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Strained Azetidinium Ylides: New Reagents for Cyclopropanation

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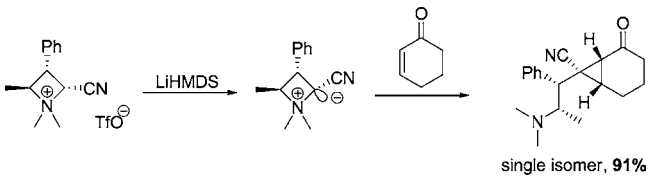


Azetidinium ylides showed a remarkable ability to perform the cyclopropanation of Michael acceptors. Ephedrine-derived azetidinium ylides allowed the formation of substituted cyclopropanes in good yields and at a high level of stereoselectivity. The determination of the relative stereochemistries in the produced cyclopropanes gave some insight into the reaction mechanism.

The cyclopropane motif is found in numerous bioactive compounds; among them amino acid-derived cyclopropanes are of particular interest. A few cyclopropane amino acids are found in nature mostly as disubstituted cycloalkanes,[1] the first one discovered and the simplest being aminocyclopropanecarboxylic acid, recognized as the biochemical source of ethylene in plant communication.[1a] Recently, betaine **1**, extracted from a Micronesian marine sponge, showed an unprecedented trisusbtituted cyclopropane ring.[2] The synthetic betaine **2** has been demonstrated to be a selective agonist for group 1 of metabotropic glutamate receptors,[3] while **3** exhibited an inhibitory activity against γ-butyrobetaine hydroxylase.[4] An aminocyclopropanecarboxylic acid (**4**) was also demonstrated to be the key element that rigidifies the structure of a peptide mimicking the very

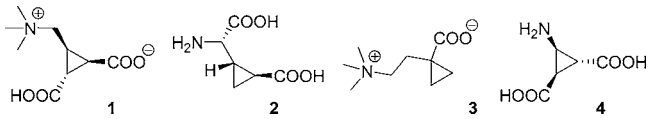
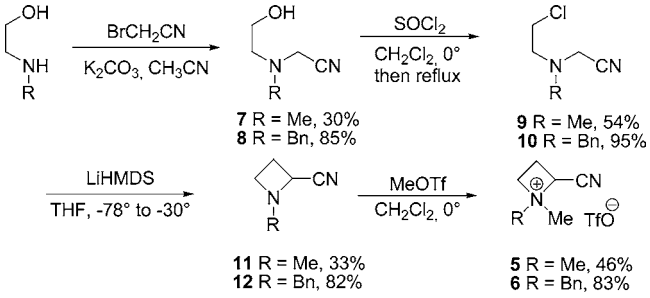


FIGURE 1. Examples of cyclopropane amino acids.

important mammalian neuropeptide Y.[5] This analogue is 3 times shorter than the native neuropeptide but still retains biological activity.

In the course of our studies on azetidinium salts, we thought that these compounds would constitute valuable precursors of such functionalized cyclopropanes. This idea was driven by two facts; the first one is the easy preparation of azetidinium salts, available in a few steps from β-amino alcohols. Second, we have previously demonstrated that these ammonium salts can efficiently generate azetidinium ylides.[6] This new type of ammonium ylide was expected to be an efficient cyclopropanation reagent behaving like previously described acyclic ylides.[7] This idea was supported by the conclusions drawn about ammonium ylide reactivity by Aggarwal and co-workers:[8] the authors demonstrated the importance of the leaving group ability of onium ylides in different reactions and concluded that ammonium ylides tend to show rather poor leaving group characteristics, thus limiting the scope of their use. In this respect, a strained azetidinium ylide was expected to greatly favor reactivity since the leaving group ability of the amine would be enhanced by ring strain release.

SCHEME 1. Preparation of Azetidinium Salts 5 and 6



As a candidate for the cyclopropanation test we chose the cyanoazetidinium **5**, which was prepared via the reaction sequence depicted in Scheme 1. The volatility and the water solubility of the intermediates **7**, **9**, and **11** led to low isolated yields; therefore, the benzylated equivalent **6** was also prepared following a similar synthetic path. Thus, commercially available *N*-methyl- or *N*-benzylaminoethanol was alkylated using bromoacetonitrile in the presence of potassium carbonate, and the produced alcohols **7** and **8** were next converted into the corresponding chlorides **9** and **10** by means of thionyl chloride in refluxing dichloromethane. At this stage the four-membered ring was closed by performing a 4-*exo-tet* cyclization of the cyanomethyl anion generated by deprotonation of **9** or **10** with

(1) Extracted from pears and apples: Burroughs, L. F. *Nature* **1957**, *179*, 360−361. Extracted from red alga: Wakamiya, T.; Nakamoto, H.; Shiba, T. *Tetrahedron Lett.* **1984**, *39*, 4411−4412. Extracted from bottlebrush buckeye: Fowden, L.; Smith, A. *Phytochemistry* **1969**, *8*, 437−443.

