Cascade Reactions

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An Organocatalytic Cascade Approach toward Polysubstituted Quinolines and Chiral 1,4-Dihydroquinolines–Unanticipated Effect of N-Protecting Groups**

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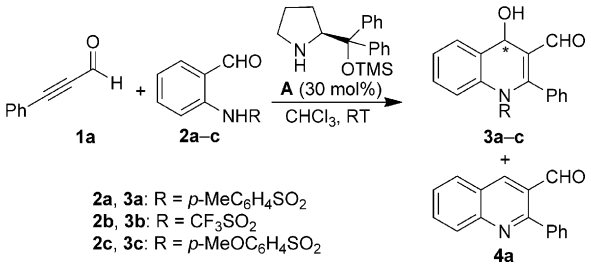
Organocatalytic cascade reactions have been established as a viable and efficient approach to complex molecular architectures,[1] however, examples of the combination of powerful divergent synthesis with an organocatalytic cascade strategy are rare.[2] Herein, we report a powerful divergent organocatalytic cascade reaction that proceeds via a chiral allenamine[3] and involves unprecedented aza-Michael/aldol and aza-Michael/aldol/aromatization sequences to give chiral 1,4-dihydroquinolines and quinolines, respectively. Notably, we made the unexpected discovery that the type of product that is formed depends on the nature of the N-protecting group of the starting material.[4] When aryl sulfonyl moieties with electron-donating groups are used as N-protecting groups, a Michael/aldol/aromatization cascade proceeds predominantly to give polysubstituted quinolines. However, when sulfonyl moieties with electron-withdrawing groups, such as the triflic group, are employed as N-protecting group, chiral 1,4-dihydroquinolines are produced through a highly enantioselective Michael/aldol cascade reaction.

The "privileged" status of quinolines and related chiral hydroquinolines in organic synthesis[5] and biological applications[6] demands more efficient strategies for their preparation. Although classic annulation reactions[7] and new, improved versions[8] have been developed, in general they require multiple steps and/or highly functionalized substrates. On the other hand, significant efforts have been made toward chiral tetrahydroquinolines[9,10] and 1,2-dihydroquinolines.[11,12] Nevertheless, the asymmetric synthesis of 1,4-dihydroquinoline architectures remains elusive,[13] and only a single example, reported by Mangeney and co-workers, was developed by using a chiral auxiliary as stereocontrol.[14] To our knowledge, a catalytic version has not been reported.

Our initial investigation focused on the model reaction of *N*-tosyl-2-aminobenzaldehyde **2a** with phenylpropargyl aldehyde **1a** in the presence of 30 mol% of diphenylprolinol TMS ether **A**[15] in $CHCl_3$ at room temperature (Table 1, entry 1).

Table 1: Exploration of organocatalytic aza-Michael/aldol/aromatization cascade reaction.[a]



Entry	2	Additive	t [h]	Yield 3 [%][b]	Yield 4a [%][b]
1	2a	none	30	0	54
2	2b	none	28	64 (7%)[c]	0
3	2c	none	35	0	51
4[d]	2c	K_2CO_3 (0.1 equiv)	16	0	99[e]

[a] For reaction conditions, see Experimental Section. [b] Yields of isolated products. [c] *ee* value. [d] 10 mol% of catalyst **A** used and reaction performed at 50°C. [e] After completion of the reaction, silica gel (80 mg) was added and the mixture was stirred at RT for 24 h. Then, Et_3N (0.18 mmol) was added and the mixture was stirred at RT for another 3 h to get free deprotonated quinoline **4a.** TMS = trimethylsilyl.

The tosyl (Ts) group was selected as protecting group for the nitrogen atom, because its strong electron-withdrawing nature enhances the acidity of the NH functionality, thus facilitating ionization, which produces a more nucleophilic nitrogen anion for the initial Michael addition.[12a] TLC and ^{1}H NMR analysis of the crude showed that seemingly the aza-Michael/aldol product **3a** was produced. However, when the reaction mixture was subjected to purification by column chromatography on silica gel, unexpected compound **4a** was obtained instead in 54% yield (Table 1, entry 1). It appeared that product **3a** was transformed into **4a** in the presence of silica gel.

