	temp (°C)	yield[b] (%)	dr[c]
1	rt	50	3:1
2	0	61	8:1
3	−20	80	>20:1

[a]The reaction was performed on a 0.2 mmol scale. [b]Combined yield of isolated product as a mixture of diastereomers after flash chromatography. [c]Diastereomeric ratio; major-(2*S*,3*S*,4*S*,5*R*,6*R*) vs minor-(2*S*,3*S*,4*S*,5*S*,6*S*) diastereomer determined by ^{1}H NMR.

Table 2. Screening for the Optimal Conditions



entry[a]	mol %	**4a** (equiv)	time[b] (d)	yield[c] (%)	dr[d]
1	4	4	4	62	>20:1
2	2	4	5	53	>20:1
3	0.7	4	5	11	n.d.[e]
4	4	10	5	46	>20:1
5	4	2	5	61	>20:1
6	4	1.5	5	52	>20:1
7	4	1.1	5	50	>20:1
8	4	2	6	59	>20:1
9	4	2	7	57	>20:1
10	4	2	9	59	>20:1
11[f]	4	2	5.5	79	>20:1

[a]The reaction was performed on a 0.2 mmol scale (0.2 M in DCM). [b]Sum of reaction time. [c]Combined yield of isolated product as a mixture of diastereomers after flash chromatography. [d]Diastereomeric ratio: major-(2*S*,3*S*,4*S*,5*R*,6*R*) vs minor-(2*S*,3*S*,4*S*,5*S*,6*S*) diastereomer determined by ^{1}H NMR. [e]Not determined. [f]Conducted in 0.4 mL of solvent (0.5 M).

was conducted with Michael adduct **3a** and aldehyde **4a** (Table 1). Reducing the reaction temperature from room temperature to −20 °C (entries 1−3) was followed by an increase in yield and diastereoselectivity. Now we focused on the one-pot procedure

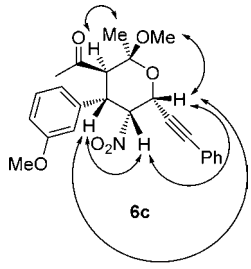


Figure 1. Determination of the relative configuration by NOE for compound **6c**.

for the synthesis of the tetrahydropyrans. Following the protocol of the Rawal group, we started with the addition of acetylacetone (**1a**) and *β*-nitrostyrene (**2a**) with 4 mol % of catalyst in DCM at room temperature (Table 2, entry 1). As opposed to the 2 equiv of acetylacetone of the Rawal group, we used a 1:1 ratio because excess acetylacetone would react with aldehyde **4a** in an aldol condensation and thus increase the complexity of the final mixture. Reducing the amount of catalyst was not successful. Although the first step occurred quantitatively, we could obtain only 53% yield at 2 mol % catalyst loading, respectively, 11% yield at 0.7 mol % (entries 2 and 3). For the next set of modifications, we changed the amount of aldehyde **4a** (Table 2, entry 4−7). With 10 equiv a lower yield as compared to 4 or 2 equiv was obtained, indicating a concentration issue. Further reduction of the amount of the aldehyde led to a small decrease in yield (entries 6 and 7). Extending the reaction time resulted in no increase in yield (entries 8−10). The amount of solvent was reduced to a concentration of 0.5 M, which resulted in an increase of yield (Table 2, entry 11). Having the proper conditions in hand, an extension of the scope was investigated (Table 3). Several different substituents R^3 on the aryl moiety of **2** (entries **b**−**d** and **f**) were introduced, giving moderate to good yields of 27−65% and very good enantioselectivities (93−97% ee). Even a heterocyclic group, like the protected *N*-Boc-indolyl, could be used (Table 3, entry **e**).

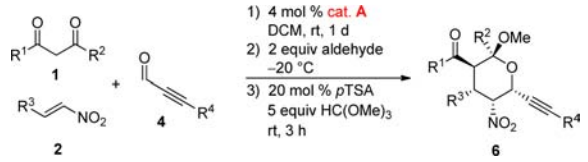
The aromatic part R^4 of the aldehyde **4** was substituted with electron-donating and electron-withdrawing groups to yield the cascade product in modest to good yields (61−80%) and in very good enantioselectivities of 94−97% ee (Table 3, entries **g**−**i**). Switching to a cyclopentyl moiety (entry **j**) led to the same range of yield (68%) and enantioselectivity (96% ee). No product was obtained with benzaldehyde or propanal. Desymmetrization of the acetylacetone to the corresponding methyl ester gave 60% yield and 97% ee (Table 3, entry **k**). Increasing the bulkiness to a *tert*-butoxy group (entry **m**) resulted in a drop of obtained product (34% yield) but still impressive 98% ee.