(2) Sakai, R.; Suzuki, K.; Shimamoto, K.; Kamiya, H. *J. Org. Chem.* **2004**, *69*, 1180−1185.

(3) Monn, J. A.; Valli, M. J.; Massey, S. M.; Wright, R. A.; Salhoff, C. R.; Johnson, B. G.; Howe, T.; Alt, C. A.; Rhodes, G. A.; Robey, R. L.; Griffey, K. R.; Tizzano, J. P.; Kallman, M. J.; Helton, D. R.; Schoepp, D. D. *J. Med. Chem.* **1997**, *40*, 528−537.

(4) Petter, R. C.; Banerjee, S.; Englard, S. *J. Org. Chem.* **1990**, *55*, 3080−3097.

(5) Koglin, N.; Zorn, C.; Beumer, R.; Cabrele, C.; Bubert, C.; Sewald, N.; Reiser, O.; Beck-Sickinger, A. G. *Angew. Chem., Int. Ed.* **2003**, *42*, 202−205.

(6) Couty, F.; David, O.; Durrat, F.; Evano, G.; Lakhdar S., Marrot, J.; Vargas-Sanchez, M. *Eur. J. Org. Chem.* **2006**, 3479−3490.

(7) (a) Bhattacarjee, S. S.; Ila, H.; Junjappa, H. *Synthesis* **1982**, 301. (b) Kowalkowska, A.; Sucholbiak, D.; Jonczyk, A. *Eur. J. Org. Chem.* **2005**, 925−933. (c) Papageorgiou, C. D.; Ley, S. V.; Gaunt, M. J. *Angew. Chem., Int. Ed.* **2003**, *42*, 828−831. Papageorgiou, C. D.; Cubillo de Dios, M. A.; Ley, S. V.; Gaunt, M. J. *Angew. Chem., Int. Ed.* **2004**, *43*, 4641−4644.

(8) Aggarwal, V. K.; Harvey, J. N.; Robiette, R. *Angew. Chem., Int. Ed.* **2005**, *44*, 5468−5471.

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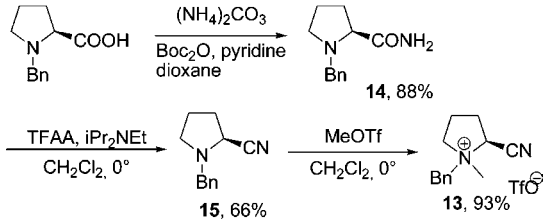
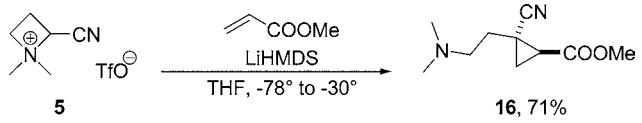
SCHEME 2. Synthesis of Pyrrolidinium Salt 13



SCHEME 3. Cyclopropanation Reaction



LiHMDS, following our previously reported methodology.[9] Azetidines **11** and **12** were finally alkylated with methyl trifluoromethanesulfonate to yield the desired azetidinium salts **5** and **6**.

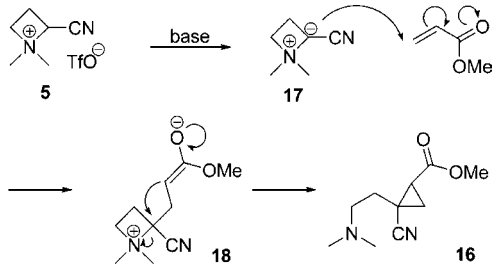
To probe the impact of the ring strain present in those cyclic ylides, we also synthesized the larger homologue of compound **6**, namely, the proline-derived pyrrolidinium salt **13** following the sequence described in Scheme 2. *N*-Benzyl-L-proline[10] was converted into cyanopyrrolidine **15** in two steps: (i) activation of the carboxylic group as a mixed anhydride with Boc_2O followed by condensation with ammonium carbonate, yielding the primary amide **14**, and (ii) dehydration of the latter into the cyano derivative **15** using trifluoroacetic anhydride in a basic medium. The pyrrolidine **15** was then alkylated with methyl trifluoromethanesulfonate to give **13** as a ca. 1/1 mixture of diastereoisomers.