We believe that acidic silica gel promotes the aromatization process through a dehydration–deprotection sequence of the sulfonyl group (see Scheme S1 in the Supporting Information). The driving force for the formation of product **4a** may be the tendency of 1,4-dihydroquinolines to dehydrate

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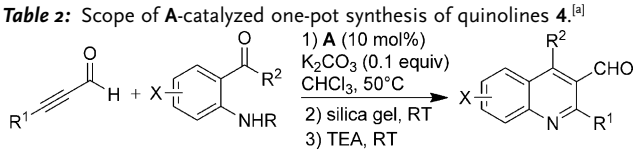
and thus aromatize under acidic conditions. An aromatic sulfonamide that bears an electron-donating moiety assists in the development of the carbocationic character for a favorable dehydration–aromatization process, while a sulfonamide that bears a strong electron-withdrawing moiety will inhibit this development. Indeed, when the Tf protecting group was used, aromatization product **4a** was not formed (Table 1, entry 2). Instead, stable, chiral 1,4-dihydroquinoline **3b** was obtained in 64% yield, but with only 7% *ee* after column chromatography on silica gel. We also found that the Michael/aldol cascade proceeded rapidly (5 h), presumably because of the tendency of the more acidic TfNH moiety to produce TfN^- more easily. The influence of the electronic effect was further demonstrated for aromatic sulfonyl groups that bear electron-donating (**2c**; Table 1, entry 3), electron-neutral, and electron-withdrawing substituents (see Table S1). Based on these studies, we decided to use *p*-$MeOC_6H_4SO_2$ as protecting group for further optimization of the reaction conditions. The screening of solvents and bases (Table S1) led to the optimal conditions, which include the use of K_2CO_3 (0.1 equiv) at 50 °C with 10 mol% catalyst loading (Table 1, entry 4). The scope of Michael/aldol/aromatization cascade reactions catalyzed by organocatalyst **A** was probed accordingly (Table 2).

The tandem process serves as a general approach to the preparation of valuable polysubstituted quinolines. In the cascade process, the reactions proceeded in high yields (76–99%) with a broad substrate scope. It seems that the electronic nature of aromatic ynals **1** has a limited effect on the process. The electron-neutral (Table 2, entries 1, 15, 17–20, and 23), electron-donating (entries 3, 4, 9, and 11), and electron-withdrawing (entries 2, 5–8, 12, 16, 21, 22, and 24) substituents could be tolerated with significant structural variation. A similar trend was observed for heteroaromatic ynals, such as thiophen-2-yl-propynal (Table 2, entry 10). Furthermore, the reaction worked well with less reactive aliphatic ynals **1** (Table 2, entries 13 and 14), although a higher catalyst loading (20 mol%) was needed and relatively low yields were observed. On the other hand, the reaction could be applied to substrates **2** with a broad structural scope. Again, the survey of the electronic effect shows that its impact is limited. Both electron-donating (X = Me; Table 2, entries 15 and 16) and electron-withdrawing (X = Cl; entries 17 and 18) groups are well tolerated. Moreover, significantly more hindered and less reactive ketone moieties in substrates **2** (i.e., $R^2 \neq H$) are compatible with this methodology (Table 2, entries 19–24). Structurally diverse ketones can be used in the process to give trisubstituted quinolines **4** with high efficiency. With an increased steric hindrance of the R^2 group, that is, $R^2 = CH_3$, (*E*)-PhCH=CH, and Ph, more drastic conditions for the aromatization reaction were required, although high yields (76–98%) could still be achieved under relatively mild conditions.

Having established an efficient protocol for the preparation of quinolines through an organocatalytic aza-Michael/aldol/aromatization cascade process, we turned our attention to aza-Michael/aldol cascade reactions for the one-pot preparation of structurally diverse chiral 1,4-dihydroquinolines. The above-mentioned study showed that the use of Tf as protecting group led to the product without subsequent

Table 2: Scope of **A**-catalyzed one-pot synthesis of quinolines **4**.[a]



