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Synthesis of Tetrahydroisoquinolines by Visible-Light-Mediated 6-*exo*-trig Cyclization of α-Aminoalkyl Radicals

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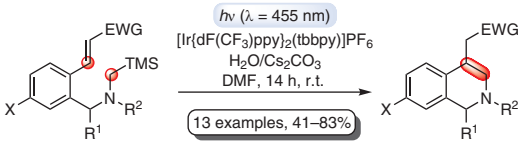


X = H, Cl, MeO; R^1 = H, Me; R^2 = alkyl, benzyl; EWG = CN, COR, COOR

Received: 14.05.2019
Accepted after revision: 01.07.2019
Published online: 17.07.2019
DOI: 10.1055/s-0039-1690006; Art ID: st-2019-r0271-l

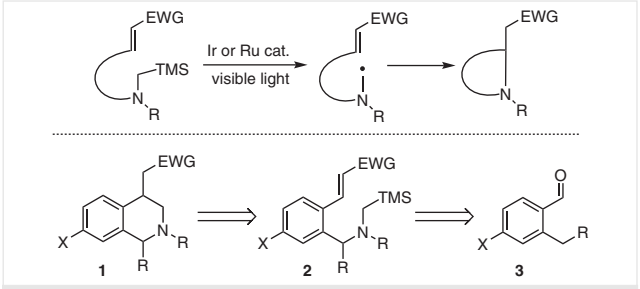
Abstract Starting from the respective tertiary α-silylmethyl amines, the intramolecular cyclization of α-aminoalkyl radicals to Michael acceptors produced tetrahydroisoquinolines. The reaction conditions included the use of 5 mol% of an iridium photoredox catalyst, dimethylformamide as the solvent, and equimolar amounts of water and cesium carbonate as the additives. 13 substrates were synthesized from *ortho*-alkylbenzaldehydes in a three-step procedure involving a carbonyl condensation, a radical bromination, and a substitution by a secondary α-silylmethyl amine. After optimization of the photocyclization, the reaction delivered tetrahydroisoquinolines in moderate to high yields (41–83%). A facial diastereoselectivity (dr ≅ 80:20) was observed with chiral substrates and a crystal structure provided evidence for the relative configuration of the major diastereoisomer. A catalytic cycle with direct electron transfer to the photoexcited metal catalyst is proposed.

Key words catalysis, cyclization, electron transfer, iridium, photochemistry, radical reaction

Photoinduced single-electron oxidation of amines provides access to nucleophilic α-aminoalkyl radicals which can act as reactive intermediates.[1] Besides the generation of α-aminoalkyl radicals by single-electron transfer (SET) and subsequent deprotonation,[2] the radicals can be produced by oxidative decarboxylation of α-amino acid derivatives,[3] by hydrogen atom transfer,[4] or by oxidative desilylation of α-silylalkyl amines.[5] The silyl group renders the formation of α-aminoalkyl radicals regioselective[6] and avoids overoxidation of the α-aminoalkyl radicals to the corresponding iminium ions.[7]

Several research groups reported the utilization of the trimethylsilyl (TMS) group as a suitable electrophilic leaving group in photosensitized electron-transfer reactions. Frequently, a consecutive reaction is the addition of the photochemically generated α-aminoalkyl radical to electron-deficient alkenes (Michael acceptors) in an inter- or intramolecular fashion.[5] Typically, the α-aminoalkyl radical is generated from α-silylmethyl amines employing ultraviolet irradiation or visible light with different sensitizers, such as anthraquinone,[8] benzophenones,[9] 1,4-dicyanonaphthalenes,[5d,f] or 9,10-dicyanoanthracene[5c,e] to induce the SET.

