Construction of Quaternary Stereogenic Carbon Centers by the Lewis Base Catalyzed Conjugate Addition of Silyl Ketene Imines to α,β-Unsaturated Aldehydes and Ketones

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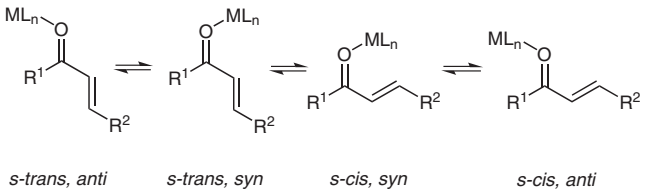
Abstract: Highly site-selective Mukaiyama–Michael additions of silyl ketene imines to α,β-unsaturated aldehydes and ketones are described. The combination of silicon tetrachloride and a chiral bisphosphoramide provides an effective catalyst system for promoting the addition of silyl ketene imines to a variety of aromatic enals with high site selectivity and moderate to good diastereo- and enantioselectivity.

Key words: Lewis base, asymmetric catalysis, Michael addition, aldehydes, quaternary carbon

The catalytic, enantioselective synthesis of compounds containing quaternary stereogenic carbon centers continues to provide organic chemists with challenges for catalyst design and reaction development.[1] The key issue in the construction of these centers is to identify catalyst systems that can overcome the substantial steric encumbrance encountered in the carbon–carbon bond-forming event, while still providing an effective environment for obtaining high asymmetric induction. Although a number of elegant solutions have recently been devised for achieving this goal, certain types of reaction frameworks still present significant obstacles and provide platforms for novel catalyst design and innovation in synthetic methods.

An important transformation that presents promising opportunities for setting quaternary stereogenic centers is the Michael reaction.[2] This venerable process has long been recognized as one the most reliable methods for carbon–carbon bond formation as it allows for the preparation of the synthetically useful class of 1,5-dicarbonyl compounds. Moreover, the high exothermicity of the catalytic Michael reaction provides the energy needed to overcome the steric strain of setting a quaternary center. The successful implementation of a catalytic, enantioselective variant of this reaction[3] requires a catalyst that can control the relative and absolute topicity for the combination of two fully substituted sp^2 centers. For activation of the nucleophile, the catalyst has to control the configuration of a disubstituted enolate. On the other hand, activation of the electrophile requires the catalyst to be coordinated selectively at one of the binding sites of the Lewis basic oxygen (*anti* vs. *syn*, Scheme 1) and also control the conformation of the conjugated double bonds in the acceptor (*s-cis* vs. *s-trans*, Scheme 1).[4] In recent years, creative solutions to these challenges have appeared that provide Michael addition products containing quaternary stereogenic carbons in good yield and high selectivity.[1,2]



Scheme 1

Despite these achievements some limitations still exist for certain combinations of donors and acceptors. For example, existing methods are limited to readily enolizable carbonyl compounds, such as β-keto esters, α-cyano ketones, and β-diketones in combination with acyclic and cyclic ketones. The addition of simple ketones, esters or nitriles to α,β-unsaturated aldehydes or ketones finds no general solution for the synthesis of quaternary stereogenic carbon centers because of the problem of controlling enolate geometry.[5] One notable exception is the work of Yamamoto et al. on the Mukaiyama variant of the Michael addition[6] of silyl enol ethers to α,β-unsaturated acyl phosphonates catalyzed by tethered bis(8-quinolato)aluminum complexes.[7] In this report, the authors obtained 1,4-addition products in moderate to good yield and with high enantioselectivity; however, the reaction scope was limited to cyclic enol ethers and acyl phosphonate electrophiles. This single accomplishment notwithstanding, no methods for the catalytic, enantioselective Mukaiyama–Michael (MM) addition of simple unsaturated aldehydes or ketones with acyclic, disubstituted nucleophiles are on record.[8,9]

Recent studies from these laboratories[10] and others[11] have documented the use of silyl ketene imines (SKIs) for the catalytic, enantioselective construction of quaternary stereogenic carbon centers. These nucleophiles possess a pair of orthogonal substituent planes that place the bulky silyl group in a region perpendicular and distal to the reactive carbon. Because of this unique geometry, SKIs are less hindered than carbonyl derived enolates and are thus