The desired candidate **5** was now ready to perform the cyclopropanation reaction test. This was conducted by deprotonation of the azetidinium salt at low temperature (−78 °C) with a strong non-nucleophilic base (LiHMDS), to prevent any competitive ring opening.[5] The deprotonation was performed in the presence of the electrophile: in this way any degradation of the generated ylide was prevented by immediate reaction with the Michael acceptor (Scheme 3). After 1 h of stirring while the temperature was allowed to rise to −30 °C, the reaction mixture was quenched with a saturated solution of ammonium chloride to give the sole cyclopropane **16** as the product.[11]

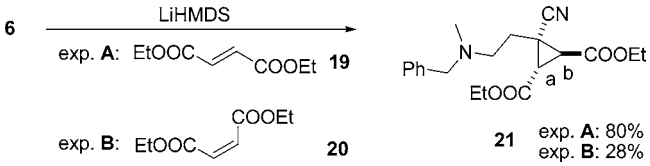
Pleased by this first result, we decided to investigate in more detail this cyclopropanation, which proceeds in three steps as depicted in Scheme 4. The generated ylide **17** acts as a nucleophile to perform a 1,4-addition onto the Michael acceptor, producing the zwitterionic ammonium enolate **18**, which finally evolves to the cyclopropane **16** via an intramolecular nucleophilic substitution in which the tertiary amine is the leaving group.

In this sequence, two points can be asserted without further experiment. The first one is the quantitative and irreversible

SCHEME 4. Mechanism of Cyclopropanation



SCHEME 5. Stereoconvergence of Cyclopropanation



formation of the ylide due to the difference in pK_a between the two species involved: the α-cyanoammonium and lithium amide base.[12] The second point is crucial for the following discussion of the mechanism, and it concerns the nonreversible nature of the last step. In fact, the attack of the enolate onto the carbon bearing the ammonium group is, at the same time, a three-membered carbon ring closure and a four-membered ring opening; in bonding terms, a stable C−C bond is formed when a highly energetic $C-N^+$ bond is broken, thus preventing the occurrence of any reverse process. Consequently, two points remain unknown, which are the reversibility of the 1,4-addition and the relative speed rates of the final two steps. To get some insight into these points, we performed another set of experiments. Two stereoisomeric alkenes (**19** and **20**) were separately tested in the cyclopropanation reaction (Scheme 5): the same cyclopropane possessing a *trans* relationship between the two ester moieties was formed in each reaction. This stereochemistry was ascertained from the proton NMR signals of the two hydrogens H_a and H_b in the cyclopropane: in compound **21** an AB system is observed as expected for a *trans* configuration; inversely, a unique signal would have been expected in a *meso* compound with a *cis* configuration. It should be noted that, in experiment B, our attempts to detect the presence of some *cis* isomer in the reaction mixture were unsuccessful and only decomposed material was formed along with the cyclopropane **21**.

This stereoconvergence can be explained through a reorganization of the intermediary enolate. Ylide **22** derived from the azetidinium salt **6** reacts with diethyl fumarate to form the enolate **23**, which is ideally positioned for the ring closure (Scheme 6). Reaction with diethyl maleate leads to the enolate **24**, assumed to be less stable than **23**, due to strong electrostatic repulsion between the electron-rich moieties (ester and enolate). The conformational change from **24** to **23**, as shown by the observed stereoconvergence, indicates a relatively slow ring closure, the transient enolate being able to reach a more reactive conformation for the ensuing ring closure.

To determine to what extent ring strain favors the course of the reaction, pyrrolidinium salt **13** was tested. The reaction produces the homologous cyclopropane **25**, however with a reproducible yield below 20%, along with decomposed material (Scheme 7). Comparison of this result with the yield observed

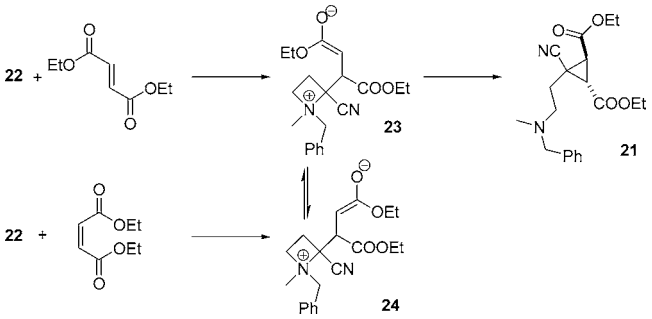
(9) Agami, C.; Couty, F.; Evano, G. *Tetrahedron: Asymmetry* **2002**, *13*, 297−302.