In recent years, several protocols have been reported for the generation of α-aminoalkyl radicals by photoredox-active iridium or ruthenium polypyridyl complexes. Visible light irradiation induces an electron transfer from the amine to the photoexcited transition-metal complex. Subsequent formation of an α-aminoalkyl radical allows for a conjugate addition to a double bond, which results – if performed intramolecularly – in a cyclization (Scheme 1).[10,11,12]



Scheme 1 Generation of α-aminoalkyl radicals through a SET and consecutive addition to a Michael system in an intramolecular fashion (top) and its application to the synthesis of tetrahydroisoquinolines **1** (bottom)

Herein, we present a visible-light-mediated cyclization reaction to tetrahydroisoquinolines **1** (THIQs) that relies on a conjugate addition of SET-generated α-aminoalkyl radicals to Michael acceptors and is catalyzed by an iridium polypyridyl complex. THIQs are usually synthesized from a β-arylethylamine and an aldehyde or ketone following the Pictet–Spengler protocol.[13] Although photoredox-based

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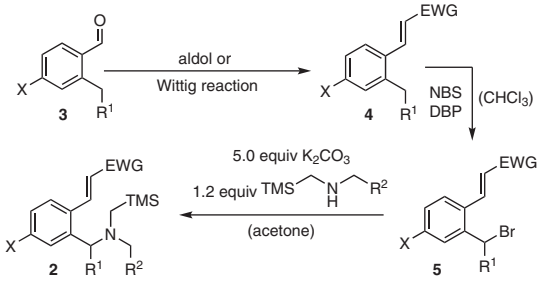
methods have been established in recent years to further modify the THIQ core structure[10b,14–17] there is not yet a method to access this skeleton by photoredox catalysis.

The synthesis of the respective starting materials **2** for the photoreactions required in all cases the corresponding *ortho*-alkyl-substituted benzaldehydes **3**. Aldehyde substrates with substituents at the phenyl skeleton (X = OMe, Cl) and R^1 = CH_3 were prepared by a halogen-metal exchange and subsequent formylation with *N*,*N*-dimethylformamide (DMF).[18] In the next synthetic step, the electron-withdrawing groups (EWG) were introduced by either an aldol condensation (nitriles, ketones) or a Wittig reaction (methyl and ethyl ester). For compounds **2a** and **2b** it was also possible to commence the synthesis with the respective cinnamates **4** (EWG = CO_2Me, CO_2Et). A literature procedure was adapted to introduce the sulfone by addition of thiophenol to 1-ethynyltoluene and subsequent oxidiation.[19] The radical bromination at the benzylic position of substrates **4** was performed by using *N*-bromosuccinimide (NBS) in chloroform and dibenzoylperoxide (DBP) as radical initiator. A nucleophilic substitution of bromides **5** by secondary α-silylmethyl amines in acetone with K_2CO_3 concluded the synthesis (Table 1). The corresponding amines

Table 1 Synthesis of Amine Substrates **2** Starting from *ortho*-Alkyl-Substituted Styrenes **4** by Bromination (**4**→**5**) and Nucleophilic Substitution (**5**→**2**)

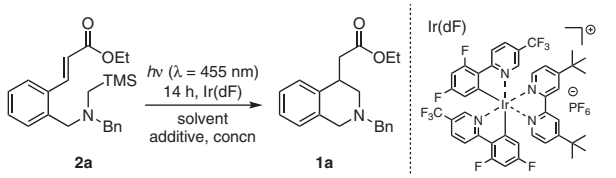


Substrate	X	R^1	R^2	EWG	Yield (%) **4**→**5**	Yield (%) **5**→**2**
2a	H	H	Ph	CO_2Et	70	81
2b	H	H	Ph	CO_2Me	80	75
2c	H	H	Ph	COMe	57	76
2d	H	H	Ph	CN	69	80
2e	Cl	H	Ph	CO_2Me	36	72
2f	OMe	H	Ph	CO_2Me	34	90
2g	H	H	isobutyl	CO_2Me	80	56
2h	H	Me	Ph	COMe	72	58
2i	H	Me	Ph	CO_2Me	85	72
2j	H	Me	Ph	CN	quant	71
2k	H	H	Ph	COPh	29	90
2l	H	H	Ph	SO_2Ph	54	95
2m	H	H	Ph-CF_3	CO_2Me	80	33

for substrates **2g**, **2m** were synthesized as previously reported.[20] All substrates exhibit oxidation potentials between E_{ox} ($\mathbf{2}^{\bullet+}$/**2**) = +0.75 V and +0.95 V vs. SCE [for further details, see the Supporting Information (SI)].