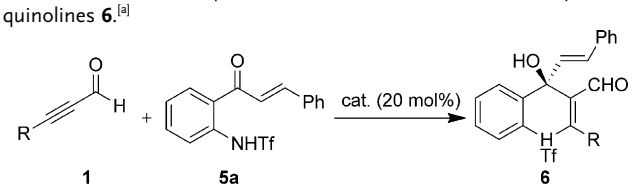
1 **2** R = *p*-$MeOC_6H_4SO_2$ **4**

Entry	R^1, R^2, X	4	*t* [h]	Yield [%][b]
1	Ph, H, H	**4a**	16	99
2	4-BrC_6H_4, H, H	**4b**	16	97
3	4-MeC_6H_4, H, H	**4c**	24	92
4	4-$MeOC_6H_4$, H, H	**4d**	21	95
5	2-ClC_6H_4, H, H	**4e**	16	96
6	4-FC_6H_4, H, H	**4f**	16	98
7[c]	4-CNC_6H_4, H, H	**4g**	20	91
8	4-ClC_6H_4, H, H	**4h**	16	92
9[d]	2-$MeOC_6H_4$, H, H	**4i**	16	95
10	2-thienyl, H, H	**4j**	16	92
11[d]	3-$MeOC_6H_4$, H, H	**4k**	16	97
12[c]	3-CNC_6H_4, H, H	**4l**	13	95
13[c]	nC_5H_{11}, H, H	**4m**	16	80
14[c]	$Ph(CH_2)_2$, H, H	**4n**	20	83
15[d]	Ph, H, 6-Me	**4o**	24	98
16[d]	4-ClC_6H_4, H, 6-Me	**4p**	24	90
17	Ph, H, 4-Cl	**4q**	16	94
18	Ph, H, 5-Cl	**4r**	16	91
19[c]	Ph, Me, H	**4s**	22	84
20[c,e]	Ph, (*E*)-PhCH=CH, H	**4t**	12	80
21[c,e]	4-ClC_6H_4, (*E*)-PhCH=CH, H	**4u**	12	78
22[e]	4-FC_6H_4, (*E*)-PhCH=CH, H	**4v**	16	76
23[f]	Ph, Ph, H	**4w**	16	96
24[f]	4-BrC_6H_4, Ph, H	**4x**	16	98

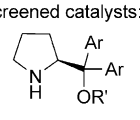
[a] For reaction conditions, see Experimental Section. [b] Yields of isolated products. [c] 20 mol% of catalyst **A** used. [d] 15 mol% of catalyst **A** used. [e] The aromatization step required heating at 50 °C for 3 h in the presence of silica gel. [f] 1.0 equiv of $NaHSO_4 \cdot H_2O$ added and mixture stirred at 50 °C for 24 h. TEA = triethylamine, Tf = trifluoromethanesulfonyl, Ts = 4-toluenesulfonyl.

aromatization (Table 1, entry 2). However, with catalyst **A**, the 1,4-dihydroquinoline was only obtained with 7% *ee*. When more bulky ketone **5a** was used, the enantioselectivity induced by (*S*)-diphenylprolinol TMS ether **A** improved dramatically under similar reaction conditions (Table 3, entry 1, 76% *ee*, 99% yield). A range of chiral α,α-diarylprolinol silyl ether catalysts (**A**–**D**) were subsequently probed, but the results were not encouraging (Table 3, entries 2–4). It should be pointed out that for the model reaction of phenylpropargyl aldehyde (**1a**) with 2′-(trifluoromethanesulfonyl)aminochalcone (**5a**), **5a** and the formed product **6a** have the same polarity, thus rendering the optimization process tedious because of difficult purification. To minimize the work load, we chose more polar 3-nitrophenyl propargyl aldehyde as model substrate for the subsequent optimization. A similar level of enantioselectivity was obtained with catalyst **A** (Table 3, entry 5, 72% *ee*). Gratifyingly, when C_2-symmetric catalyst (2*R*,5*R*)-diphenylpyrrolidine (**E**)[16] was employed, the enantioselectivity was significantly enhanced to 87%, and full conversion was achieved in only one hour (Table 3, entry 6). Furthermore, solvent screening showed that the enantioselectivity was

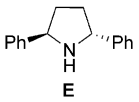
Table 3: Optimization of reaction conditions for organocatalytic enantioselective aza-Michael/aldol cascade reactions toward 1,4-dihydroquinolines **6**.[a]



screened catalysts:



A: Ar = Ph, R' = TMS
B: Ar = Ph, R' = TES
C: Ar = Ph, R' = TBDMS
D: Ar = 3,5-$(CF_3)_2C_6H_3$, R' = TMS

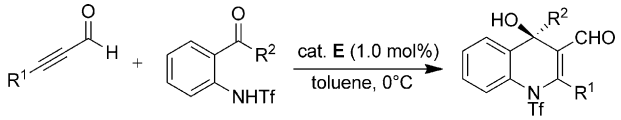


E

Entry	R	Cat.	Solvent	*t* [h]	Yield [%][b]	*ee* [%][c]
1	Ph	**A**	CH_2Cl_2	12	99	76
2	Ph	**B**	CH_2Cl_2	12	93	75
3	Ph	**C**	CH_2Cl_2	12	92	71
4	Ph	**D**	CH_2Cl_2	12	84	40
5	3-NO_2Ph	**A**	CH_2Cl_2	12	93	72
6	3-NO_2Ph	**E**	CH_2Cl_2	1	97	87
7	3-NO_2Ph	**E**	$(CH_2Cl)_2$	1	99	94
8	3-NO_2Ph	**E**	toluene	1	99	98
9	3-NO_2Ph	**E**	MeOH	6	61	75
10	3-NO_2Ph	**E**	*t*BuOMe	4	96	98
11[d]	3-NO_2Ph	**E**	toluene	3	99	99

[a] For reaction conditions, see Experimental Section. [b] Yields of isolated products. [c] Determined by HPLC analysis on a chiral stationary Phase (Chiralpak AS-H or IB column). [d] Reaction performed at 0 °C with 1 mol% of catalyst loading.

Table 4: Enantioselective organocatalytic cascade aza-Michael/aldol reactions between ynals **1** and 2′-(trifluoromethanesulfonyl)aminoketones **5**.[a]



Entry	R^1, R^2	**6**	*t* [h]	Yield [%][b]	*ee* [%][c]
1[d]	Ph, (*E*)-PhCH=CH	**6a**	18	95	97
2	3-NO_2Ph, (*E*)-PhCH=CH	**6b**	3	99	99
3[d]	Ph, (*E*)-(4-BrC_6H_4)CH=CH	**6c**	18	93	98
4	3-NO_2Ph, (*E*)-(4-BrC_6H_4)CH=CH	**6d**	3	99	98
5	4-ClPh, (*E*)-PhCH=CH	**6e**	4	99	98
6	4-CNPh, (*E*)-(4-BrC_6H_4)CH=CH	**6f**	3	91	99
7	4-CNPh, (*E*)-(3-$MeOC_6H_4$)CH=CH	**6g**	8	98	98
8	4-BrPh, (*E*)-(4-$NO_2C_6H_4$)CH=CH	**6h**	5	96	98
9	4-BrPh, (*E*)-(2-MeC_6H_4)CH=CH	**6i**	9	99	97
10[d]	4-MeOPh, (*E*)-PhCH=CH	**6j**	18	92	96
11	2-thienyl, (*E*)-PhCH=CH	**6k**	9	90	96
12[d]	$Ph(CH_2)_2$, (*E*)-PhCH=CH	**6l**	12	99	96
13[e]	*n*-C_5H_{11}, (*E*)-PhCH=CH	**6m**	20	98	97
14[f]	(*E*)-PhCH=CH, (*E*)-PhCH=CH	**6n**	18	70	94
15[f]	Ph, Me	**6o**	18	96	95
16[e,g]	3-$NO_2C_6H_4$, Ph	**6p**	3	84	99

[a] For reaction conditions, see Experimental Section. [b] Yields of isolated products. [c] Determined by HPLC analysis on a chiral stationary phase (Chiralpak AS-H or IB column). [d] 5 mol% of catalyst **E** used. [e] 20 mol% of catalyst **E** used. [f] 8 mol% of catalyst **E** used. [g] Reaction carried out at RT.

highly dependent on the solvent. Remarkably, compared with dichloromethane, significantly higher enantioselectivity was observed with toluene and *t*BuOMe (Table 3, entries 8 and 10). Polar protic solvents, such as MeOH, had a deleterious effect on both the yield and enantioselectivity of the reaction (Table 3, entry 9). Given the high reaction rate and the practical advantage of carrying out the reaction at 0 °C, the catalyst loading was drastically reduced to 1 mol% and the reaction was performed at 0 °C in toluene, thus affording the desired product almost quantitatively and with 99% *ee* within only three hours (Table 3, entry 11).