(10) Belokon', Y. N.; Tararov, V. I.; Maleev, V. I.; Savel'eva, T. F.; Ryshov, M. G. *Tetrahedron: Asymmetry* **1998**, *9*, 4249−4252.

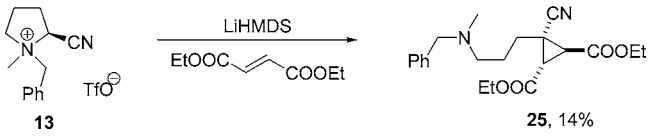
(11) The relative stereochemistry was assigned by comparison of the ^{1}H NMR signal of the proton next to the ester function with those of the related compounds described by Doyle et al.: Doyle, M. P.; Dorow, R. L.; Tamblyn, W. H. *J. Org. Chem.* **1982**, *47*, 4059−4068. This particular proton is reported at 1.86 ppm for the *cis* isomer and at 2.31 ppm for the *trans* isomer. Ours resonates at 2.30 ppm, thus indicating a *trans* relationship between the ester and the cyano moeties.

(12) Bordwell, F. G.; Fried, H. E. *J. Org. Chem.* **1981**, *46*, 4327−4331.

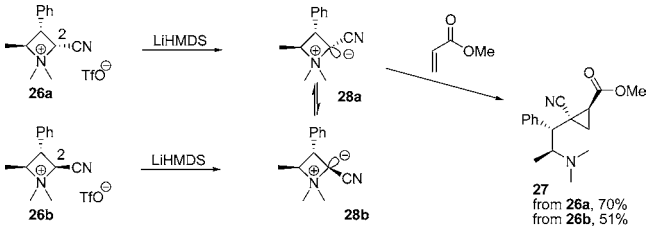
SCHEME 6. Explanation of Stereoconvergence



SCHEME 7. Reaction with Pyrrolidinium Salt 13



SCHEME 8. Epimerization of Ylides 28

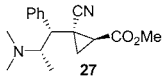
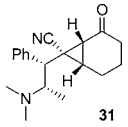
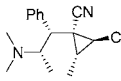
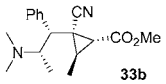
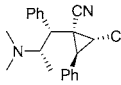
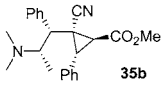
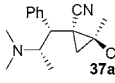
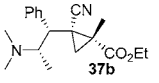


for the azetidinium **6** (80%) highlights the utmost importance of ring strain in cyclic ylides to achieve reaction efficiency. We can postulate a high energetic barrier for the final ring closure, this activation energy being lowered when ring strain reinforces the leaving group ability of the amine. Azetidinium ylides can therefore smoothly evolve to the three-membered ring, while pyrrolidinium ylides are liable to decompose because the cyclization process is more energetically demanding.

Having gathered this mechanistic information, we went with some substrates that have stereogenic centers to collect some data about the stereochemical outcome of this cyclopropanation. To this end, the enantiomerically pure azetidinium salts **26a** and **26b**[5] were engaged in the reaction with different Michael acceptors. These salts possess three asymmetric centers; as a result the two faces of the azetidine ring are now inequivalent. (Following the depiction in Scheme 8, the bottom face is hindered by the phenyl group, while the top face is more accessible.) One of these stereocenters is affected during the deprotonation step; C2 is the site of deprotonation. As has been proven, the anionic center of an ammonium ylide is not planar,[13] the carbon atom remains tetrahedric but is not configurationally stable, and racemization is then unavoidable. To check the influence of this epimerization, the diastereoisomeric azetidinium salts **26a** and **26b** were reacted separately with the same electrophile. In both cases, only the cyclopropane **27** was isolated and the depicted stereochemistries were determined by X-ray diffraction analysis. The action of the base on the salt **26a** or **26b** generates two diastereoisomeric ylides (**28a** and **28b**, respectively); these probably undergo a rapid equilibration in which only **28a** attacks the alkene to provide **27**.