A further domino product was obtained in 69% yield and 96% ee after extending the side chain to an ethyl group (Table 3, entry **l**). The relative configuration was determined by NOE measurements for compound **6c** (Figure 1) as well as the absolute configuration by single-crystal X-ray analysis of compound **6a** (Figure 2).[19]

In summary, we have developed an organocatalytic Michael/Henry/ketalization cascade sequence to access highly funtionalized tetrahydropyrans. A hydrogen-bonding organocatalyst on a squaramide basis was used to merge acetylacetone or different *β*-keto esters with nitroalkenes and ynals. In this manner, tetrahydropyrans bearing five contiguous stereocenters were obtained in moderate to good yields (27−80%), after one

dx.doi.org/10.1021/ol501236a | *Org. Lett.* 2014, 16, 3636−3639

Table 3. Scope of the Michael/Henry/Ketalization Sequence To Form Tetrahydropyrans



6[a]	R^1	R^2	R^3	R^4	time[b] (d)	yield[c] (%)	dr[d]	ee[e] (%)
a	Me	Me	Ph	Ph	5.5	79	>20:1	>99
b	Me	Me	2-BrC_6H_4	Ph	5.5	65	13:1	93 (99)
c	Me	Me	3-$MeOC_6H_4$	Ph	6.5	45	6:1	97 (99)
d	Me	Me	3,4−$OCHH_2OC_6H_3$	Ph	5	27	2:1	95 (99)
e	Me	Me	3-(*N*-Boc-indolyl)	Ph	6	38	8:1	95
f	Me	Me	4-$NO_2C_6H_4$	Ph	9	46	2:1	93
g	Me	Me	Ph	3-FC_6H_4	5.5	67	5:1	94 (99)
h	Me	Me	Ph	4-MeC_6H_4	5.5	61	7:1	97
i	Me	Me	Ph	2-$MeOC_6H_4$	5.5	80	3:1	95 (99)
j	Me	Me	Ph	cyclopentyl	5.5	68	4:1	96
k	OMe	Me	Ph	Ph	5.5	60	4:1	97 (99)
l	OMe	Et	Ph	Ph	5	69	3:1	96 (99)
m	O^{t}Bu	Me	Ph	Ph	9	34	2:1	98

[a]The reaction was performed on a 0.4 mmol scale (0.5 M in DCM). [b]Sum of reaction time. [c]Combined yield of isolated product as a mixture of diastereomers after flash chromatography. [d]Diastereomeric ratio: major-(2*S*,3*S*,4*S*,5*R*,6*R*) vs minor-(2*S*,3*S*,4*S*,5*S*,6*S*) diastereomer determined by ^{1}H NMR; after one recrystallization dr > 20:1. [e]Determined by HPLC analysis on a chiral stationary phase for the major diastereomer; value in parentheses after one recrystallization.

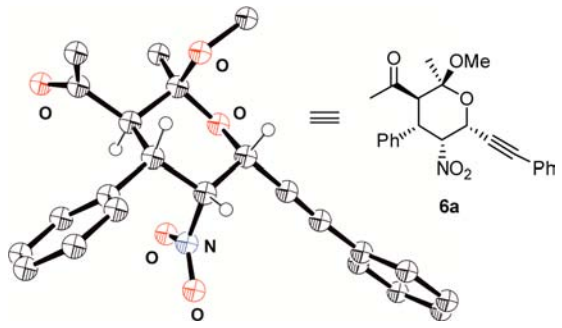


Figure 2. Determination of the absolute configuration by X-ray crystal structure analysis of compound **6a**.

recrystallization in high diastereomeric ratios (dr > 20:1) and excellent enantiomeric excesses (93−99% ee).

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and the characterization of all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Support from the European Research Council (ERC Advanced Grant "DOMINOCAT") is gratefully acknowledged.

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(19) CCDC 999310 (**6a**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.