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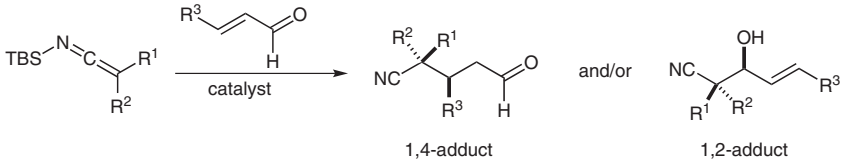


Scheme 2

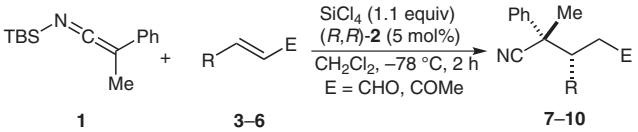
very reactive nucleophiles. In addition, the orthogonal planes obviate the problems of producing geometrically defined, disubstituted enoxysilane nucleophiles.[5] The Mukaiyama–Michael reaction of SKIs with unsaturated aldehydes would produce γ-cyano aldehydes containing a quaternary stereogenic carbon center (Scheme 2). These compounds can be versatile synthetic intermediates, as manipulation of the aldehyde and nitrile functional groups could provide access to lactones, lactams, and piperidines.[12]

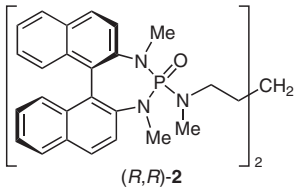
Early studies by Frainnet and co-workers on the uncatalyzed reactions of diphenyl silyl ketene imines with various carbonyl acceptors show the tendency of this nucleophile to undergo selective 1,4-additions with α,β-unsaturated aldehydes such as crotonaldehyde and cinnamaldehyde.[13] Despite this promising result, no subsequent reports have appeared on the enantioselective 1,4-additions of SKIs to conjugated carbonyl compounds. Herein we report our initial studies on the Lewis base catalyzed, $SiCl_4$-mediated additions of disubstituted silyl ketene imines to α,β-unsaturated aldehydes and ketones for the catalytic, diastereoselective, and enantioselective construction of quaternary stereogenic centers.

The combination of $SiCl_4$ and a chiral, nonracemic bisphosphoramide is a highly effective catalyst system for the enantioselective 1,2-addition of a number of different silylated nucleophiles with aldehydes.[14,15] Although α,β-unsaturated aldehydes are known to be effective electrophiles under these reaction conditions, selective 1,4-addition has rarely been observed with this catalyst system.[16] To test the ability of SKIs to participate in a MM-type addition, 2-phenylpropanenitrile derived SKI **1** was prepared by lithiation of the nitrile followed by trapping with TBSCl and its reactivity was assayed in the addition to cinnamaldehyde under the catalytic action of $SiCl_4$ and bisphosphoramide (*R*,*R*)-**2** (Table 1, entry 1).[17] Gratifyingly, the major product obtained after hydrolysis of the in situ formed trichlorosilyl enol ether, resulted from selective 1,4-addition (92:8) and was produced in good yield and with moderate diastereo- and enantioselectivity. On the basis of this encouraging result, a broader survey of α,β-unsaturated electrophiles was carried out (Table 1).

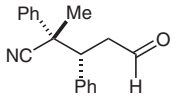
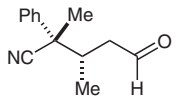
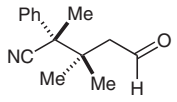
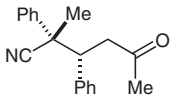
α,β-Unsaturated aldehydes and ketones bearing both aliphatic and aromatic substituents underwent highly site-selective 1,4-additions in good yield (Table 1, entries 1–4). However, the stereoselectivity of the reactions were poor for the cases of aliphatic enals such as crotonaldehyde (Table 1, entry 2). Moreover, when the β-disubstituted electrophile 3-methyl-2-butenal was tested, competitive 1,2-addition was observed, suggesting that steric effects greatly influence the site of addition in this reaction (Table 1, entry 3). The aromatic enone (*E*)-4-phenyl-3-buten-2-one reacted exclusively via 1,4-addition, and the resulting ketone product **10** was isolated in good yield, but poor diastereoselectivity (Table 1, entry 4). Interestingly, the enantioselectivity differed greatly within each diastereomer; moderate er was obtained for the favored *syn*-diastereomer, whereas the minor *anti*-diastereomer was racemic. This observation is consistent with a stereochemical model in which each diastereomer is formed from different enone–catalyst bound complexes (Scheme 1); however, other scenarios that account for the selectivity cannot be ruled out at this time.[18] Additional classes of