The optimized protocol can be employed for the reactions of a variety of ynals **1** and 2′-(trifluoromethanesulfonyl)aminoketones **5** (Table 4). Notably, the reactions served as a synthetically efficient one-pot approach to diverse enantioenriched 1,4-dihydroquinolines with a quaternary stereogenic center. They proceeded in high yields (70–99%) and with excellent enantioselectivities (94–99% *ee*). Both substrates, ynals **1** and aminoketones **5**, can be tolerated with significant structural variations. The electronic and steric factors associated with the α,β-unsaturated ketone moieties of 2′-(trifluoromethanesulfonyl)aminochalcones **5** appeared to have minimal impact on the reaction efficiencies with regard to enantioselectivity and yields (Table 4, entries 1–14). The electronic effect of ynals **1** also influences the reaction rate. Electron-withdrawing groups on aromatic ynal substrates tend to accelerate the reaction, which is illustrated by the higher turnover (1 mol% of catalyst loading) and short reaction time (3–9 h; Table 4, entries 2 and 4–9). For ynals **1** that bear electron-neutral (Table 4, entries 1 and 3) or electron-donating substitutents (entry 10), an increase of the catalyst loading is necessary to guarantee full conversion. Less reactive aliphatic ynals can also efficiently participate in the process to give desired products **6l** and **6m** in excellent yields (99 and 98%, respectively) and with excellent *ee* values (96 and 97%, respectively), but with relatively small reaction rates (Table 4, entries 12 and 13). We have also investigated more sterically hindered aliphatic alkynals, such as *tert*-butyl propynal and cyclopentyl propynal, however, no reaction was observed. Structurally altered ketones **5**, such as acetophenone and benzophenone, are also compatible with the protocol, thus leading to compounds **6o** and **6p** with different substituents next to the chalcone moiety (Table 4, entries 15 and 16) with high efficiency. The absolute configuration of **6g**, which was prepared under the optimized conditions, was determined by X-ray crystallography (Figure S1).[17] The observed stereochemistry and high enantioselectivity can be rationalized by the proposed transition state (Scheme S2).

In conclusion, we have developed a divergent organocatalytic cascade approach to synthetically valuable polysubstituted quinolines and highly enantioenriched 1,4-dihydroquinolines. The type of product that is formed depends on the sulfonyl protecting group that is used for the nitrogen atom. Electron-donating aryl sulfonamides facilitate the dehydration–aromatization of the aza-Michael/aldol adducts to give quinolines. However, when the strongly electron-withdrawing Tf group is used, chiral 1,4-dihydroquinolines are produced.

The studies show a scarce example of the electronic effect on the course of the reaction and the nature of the products.[11] Further exploration of this powerful divergent organocatalytic cascade strategy in synthesis is currently pursued in our laboratories.

Experimental Section

General procedure for aza-Michael/aldol/aromatization cascade reactions (Table 2): Compound **2c** (0.15 mmol) and K_2CO_3 (0.015 mmol) were added to a solution of ynal **1** (0.16 mmol) and organocatalyst **A** (10–20 mol%) in chloroform (1.0 mL). The resulting solution was stirred at 50°C for the specified time. After the reaction (monitored by TLC) was finished, silica gel (80 mg) was added and the mixture was stirred at RT for 24 h, then Et_3N (0.18 mmol) was added and the mixture was stirred at RT another for 3 h. The reaction mixture was directly purified by column chromatography on silica gel (eluent: hexane/EtOAc = 20:1) to afford the desired product.

General procedure for cascade aza-Michael/aldol reactions (Table 4)**:** 2′-NH-Tf-protected ketone **5** (0.08 mmol) was added to a solution of ynal **1** (0.0 8 mmol) and organocatalyst **E** (1 mol%) in toluene (0.8 mL). The resulting solution was stirred at 0°C for the specified time. Then, the reaction mixture was directly purified by column chromatography on silica gel (eluent: hexane/EtOAc = 8:1) to afford the desired product. The *ee* value was determined by HPLC analysis on a chiral stationary phase (see the Supporting Information for details).