(13) Yates, B. F.; Bouma, W. J.; Radom, L. *J. Am. Chem. Soc.* **1987**, *109*, 2250−2263.

TABLE 1

entry[a]	Michael acceptor	Major isomer	Minor isomer	(Ratio, %)[b] yield[c]
1	 **29**	 **27**		70%
2	 **30**	 **31**		90%
3	 **32**	 **33a**	 **33b**	(75:25) **33a**, 72% **33b**, 22%
4	 **34**	 **35a**	 **35b**	(72:28) **35a**, 56% **35b**, 19%
5	 **36**	 **37a**	 **37b**	(90:10) **37a**, 82% **37b**, 8%

[a] Conditions: THF, LiHMDS, from −78 to −30 °C. [b] Determined by ^{1}H NMR of the crude mixture. [c] Yield of isolated products.

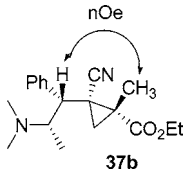


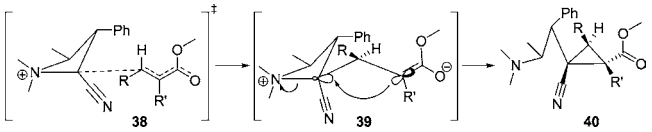
FIGURE 2. Assignment of the stereochemistry of compound **37b**.

Starting with the azetidinium **26a**, various Michael acceptors were used in the reaction, and the results are presented in Table 1. All cyclopropanations proceeded smoothly, yielding a single isomer with the already seen methyl acrylate (**29**) and with cyclohexenone (**30**). The *E*-disubstituted alkenes **32**, **34**, and **36** gave a mixture of two isomers (among the eight possible) with moderate to good diastereoselectivity, all these compounds being separable by chromatography on silica gel. Some of these were solid and, after recrystallization from heptane, gave single crystals suitable for X-ray diffraction analysis.

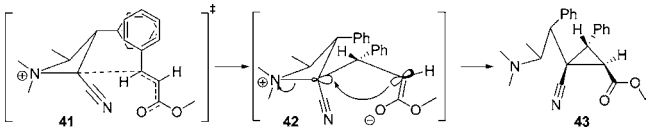
The structure of the adduct from ethyl methacrylate was deduced from ^{1}H NMR analysis, the isomer **37b** giving rise to a clear nuclear Overhauser effect between the methyl group on the cyclopropane and the benzylic proton on the side chain, establishing the *cis* relationship of the two substituents (Figure 2).

As regards the stereochemical outcome of the reaction, the most important information that can be gathered from these data concerns the geometry of the facial approach of the ylide on the Michael acceptor. Every major compound arises from the attack of the upper face of the ylide onto the *Si* face of the alkene, with a notable exception for ethyl cinnamate (**34**) (Table 1, entry 4). The course of the reaction can be summarized as represented in Scheme 9. In this model, the anion attacks from the opposite face relative to the phenyl group and the Michael acceptor presents its *Si* face to reach the transition state **38**, with minimal steric interactions as well as electrostatic repulsions

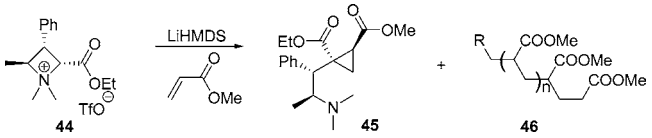
SCHEME 9. Facial Approach of the Ylide on the Michael Acceptor



SCHEME 10. Particular Approach with Cinnamate 34



SCHEME 11. Cyclopropanation with Ester 44



between the nitrile and the ester groups. Upon formation of the C−C bond, the zwitterion **39** is produced. Finally, the reaction is completed by nucleophilic substitution resulting from overlap of the π-orbital of the enolate with the σ^* orbital of the C−N$^+$ bond. This model readily accounts for the absolute configuration—invariably *R*—of the carbon bearing the cyano group in the produced cyclopropane as well as for the *trans* relationship between the two electron-withdrawing groups (depending on the *Si* or *Re* nature of the attacked face of the alkene).

However, a problem remains: how can one explain the formation of the major *cis* isomer when ethyl cinnamate (**34**) is used? Here again, the ylide attacks the Michael acceptor from the upper face, since the *R* configuration is retained, but the position of the cyano and ester groups on the same side of the cyclopropane indicates an *Re* face approach of the alkene. As an explanation, we can postulate a favorable π-stacking interaction between the phenyls of the cinnamate and of the azetidinium, thus stabilizing the transition state **41** in this particular case as depicted in Scheme 10.