Table 1 Survey of α,β-Unsaturated Electrophiles in the 1,4-Addition of SKI-**1** Catalyzed by 5 mol% (*R*,*R*)-**2**





(*R*,*R*)-**2**

Entry	Product	Yield (%)[a]	1,4/1,2[b]	dr[b]	er[c]
1	 **7**	84	92:8	82:18	72:28
2	 **8**	74	92:8	84:16	51:49
3	 **9**	78	48:52	n.a.	55:45
4	 **10**	80	99:1	54:46	80:20[d]

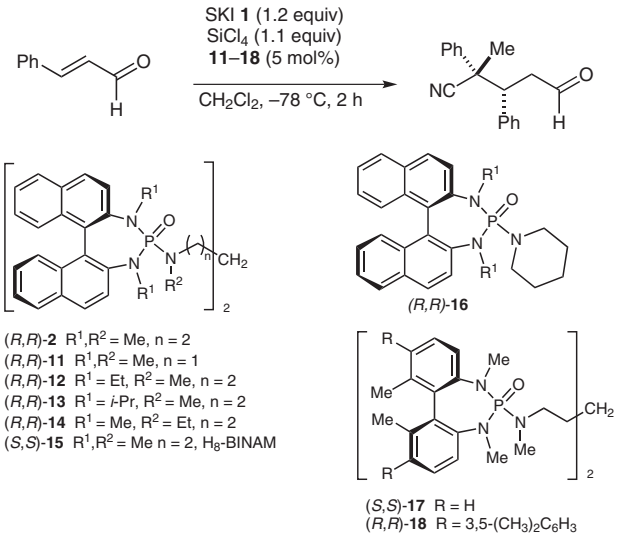
[a] Overall yield of chromatographically homogeneous material.
[b] Determined by ^{1}H NMR analysis of the crude reaction mixture.
[c] Determined by CSP-SFC analysis on the major diastereomer after $NaBH_4$ reduction to the corresponding alcohol.
[d] CSP-SFC analysis performed on the cyano ketone. Minor diastereomer er was determined to be 54:46 by CSP-SFC.

conjugated electrophiles, including α,β-unsaturated esters, nitriles, and nitroalkenes were also tested, but proved unreactive under these reaction conditions.

To optimize the selectivity of the reaction, a survey of Lewis base catalysts was performed (Table 2). The series of catalysts tested in the 1,4-addition examined the sensitivity of the reaction to a number of different structural features of the parent phosphoramide catalyst (*R*,*R*)-**2**, including: (1) the alkyl group on the nitrogens of both the binaphthyldiamine and the diamine tether (Table 2, entries 2–4), (2) the tether length (Table 2, entry 1), (3) monomeric catalyst (Table 2, entry 6), and (4) the dihedral angle of the biaryl unit (Table 2, entry 5 and entries 7 and 8).

Unfortunately, none of the structural modifications resulted in a significant increase in the enantioselectivity of the addition. Surprisingly though, both the reduced dimeric catalyst (Table 2, entry 5) and the biphenyl-derived catalysts (Table 2, entries 7 and 8) afforded the 1,4-addition products in similar yields, site selectivities, and enantioselectivities, but with increased diastereoselectivities. To rule out whether the modest enantioselectivity was arising from a competitive achiral background reaction, the addition was carried out at higher catalyst loading (Table 2, entry 9). Performing the reaction with 15 mol% (*R*,*R*)-**2** produced the 1,4-product in similar yield and selectivities as compared to previous runs with 5 mol% catalyst.[19] The result demonstrates that even at 3× the loading of (*R*,*R*)-**2**, no significant change in the enantioselectivity of the reaction is observed, suggesting that the low selectivity is not solely resulting from an uncatalyzed pathway. Alternative explanations that could account for the moderate enantioselectivity are that the catalyst modifications are not far reaching enough to influence addition at the β-carbon of the enal, and/or the reaction is proceeding through multiple catalyst–acceptor complexes (Scheme 1).