Our investigation of the intramolecular cyclization commenced with model substrate **2a**, which was irradiated in the presence of 5 mol% [Ir{dF(CF_3)ppy}$_2$(tbbpy)]PF_6 [Ir(dF)] [$E_{1/2}(Ir^{III*}/Ir^{II})$ = +1.21 V vs. SCE][21] as a photocatalyst. After irradiation for 14 hours in DMF at 25 °C with a blue LED (30 W, λ = 455 nm), 29% of the desired product was obtained (Table 2, entry 1).

Table 2 Optimization Studies for the Intramolecular Photocyclization of **2a** to Tetrahydroisoquinoline **1a**



2a **1a**

Entry	Ir cat. (mol%)	Solvent	Concn (mM)	Additive[a]	Yield (%)[b]
1	5	DMF	50	–	29
2	5	MeCN	50	–	7
3	5	CH_2Cl_2	50	–	12
4	5	DMF	25	–	17
5	5	DMF	100	–	22
6	5	DMF	50	AcOH	28
7	5	DMF	50	H_2O	40
8	5	DMF	50	H_2O/$LiBF_4$	32
9	5	DMF	50	H_2O/Cs_2CO_3	52
10	2	DMF	50	H_2O/Cs_2CO_3	23
11[c]	5	DMF	50	H_2O/Cs_2CO_3	0
12[d]	–	DMF	50	H_2O/Cs_2CO_3	0
13[e]	5	DMF	50	H_2O/Cs_2CO_3	0
14[f]	5	DMF	50	H_2O/Cs_2CO_3	28
15[g]	5	DMF	50	H_2O/Cs_2CO_3	55

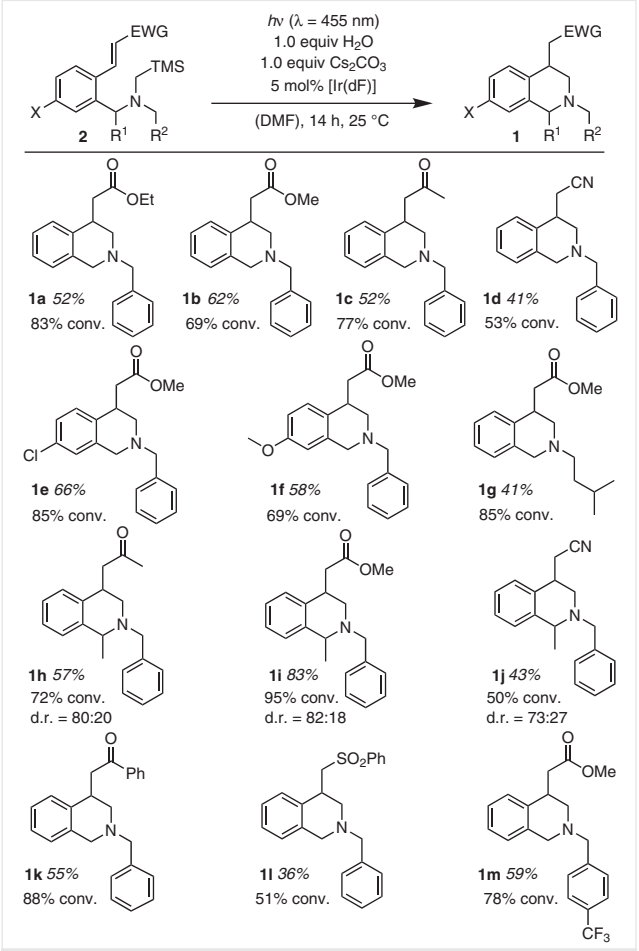
[a] Addition of additive in stoichometric amounts.
[b] Yield of isolated product after chromatographic purification.
[c] No light.
[d] No photocatalyst (71% recovered starting material).
[e] $Ru(bpy)_3(PF_6)_2$ as photocatalyst.
[f] [Ir(dF(CF_3)ppy)$_2$(bpy)]PF_6 as photocatalyst.
[g] Irradiation of photoproduct **1a** under optimized conditions.