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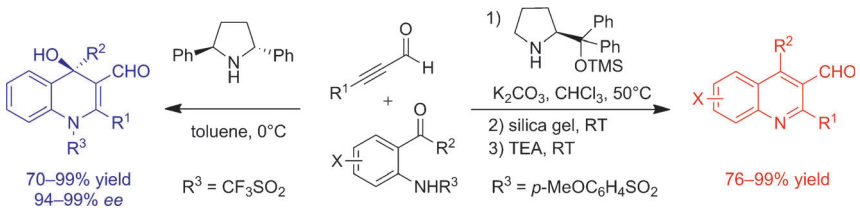
Communications

Cascade Reactions

X.-S. Zhang, X.-X. Song, H. Li,
S.-L. Zhang, X. Chen, X.-H. Yu,*
W. Wang* _____ ■■■■–■■■■

An Organocatalytic Cascade Approach toward Polysubstituted Quinolines and Chiral 1,4-Dihydroquinolines—Unanticipated Effect of N-Protecting Groups



A matter of protection: The outcome of a divergent organocatalytic aza-Michael/aldol cascade process toward quinolines and 1,4-dihydroquinolines depends on the choice of the N-protecting group (see scheme; TEA = triethylamine, TMS = trimethylsilyl). Use of an electron-donating sulfonyl group results in an unanticipated aza-Michael/aldol/aromatization cascade to give polysubstituted quinolines (right). In contrast, chiral 1,4-dihydroquinolines are obtained with an electron-withdrawing sulfonyl group (left).

Kaskadenreaktionen

X.-S. Zhang, X.-X. Song, H. Li,
S.-L. Zhang, X. Chen, X.-H. Yu,*
W. Wang* _____ ■■■■–■■■■

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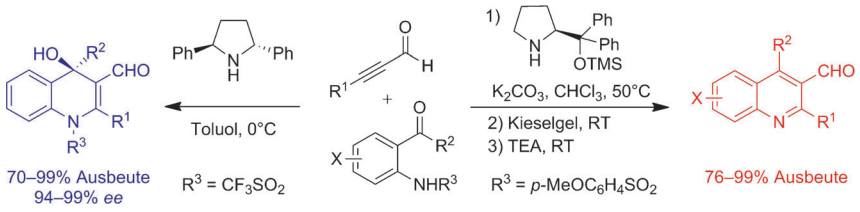

Eine Frage der Schutzgruppe: Das Ergebnis einer divergenten organokatalytischen Aza-Michael/Aldol-Kaskade zur Herstellung von Chinolinen und 1,4-Dihydrochinolinen hängt von der Wahl der N-Schutzgruppe ab (siehe Schema; TEA = Triethylamin, TMS = Trimethylsilyl). Eine elektronenschiebende Sulfonylgruppe führt zu polysubstituierten Chinolinen (rechts), während eine elektronenziehende Sulfonylgruppe chirale 1,4-Dihydrochinoline ergibt (links).

Communications

Cascade Reactions

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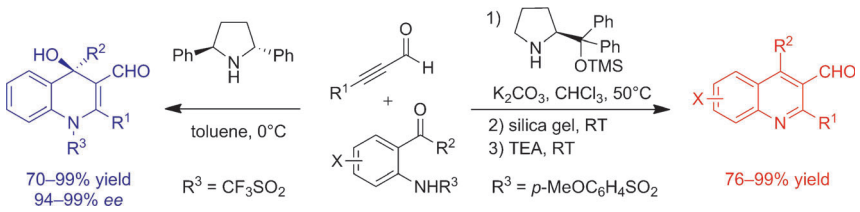

A matter of protection: The outcome of a divergent organocatalytic aza-Michael/aldol cascade process toward quinolines and 1,4-dihydroquinolines depends on the choice of the N-protecting group (see scheme; TEA = triethylamine, TMS = trimethylsilyl). Use of an electron-donating sulfonyl group results in an unanticipated aza-Michael/aldol/aromatization cascade to give polysubstituted quinolines (right). In contrast, chiral 1,4-dihydroquinolines are obtained with an electron-withdrawing sulfonyl group (left).