Table 2 Phosphoramide Catalyst Survey in the 1,4-Addition of SKI **1** with Cinnamaldehyde



Entry	Catalyst	1,4/1,2[a]	dr[a]	er[b]
1	(*R*,*R*)-**11**	94:6	82:18	64:36
2	(*R*,*R*)-**12**	80:20	80:20	65:35
3	(*R*,*R*)-**13**	75:25	78:22	52:48
4	(*R*,*R*)-**14**	91:9	82:18	69:31
5	(*S*,*S*)-**15**	92:8	90:10	65:35
6	(*R*,*R*)-**16**	92:8	85:15	60:40
7	(*S*,*S*)-**17**	94:6	91:9	68:32
8	(*R*,*R*)-**18**	92:8	90:10	70:30
9	(*R*,*R*)-**2**	92:8	90:10	74:26[c]

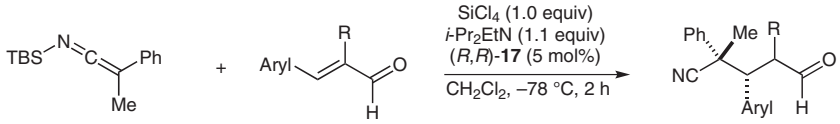
[a] Determined by ^{1}H NMR analysis of the crude mixture.
[b] Determined by CSP-SFC analysis on the major diastereomer resulting after $NaBH_4$ reduction to the corresponding alcohol.
[c] Reaction ran with 15 mol% catalyst.

The final study examined the scope of the reaction with respect to the aryl substituent of the α,β-unsaturated aldehyde. In view of the beneficial effect of the biphenyl-based catalyst on the diastereoselectivity, reactions were carried out with 5 mol% of bisphosphoramide (*R*,*R*)-**17**. Additionally, *N*,*N*-diisopropylethylamine was employed in these reactions to scavenge any adventitious HCl (formed by hydrolysis of $SiCl_4$), which could be acting as a promoter for an achiral background reaction. Under this new set of reaction conditions the addition of SKI **1** to a variety of commercially available β-aryl enals was conducted (Table 3). The results of this study show that both electron-rich and heteroaromatic enals undergo selective 1,4-addition in good yield and with moderate to good diastereo- and enantioselectivity.

One intriguing result that the survey revealed is that substitution on the aryl ring does affect the enantioselectivity of the reaction. This influence was clearly exemplified by the difference in enantiomeric ratio observed for the addition to (*E*)-3-(2-methoxyphenyl)propenal (Table 3, entry 4, 86:14 er) vs. (*E*)-3-(4-methoxyphenyl)propenal (Table 3, entry 2, 72:28 er). The addition to α-methylcinnamaldehyde illustrates the ability of this reaction to set multiple stereogenic centers in a single reaction (Table 3, entry 6). Furthermore, this example demonstrates that protonation of the in situ formed trichlorosilyl enol ether occurs with fairly high diastereoselectivity and suggests that tandem processes could be developed that harness the reactivity of the direct product formed under the reaction conditions.[20]

The *syn* relative configuration of the major diastereomer resulting from 1,4-addition of SKI **1** to cinnamaldehyde was unambiguously established by single crystal X-ray analysis of the product.[21] However, the depicted absolute configuration is assumed from a *Re*-face addition of the SKI to the enal bound in an *s-cis* conformation to the Lewis base–catalyst complex. Although this assignment employs the stereochemical model developed from previous mechanistic and computational studies on 1,2-additions to aldehydes catalyzed by (*R*,*R*)-**2**/$SiCl_4$, it has not been unequivocally confirmed for this reaction.[22]

Table 3 Survey of Aryl Enals in the Addition of SKI **1** Catalyzed by (*R*,*R*)-**17**



1 **3**, **19–23** **7**, **24–28**

Entry	Aryl	R	Product	Yield (%)[a]	1,4/1,2[b]	dr[b]	er[c]
1	Ph	H	**7**	84	92:8	90:10	70:30
2	4-$MeOC_6H_4$	H	**24**	79	95:5	91:9	72:28
3	4-$Me_2NC_6H_4$	H	**25**	94	95:5	68:32	59:41
4	2-$MeOC_6H_4$	H	**26**	83	95:5	68:32	86:14[d]
5	2-furyl	H	**27**	78	92:8	81:19	79:21
6	Ph	Me	**28**	86	93:7	84:10:4:2[e]	69:31[f]

[a] Overall yield of chromatograpically homogeneous material.
[b] Determined by ^1H NMR analysis of the crude reaction mixture.
[c] Determined by CSP-SFC analysis on the major diastereomer after $NaBH_4$ reduction to the corresponding alcohol.
[d] Minor diastereomer er was determined to be 73:27 by CSP-SFC.
[e] The relative configuration at the α-stereogenic center could not be assigned.
[f] The er of 82:18 was obtained with 5 mol% (*R*,*R*)-**2**.