Variation of the solvent led to decomposition of the starting material and a low product yield (entries 2–3). Entries 4 and 5 show that a change in the substrate concentration did not improve the yield. The addition of Brønsted acid has been reported to accelerate the rate-determining carbon–carbon bond formation step[10b] but use of acetic acid as proton source did not alter the reaction outcome (entry 6). However, the addition of water in stoichiometric

amounts had a positive effect, improving the yield to 40% (entry 7). From a screening of several Lewis acids and inorganic bases (for further additive screening, see the SI), cesium carbonate evolved as the most beneficial additive increasing the yield up to 52% at a conversion of 83% (entry 9). Lowering the catalyst loading only decreased the yield (entry 10). Control experiments (entry 11 and 12) validated the necessity of light and catalyst in the reaction. Only 71% of starting material and no product could be re-isolated after irradiation of a sample without a catalyst, which demonstrates the limited stability of the starting material. Neither $Ru(bpy)_2(PF_6)_2$ nor a different iridium catalyst $[Ir\{dF(CF_3)ppy\}_2(bpy)]PF_6$ proved to be a suitable catalyst in the cyclization reaction (entry 13 and 14). The excited state potential of $Ru(bpy)_2(PF_6)_2$ [$E_{1/2}$ (Ru^{II*}/Ru^{I}) = +0.80 V vs. SCE][22] might be too low to oxidize the tertiary amine. Eventually, we checked the stability of the photoproduct under the optimized conditions and observed decomposition during irradiation (entry 15). With an oxidation potential of E_{ox} (**1a**$^{+\bullet}$/**1a**) = +1.15 vs. SCE, the photoproduct could potentially still be oxidized by the excited state of the iridium catalyst, resulting in decomposition as previously described.[23] No reaction was observed with an amine substrate without a trimethylsilyl group in the α position (see the SI).

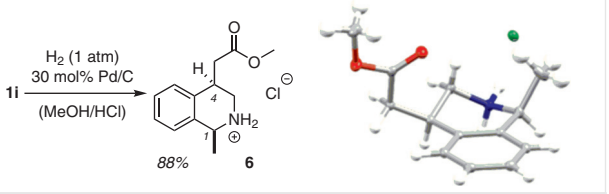
In the next set of experiments, we examined the substrate scope of this transformation under the optimized reaction conditions (Table 2, entry 9).[24] As shown in Scheme 2 the reaction seems to be fairly general and applicable to a range of substrates with moderate to high yields (41–83%). By changing the EWG from the model substrate **2a** to a methoxycarbonyl substituent (**2b**) the yield increased to 62% but the conversion dropped to 69%. With a stronger EWG such as cyano or sulfonyl the yields decreased to 41% (**1d**) and 36% (**1l**) and in both cases the conversion was only around 50% (53% for **1d**, 51% for **1l**). With acetyl or benzoyl as EWG, products **1c** and **1k** were isolated in 52% and 55% yield, respectively, at a conversion of 77% for **1c** and 88% for **1k**. Variation of the substituents at the aryl core resulted in a yield of 66% for **1e** with a weakly deactivating chloro substituent and 58% for **1f** with a strongly activating methoxy group attached to the phenyl ring. In both reactions, the starting material was not fully converted to the products (85% and 69% conversion). Different substituents at the amine moiety such as a 4-trifluoromethylbenzyl group **1m** (59%) or an aliphatic isobutyl group **1g** (41% yield) were also tolerated with conversions of 78% and 85%, respectively. Acetyl- (**2h**), methoxycarbonyl- (**2i**), and cyano-substituted (**2j**, *E*/*Z* = 73:27) substrates with a methyl group at the 1-position of the THIQ core successfully afforded the desired products **1h–j** in 57, 83, and 43% yield. The conversion in the three reactions was 72%, 95%, and 50%, respectively.