Finally, the important dependency of the reactant characteristics on the reaction's outcome prompted us to determine whether the nature of the stabilizing group on the ylide had an influence on the cyclopropanation. Therefore, the ester-bearing azetidinium **44**, previously prepared in our laboratory,[5] was reacted with methyl acrylate using the same standard conditions. The expected cyclopropane **45** was indeed detected in the crude mixture, though contaminated with polymeric material **46**, Scheme 11.

Attempts to isolate compound **45** were unsatisfactory, all resulting in impure material. Ylide-induced polymerizations of acrylate derivatives have been reported,[14] but the factor governing this change of reactivity between the cyano- and ester-stabilized ylides is rather unclear. The deprotonation step is hardly in question, since the respective pK_a values are virtually equal as extrapolated from cyano- or ester-substituted methylenetrimethylammonium salts[12] (pK_a of 20.6 in DMSO for both ammoniums). Two hypotheses can be proposed: First, a greater mesomeric delocalization of the anion in the ester moiety results in a lowering of the ylide's nucleophilicity. Alternatively, the 1,4-addition is effective in both cases, but the ring closure might be hampered by the "bulky" ester group, thus allowing the enolate to react with another acrylate molecule, starting the polymerization process.

Azetidinium ylides proved capable of effecting cyclopropanation of Michael acceptors in good yields. Novel (aminoethyl)-cyclopropane esters were prepared by this method. Enantiopure azetidinum salts reacted with good to excellent diastereoselectivities to provide tri- or tetrasubstituted cyclopropanes possessing one or two quaternary carbon centers along with one or two tertiary centers as a major isomer among the eight possible. Some critical parameters of this three-step transformation have been delineated. First, the ring strain present in the substrate is essential to overcome the energetic barrier of the final ring closure. Second, the nature of the functional group in the ylide (a nitrile) is of great importance. Finally, a simple facial approach model is proposed to account for the observed stereochemistries. The reactivity of azetidinium ylides is currently under study to aim at biologically relevant targets.

Experimental Section

A solution of azetidinium salt **26a** (0.80 mmol) in dry THF was cooled to −78 °C, and cyclohexanone (0.97 mmol, 1.2 equiv) was added, followed by lithium hexamethyldisilazane (c = 2 mol·L^{-1}) in THF (1.70 mmol, 2 equiv). The mixture was stirred while being allowed to warm to −30 °C over a 1 h period. The reaction was then stopped by addition of 10 mL of a saturated solution of ammonium chloride. Water was added, and the aqueous layer was extracted three times with 15 mL of dichloromethane. After drying over magnesium sulfate and evaporation, the crude material was checked in proton NMR. Chromatographic purification using silica gel (Et_2O/pentane (4/6), R_f = 0.48) gave the cyclopropane **31**, 312 mg, 90% yield, as a white solid: mp 118 °C; $[\alpha]_D^{20}$ = +88.9 (c = 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40−7.25 (m, 5H), 3.30−3.20 (m, 1H), 2.53−2.42 (m, 1H), 2.35 (s, 6H), 2.32−2.25 (m, 2H), 2.07−2.02 (m, 4H), 2.00−1.71 (m, 2H), 0.70 (d, 3H, J = 6.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.5 (Cq), 139.9 (Cq), 129.1 (CH), 128.7 (CH), 127.9 (CH), 120.0 (Cq), 62.0 (CH), 57.7 (CH), 40.5 (CH_3), 38.9 (CH_2), 34.0 (CH), 33.5 (CH), 32.0 (Cq), 24.6 (CH_2), 20.0 (CH_2), 9.0 (CH_3); IR (KBr, cm^{-1}) ν 3032, 2970, 2939, 2852, 2827, 2770, 2217, 1700, 1608, 1597; HRMS (ESI, TOF MS) m/z calcd for [MH$^+$] 297.1967, found 297.1972.

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Supporting Information Available: Detailed procedures and full characterization. This material is available free of charge via the Internet at http://pubs.acs.org. The crystal structures of compounds **27**, **31**, **33b**, and **35a** were deposited at the Cambridge Crystallographic Data Centre with the numbers CCDC 625288−625291, respectively.

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