In conclusion, a novel Lewis base catalyzed Mukaiyama–Michael reaction has been described for the generation of quaternary stereogenic carbon centers via the 1,4-addition of silyl ketene imines to α,β-unsaturated aldehydes and ketones. The reactions are selective for 1,4-addition and yield aldehyde or ketone products in moderate to good yield and diastereoselectivity and with moderate enantioselectivity. Future work will focus on mechanistic studies to elucidate the conformation of the bound electrophile–catalyst complex as well as new Lewis base catalyst architectures that can engender higher stereoselectivities.

General Procedure for the MM Reaction of 1 with Aryl Enals Preparation of 2-Methyl-5-oxo-2,3-diphenylpentanenitrile (7)

To a flame-dried 10 mL Schlenk flask under Ar were added (*R*,*R*)-**2** (42 mg, 0.05 mmol, 0.05 equiv), cinnamaldehyde (126 μL, 1.00 mmol), and anhyd CH_2Cl_2 (5.0 mL, 0.2 M in enal). The solution was stirred, cooled to –78 °C, and $SiCl_4$ (130 μL, 1.1 mmol, 1.1 equiv) and DIPEA (175 μL, 1.0 mmol, 1.0 equiv) were added via syringe. The resulting solution was stirred for 5 min at –78 °C, and then a 1.38 M solution of SKI **1** (0.87 mL, 1.2 mmol, 1.2 equiv) in CH_2Cl_2 was added dropwise over 3 min. The reaction mixture was allowed to stir for 2 h at –78 °C and was then quenched by pouring the cold solution into a rapidly stirring solution of sat. aq $NaHCO_3$ and KF (1:1, 20 mL). This biphasic mixture was stirred for 1 h at ambient temperature before being filtered through Celite. The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, hexanes–EtOAc, 8:1) to give 183 mg (70%) of **7** as clear, colorless needles.

Data for Compound 7

^1H NMR (500 MHz, $CDCl_3$): δ = 9.35 (s, 1 H), 7.57 (d, *J* = 7.9 Hz, 2 H), 7.45 (dd, *J* = 15.1, 7.7 Hz, 4 H), 7.35 (dt, *J* = 24.9, 7.2 Hz, 4 H), 3.63 (dd, *J* = 10.8, 3.5 Hz, 1 H), 3.17 (dd, *J* = 17.7, 10.8 Hz, 1 H), 2.58 (dd, *J* = 17.6, 3.5 Hz, 1 H), 1.48 (s, 3 H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 199.0, 139.2, 137.8, 129.1, 129.0, 128.7, 128.3, 128.1, 125.8, 121.7, 49.0, 47.2, 45.7, 26.4. ESI-HRMS: *m/z* calcd for $C_{18}H_{17}NONa^+$: 286.1208; found: 286.1198.

General Procedure for $NaBH_4$ Reduction of Aldehydes Preparation of 5-Hydroxy-2-methyl-2,3-diphenylpentanenitrile (alc-7)

Aldehyde **7** (98 mg, 0.37 mmol) was dissolved in THF–EtOH (1:1, 3.7 mL, 0.1 M) and then $NaBH_4$ (15 mg, 0.4 mmol, 1.1 equiv) was added. The heterogeneous mixture was stirred for 15 min and then was acidified with a few drops of 1 M HCl (pH 3). H_2O (10 mL) was added, the phases were separated, and the aqueous layer was extracted with EtOAc (2 × 20 mL). The combined organic extracts were washed successively with $NaHCO_3$ (1 × 20 mL) and brine (1 × 20 mL), dried over Na_2SO_4, and then filtered and concentrated in vacuo. The residue was purified by column chromatography (silica gel, hexanes–EtOAc, 2:1) to give 98 mg (98%) of **alc-7** as a clear, colorless oil.

Data for Compound alc-7

^1H NMR (400 MHz, $CDCl_3$): δ = 7.59–7.53 (m, 2 H), 7.46–7.30 (m, 8 H), 3.51–3.31 (m, 1 H), 3.18 (dd, *J* = 12.1, 3.1 Hz, 2 H), 3.22–3.11 (m, 2 H), 2.18–2.00 (m, 1 H), 1.83–1.66 (m, 1 H), 1.44 (s, 3 H), 1.01 (s, 1 H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 140.2, 138.2, 129.1, 128.9, 128.6, 127.8, 127.8, 125.8, 122.3, 60.1, 51.5, 47.5, 33.8, 26.9. ESI-HRMS: *m/z* calcd for $C_{18}H_{20}NO^+$: 266.1545; found: 266.1538. SFC: t_R = 3.83 min (72.6%); t_R = 4.42 min (27.4%) (AD, 125 bar, 8% MeOH in CO_2, 3.0 mL/min, 220 nm, 40 °C).