THIQs **1h–j** were isolated as a mixture of diastereomeric products, which could be separated by column chromatography. In all three cases, the formation of a major diastereoisomer was observed (dr ≅ 80:20). The assignment of the relative configuration of product **1i** was accomplished after a palladium-catalyzed debenzylation of the tertiary amine (Scheme 3). The crystal structure of the corresponding ammonium salt **6** revealed for the major diastereoisomer a *cis* configuration of the substituents in positions C1 and C4. Comparing the ^{1}H NMR spectra for products **1i** showed that the shift of the signal for the proton in position C1 is distinctly different for the major (3.75 ppm) and minor (4.10 ppm) diastereoisomer. The same chemical shift difference was also observed for products **1h** and **1j** suggesting that in all diastereomeric mixtures the major product displays a *cis* configuration of the substituents in positions C1 and C4. The diastereoselectivity can be rationalized by assuming that the conformation of the cyclization precursor is governed by 1,3-allylic strain.[25] Accordingly, the hydrogen atom at the stereogenic center that is located in the plane of the aryl group, minimizes the steric strain between the Michael system and substituents in *ortho* position. The conju-

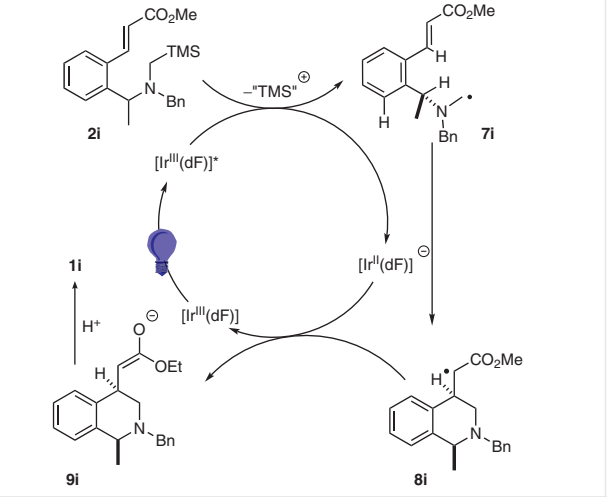


Scheme 2 Intramolecular photocatalytic cyclization of α-silylated amines **2** to products **1** under optimized reaction conditions. Yields are given for isolated products and are not based on the conversion.

gate addition of the α-aminoalkyl radical **7i** presumably proceeds from the bottom face generating the major product with a *cis* configuration (Scheme 4). Scheme 4 describes a reasonable mechanistic scenario for the photocatalytic cyclization of **2i** to THIQ **1i** as representative product. The first step involves a reductive quench of the photoexcited iridium complex by the amine producing a radical cation, which loses the TMS group generating the α-aminoalkyl radical.



Scheme 3 Palladium-catalyzed deprotection of the *N*-benzyl group and confirmation of the relative configuration of the major diastereoisomer by X-ray crystal structure analysis.



Scheme 4 Mechanistic scenario for the catalytic cycle in the photochemical transformation of **2j** to the THIQ **1i** and model for an 1,3-allylic strain stereocontrol

Intramolecular addition of the radical to the double bond closes the ring in a 6-*exo*-trig fashion. The catalytic cycle is completed by oxidation of the photocatalyst and the formation of enolate **9i**, which gets trapped by a TMS source or is directly hydrolyzed. Intermediate **9i** can also be formed from **8i** by simultaneous oxidation of amine **2i** (chain process).