2-Methyl-5-oxo-2,3-diphenylhexanenitrile (10)

^1H NMR (500 MHz, $CDCl_3$): δ = 7.25–7.21 (m, 1 H), 7.19–7.15 (m, 1 H), 7.13–7.08 (m, 1 H), 6.93 (dd, *J* = 7.3, 2.0 Hz, 1 H), 3.67 (dd, *J* = 9.4, 4.5 Hz, 1 H), 3.18 (dd, *J* = 17.1, 9.4 Hz, 1 H), 3.09 (dd, *J* = 17.1, 4.5 Hz, 1 H), 2.05 (s, 1 H), 1.80 (s, 1 H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 205.7, 138.3, 138.1, 128.9, 128.3, 127.9, 127.8, 127.4, 126.4, 122.7, 50.0, 46.9, 45.5, 30.8, 25.4. ESI-HRMS: *m/z* calcd for $C_{19}H_{20}NO^+$: 278.1545; found: 278.1543. SFC: t_R = 5.8 min

(79.3%); t_R = 6.3 min (20.7%) (Chiralpak AD, 125 bar, 2.5% MeOH in CO_2, 2.25 mL/min, 220 nm, 40 °C).

3-(4-Methoxyphenyl)-2-methyl-5-oxo-2-phenylpentanenitrile (24)

^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.34 (d, *J* = 1.1 Hz, 1 H), 7.56–7.53 (m, 2 H), 7.43 (dd, *J* = 10.4, 4.9 Hz, 2 H), 7.36 (d, *J* = 8.8 Hz, 3 H), 6.90 (d, *J* = 8.8 Hz, 2 H), 3.80 (s, 3 H), 3.57 (dd, *J* = 11.0, 3.7 Hz, 1 H), 3.10 (ddd, *J* = 17.4, 11.0, 2.0 Hz, 1 H), 2.53 (ddd, *J* = 17.4, 3.6, 0.6 Hz, 1 H), 1.48 (s, 3 H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 199.2, 159.3, 139.3, 130.0, 129.6, 129.1, 128.2, 125.7, 121.8, 114.0, 55.2, 48.4, 47.5, 45.7, 26.3. ESI-HRMS: *m/z* calcd for $C_{19}H_{19}NO_2Na^+$: 316.1313; found: 316.1312.

5-Hydroxy-3-(4-methoxyphenyl)-2-methyl-2-phenylpentanenitrile (alc-24)

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.52 (d, *J* = 7.4 Hz, 2 H), 7.41 (t, *J* = 7.7 Hz, 2 H), 7.35–7.29 (m, 3 H), 6.90 (d, *J* = 8.8 Hz, 2 H), 3.82 (s, 3 H), 3.43–3.36 (m, 1 H), 3.20–3.15 (m, 1 H), 3.13 (dd, *J* = 12.2, 3.0 Hz, 1 H), 2.11–1.97 (m, 1 H), 1.76–1.63 (m, 1 H), 1.43 (s, 3 H), 1.16 (s, 1 H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 159.01 140.3, 130.1, 128.9, 127.8, 125.9, 122.4, 113.9, 60.2, 55.2, 50.8, 47.8, 33.8, 26.9. ESI-HRMS: *m/z* calcd for $C_{19}H_{22}NO_2^+$: 296.1651; found: 296.1657. SFC: t_R = 2.89 min (72.5%); t_R = 3.84 min (27.5%) (AD, 125 bar, 12.5% MeOH in CO_2, 3.0 mL/min, 220 nm, 40 °C).

3-[4-(Dimethylamino)phenyl]-2-methyl-5-oxo-2-phenylpentanenitrile (25)

^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.34 (dd, *J* = 1.9, 0.9 Hz, 1 H), 7.55 (d, *J* = 7.3 Hz, 2 H), 7.42 (t, *J* = 7.6 Hz, 2 H), 7.35 (t, *J* = 6.8 Hz, 1 H), 7.29 (d, *J* = 8.7 Hz, 2 H), 6.71 (d, *J* = 8.8 Hz, 2 H), 3.51 (dd, *J* = 11.1, 3.8 Hz, 1 H), 3.09 (ddd, *J* = 17.2, 11.1, 2.2 Hz, 1 H), 2.96 (s, 6 H), 2.49 (ddd, *J* = 17.2, 3.7, 0.9 Hz, 1 H), 1.49 (s, 3 H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 199.8, 150.2, 139.6, 129.7, 129.1, 128.11, 125.8, 124.8, 122.0, 112.3, 48.6, 47.7, 45.7, 40.4, 26.4. ESI-HRMS: *m/z* calcd for $C_{20}H_{23}N_2O^+$: 307.1810; found: 307.1801.