In summary, we have described a new intramolecular 6-*exo*-trig photocyclization to tetrahydroisoquinolines induced by visible-light-mediated photoredox catalysis with an iridium complex. A three-step synthesis route has been developed to access a variety of substrates incorporating the α-silylmethyl amine. The latter entity proved to be essential for the generation of the nucleophilic α-aminoalkyl radical. All substrates show relatively high redox potentials compared to other α-silylmethyl anilines.[26] The photocyclization occurs in moderate to high yields and offers a yet unexplored entry to biologically relevant tetrahydroisoquinolines.

Acknowledgment

This project was supported by the Deutsche Forschungsgemeinschaft (DFG). M.G. acknowledges the TUM graduate school for financial support and Prof. Corinna Hess for valuable discussions.

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0039-1690006.

Primary Data

for this article are available online at https://doi.org/10.1055/s-0039-1690006 and can be cited using the following DOI: 10.4125/pd0105th.

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(24) **Cyclization Reaction; General Procedure**
Substrate (1.00 equiv), Cs_2CO_3 (1.00 equiv), H_2O (1.00 equiv), and photoredox catalyst [Ir{dF(CF_3)ppy}(dtbpy)]PF_6 [Ir(dF)] (0.05 equiv) were dissolved in dry DMF (ca. 2 mL/0.1 mmol substrate). The yellow mixture was degassed by repeating a freeze-pump-thaw cycle (3×) and irradiated for 14 h with 30 W blue LED lamps (λ = 455 nm) at r.t. whilst continuously stirring under an argon atmosphere. After 14 h, water (ca. 5 mL/0.1 mmol) was added. The layers were separated and the aqueous layer was extracted with diethyl ether (3× ca. 6 mL/0.1 mmol). The combined organic layers were washed with brine and dried with Na_2SO_4. After filtration, residual solvent was removed under reduced pressure. The crude product was purified by column chromatography to obtain the photoproduct.
Representative NMR data (**1a**): ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.40–7.34 (m, 2 H, 2× *meta*-C_{Ph}-H), 7.34–7.28 (m, 2 H, 2× *ortho*-C_{Ph}-H), 7.27–7.21 (m, 1 H, *para*-C_{Ph}-H), 7.17–7.07 (m, 3 H, H-6, H-7, H-8), 7.00–6.94 (m, 1 H, H-5), 4.13–3.99 (m, 2 H, CH_2CH_3), 3.80 (d, ^2J = 14.9 Hz, 1 H, CHH-1), 3.71 (d, ^2J = 13.1 Hz, 1 H, Ph-CHH), 3.58 (d, ^2J = 13.1 Hz, 1 H, Ph-CHH), 3.42 (d, ^2J = 14.9 Hz, 1 H, CHH-1), 3.38–3.31 (m, 1 H, H-4), 2.88 (dd, ^2J = 16.0 Hz, ^3J = 9.7 Hz, 1 H, $CH(CO_2Et)$), 2.80 (ddd, ^3J = 11.7 Hz, ^4J = 3.2, 1.3 Hz, 1 H, CHH-3), 2.61–2.58 (m, 2 H, CHH-3, $CH(CO_2Et)$), 1.20 (t, ^3J = 7.1 Hz, 3 H, CH_2CH_3). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 172.9 (s, CO_2Et), 138.7 (s, CH_2-C_{Ph}), 137.6 (s, C-4a), 135.3 (s, C-8a), 129.1 (d, *meta*-CH_{Ph}), 128.4 (d, C-8), 128.4 (d, *ortho*-CH_{Ph}), 127.2 (d, *para*-CH_{Ph}), 126.7 (d, C-6*), 126.5 (d, C-7*), 126.2 (d, C-5), 62.8 (t, CH_2-C_{Ph}), 60.4 (t, CH_2CH_3), 56.5 (t, C-1), 54.7 (t, C-3), 41.2 (t, CH_2CO_2Et), 35.8 (d, C-4), 14.3 (q, CH_2CH_3). * Assignment is interconvertible. Major diastereoisomer (**1i**): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39–7.36 (m, 2 H, 2× *meta*-C_{Ph}-H), 7.33–7.29 (m, 2 H, 2× *ortho*-C_{Ph}-H), 7.27–7.22 (m, 1 H, *para*-C_{Ph}-H), 7.22–7.13 (m, 4 H, H-5, H-6, H-7, H-8), 4.10 (d, ^2J = 13.6 Hz, 1 H, Ph-CHH), 3.75 (q, ^3J = 6.3 Hz, 1 H, H-1), 3.55 (s, 3 H, CO_2CH_3), 3.40 (d, ^2J = 13.6 Hz, 1 H, Ph-CHH), 3.26 (dq, ^3J = 9.0 Hz, ^3J = 5.0 Hz, 1 H, H-4), 2.90–2.80 (m, 2 H, CHH-3, $CH(CO_2CH_3)$), 2.66 (dd, ^2J = 16.0 Hz, ^3J = 5.0 Hz, 1 H, $CH(CO_2CH_3)$), 2.62–2.56 (m, 1 H, CHH-3), 1.53 (d, ^3J = 6.3 Hz, 3 H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 173.2 (s, CO), 140.4 (s, C-8a), 139.6 (s, CH_2-C_{Ph}), 137.7 (s, C-4a), 128.9 (d, *meta*-CH_{Ph}), 128.3 (d, *ortho*-CH_{Ph}), 128.1 (d, C-8*), 127.3 (d, C-5*), 127.0 (d, *para*-CH_{Ph}), 126.4 (d, C-6**), 126.1 (d, C-7**), 58.9 (t, CH_2-C_{Ph}), 57.8 (d, C-1), 51.5 (q, CO_2CH_3), 50.9 (t, C-3), 39.9 (t, CH_2CO_2H3), 35.1 (d, C-4), 21.9 (q, CH_3). */** Assignments are interconvertible. Minor diastereoisomer (**1i**): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39–7.35 (m, 2 H, 2× *meta*-C_{Ph}-H), 7.33–7.28 (m, 2 H, 2× *ortho*-C_{Ph}-H), 7.27–7.22 (m, 1 H, *para*-C_{Ph}-H), 7.17–7.09 (m, 3 H, H-6, H-7, H-8), 7.06–7.00 (m, 1 H, H-5), 4.10 (q, ^3J = 6.6 Hz, 1 H, H-1), 3.83 (d, ^2J = 13.1 Hz, 1 H, Ph-CHH), 3.63 (d, ^2J = 13.1 Hz, 1 H, Ph-CHH), 3.52 (s, 3 H, CO_2CH_3), 3.23–3.17 (m, 1 H, H-4), 3.00 (d, ^2J = 10.6 Hz, 1 H, CHH-3), 2.88 (dd, ^2J = 16.2 Hz, ^3J = 10.1 Hz, 1 H, $CH(CO_2CH_3)$), 2.55–2.45 (m, 2 H, CHH-3, $CH(CO_2CH_3)$), 1.28 (d, ^3J = 6.6 Hz, 3 H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 173.5 (s, CO), 141.4 (s, C-8a), 139.4 (s, CH_2-C_{Ph}), 137.5 (s, C-4a), 129.2 (d, *meta*-CH_{Ph}), 128.8 (d, C-8), 128.3 (d, *ortho*-CH_{Ph}), 127.4 (d, *para*-CH_{Ph}), 127.0 (d, C-5), 126.4 (d, C-6*), 126.2 (d, C-7*), 58.4 (t, CH_2-C_{Ph}), 56.0 (d, C-1), 51.5 (q, CO_2CH_3), 45.8 (t, C-3), 41.1 (t, $CH_2CO_2CH_3$), 35.9 (d, C-4), 14.8 (q, CH_3). * Assignment is interconvertible.

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