3-[4-(Dimethylamino)phenyl]-5-hydroxy-2-methyl-2-phenylpentanenitrile (alc-25)

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.53 (d, *J* = 7.5 Hz, 2 H), 7.40 (t, *J* = 7.7 Hz, 2 H), 7.32 (t, *J* = 7.3 Hz, 1 H), 7.26 (d, *J* = 7.9 Hz, 2 H), 6.72 (d, *J* = 8.8 Hz, 2 H), 3.43–3.31 (m, 1 H), 3.18 (dd, *J* = 14.0, 8.8 Hz, 1 H), 3.05 (dd, *J* = 12.2, 2.9 Hz, 1 H), 2.96 (s, 6 H), 2.03 (tt, *J* = 13.4, 4.8 Hz, 1 H), 1.74–1.61 (m, 1 H), 1.44 (s, 3 H), 1.27 (s, 1 H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 150.0, 140.5, 129.7, 128.8, 127.6, 125.8, 125.5, 122.6, 112.4, 60.4, 50.8, 47.9, 40.4, 33.7, 26.9. ESI-HRMS: *m/z* calcd for $C_{20}H_{25}N_2O^+$: 309.1967; found: 309.1974. SFC: t_R = 3.5 min (59.4%); t_R = 5.70 min (40.6%) (AD, 125 bar, 12.5% MeOH in CO_2, 3.0 mL/min, 220 nm, 40 °C).

3-(2-Methoxyphenyl)-2-methyl-5-oxo-2-phenylpentanenitrile (26)

^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.27 (s, 1 H), 7.61 (d, *J* = 7.8 Hz, 2 H), 7.56 (d, *J* = 7.3 Hz, 1 H), 7.44 (t, *J* = 7.8 Hz, 2 H), 7.39–7.33 (m, 1 H), 7.33–7.28 (m, 1 H), 7.04 (t, *J* = 7.5 Hz, 1 H), 6.94 (d, *J* = 8.3 Hz, 1 H), 4.45 (s, 1 H), 3.91 (s, 3 H), 3.17–2.97 (m, 1 H), 2.50 (dd, *J* = 17.2, 4.1 Hz, 1 H), 1.49 (s, 3 H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 199.6, 157.7, 139.8, 129.1, 128.9, 128.1, 127.7, 126.3, 125.8, 121.7, 121.1, 110.7, 55.6, 48.0, 45.5, 38.9, 25.3. ESI-HRMS: *m/z* calcd for $C_{19}H_{20}NO_2^+$: 294.1494; found: 294.1492.

5-Hydroxy-3-(2-methoxyphenyl)-2-methyl-2-phenylpentanenitrile (alc-26)

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.65 (d, *J* = 7.6 Hz, 1 H), 7.59 (d, *J* = 7.5 Hz, 2 H), 7.42 (t, *J* = 7.7 Hz, 2 H), 7.36–7.22 (m, 2 H), 7.06 (t, *J* = 7.5 Hz, 1 H), 6.94 (d, *J* = 8.2 Hz, 1 H), 4.02 (dd, *J* = 12.4, 3.1 Hz, 1 H), 3.86 (s, 3 H), 3.33 (ddd, *J* = 10.6, 6.7, 4.0 Hz, 1 H), 3.21–3.10 (m, 1 H), 2.03 (ddd, *J* = 13.1, 9.8, 4.8 Hz, 1 H), 1.83–1.64 (m, 1 H), 1.43 (s, 3 H), 1.27 (s, 1 H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 158.1, 140.8, 128.8, 128.4, 127.7, 127.6, 126.8, 125.9, 122.4, 121.2, 110.5, 60.4, 55.7, 48.1, 40.3, 33.8, 25.9. ESI-HRMS: *m/z* calcd for $C_{19}H_{22}NO_2^+$: 296.1651; found: 296.1644. SFC: t_R = 9.1 min (14.3%); t_R = 11.6 min (85.7%) (Chiralpak OD, 125 bar, 5.0% MeOH in CO_2, 2.5 mL/min, 220 nm, 40 °C).

3-(Furan-2-yl)-2-methyl-5-oxo-2-phenylpentanenitrile (27)

^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.46 (s, 1 H), 7.51 (d, *J* = 8.5 Hz, 2 H), 7.47–7.39 (m, 3 H), 7.39–7.32 (m, 1 H), 6.37 (dd, *J* = 3.1, 1.8 Hz, 1 H), 6.33 (d, *J* = 3.2 Hz, 1 H), 3.81 (dd, *J* = 11.2, 3.2 Hz, 1 H), 3.14 (ddd, *J* = 17.7, 11.2, 1.4 Hz, 1 H), 2.50 (dd, *J* = 17.8, 3.3 Hz, 1 H), 1.58 (s, 3 H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 198.5, 151.7, 142.3, 138.7, 129.2, 128.4, 125.7, 121.3, 110.6, 108.6, 47.2, 44.3, 42.6, 26.0. ESI-HRMS: *m/z* calcd for $C_{16}H_{16}NO_2^+$: 254.1181; found: 254.1171.

3-(Furan-2-yl)-5-hydroxy-2-methyl-2-phenylpentanenitrile (alc-27)

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.49 (d, *J* = 7.4 Hz, 2 H), 7.44–7.37 (m, 3 H), 7.33 (t, *J* = 7.3 Hz, 1 H), 6.37 (dd, *J* = 3.1, 1.9 Hz, 1 H), 6.32 (d, *J* = 3.2 Hz, 1 H), 3.55–3.45 (m, 1 H), 3.40 (dd, *J* = 12.2, 3.0 Hz, 1 H), 3.26 (dq, *J* = 15.2, 5.1 Hz, 1 H), 2.05 (tt, *J* = 13.4, 4.3 Hz, 1 H), 1.76–1.61 (m, 1 H), 1.54 (s, 3 H), 1.24 (s, 1 H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 152.6, 142.1, 139.6, 128.9, 128.0, 125.7, 122.0, 110.4, 108.5, 60.0, 47.5, 45.2, 33.1, 26.3. ESI-HRMS: *m/z* calcd for $C_{16}H_{18}NO_2^+$: 256.1338; found: 256.1326. SFC: t_R = 8.7 min (79.0%); t_R = 9.4 min (21.0%) (Chiralpak AD, 125 bar, 4.0% MeOH in CO_2, 2.25 mL/min, 220 nm, 40 °C).

2,4-Dimethyl-5-oxo-2,3-diphenylpentanenitrile (28)

^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.57 (d, *J* = 2.5 Hz, 1 H), 7.62 (d, *J* = 7.4 Hz, 2 H), 7.45 (t, *J* = 7.8 Hz, 4 H), 7.40–7.32 (m 4 H), 3.35 (d, *J* = 7.7 Hz, 1 H), 3.02 (ddq, *J* = 7.2, 2.4 Hz, 1 H), 1.41 (s, 3 H), 0.76 (d, *J* = 7.0 Hz, 3 H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 201.9, 140.5, 137.6, 129.4, 129.2, 129.0, 128.2, 125.7, 122.4, 56.8, 49.5, 46.0, 29.2, 14.2. ESI-HRMS: *m/z* calcd for $C_{19}H_{19}NONa^+$: 300.1364; found: 300.1354.

2,4-Dimethyl-5-hydoxy-2,3-diphenylpentanenitrile (alc-28)

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.60 (d, *J* = 7.8 Hz, 2 H), 7.45–7.36 (m, 5 H), 7.32 (t, *J* = 7.4 Hz, 3 H), 3.55 (dd, *J* = 10.7, 3.1 Hz, 1 H), 3.25–3.16 (m, 2 H), 2.32–2.22 (m, 1 H), 1.29 (s, 3 H), 0.71 (d, *J* = 6.9 Hz, 3 H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 142.0, 139.6, 128.9, 128.7, 127.5, 127.5, 125.5, 123.0, 66.0, 56.3, 45.8, 39.2, 30.4, 17.3. ESI-HRMS: *m/z* calcd for $C_{19}H_{22}NO^+$: 280.1701; found: 280.1693. SFC: t_R = 10.1 min (30.6%); t_R = 11.7 min (69.4%) (Chiralpak AD, 125 bar, 2.5% MeOH in CO_2, 2.5 mL/min, 220 nm, 40 °C).

Supporting Information

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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