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Diastereoselectivity Control of the Radical Carboazidation of Substituted Methylenecyclohexanes

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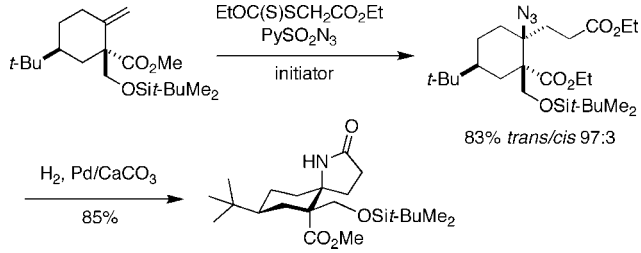
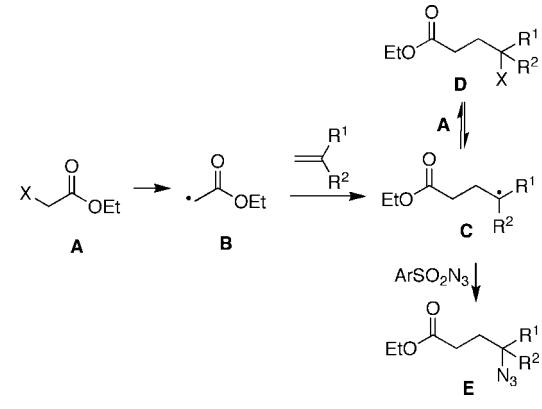


A systematic study of the diastereoselectivity of the radical carboazidation of methylenecyclohexane derivatives is presented. Several substitution patterns leading to a high level of stereocontrol have been identified. Axial attack is the preferred reaction pathway for cyclohexyl radicals, and excellent stereoselectivities can be obtained by introducing an axial substitutent at position 2. In this case, a second equatorial substituent at position 2 may be tolerated without a large detrimental effect on the diastereoselectivity. Finally, a high level of equatorial attack is observed with a very bulky substituent at position 2.

Introduction

Not long ago, we developed a method for the efficient formation of carbon−nitrogen bonds using the reaction of radicals with sulfonyl azides.[1] The radical azidation process can be coupled with the formation of a carbon−carbon bond allowing the carboazidation of olefins (Scheme 1).[2,3] In this reaction, an electrophilic enolate radical **B** is generated from an iodide or a xanthate **A** and reacts selectively with an electron-rich alkene. The resulting radical adduct **C** possesses a nucleophilic character and may abstract in a reversible manner an halogen atom or a xanthate to afford **D** or react directly with the arenesulfonyl azide, a radical azidating agent with electrophilic character, to deliver the final azide **E**. This reaction proved to be very effective for the synthesis of alkaloids and related nitrogen-containing heterocyclic compounds.[3]

SCHEME 1. Radical Carboazidation



Recently, we have reported the total synthesis of hyacinthacine[4] using this key reaction. A detailed study of the stereoselectivity of the carboazidation of acyclic olefins proved that by using suitable substrates such as allylsilanes, a good level of stereocontrol can be achieved.[5] Substituted methylenecyclohexanes are particularly appealing substrates for the application

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(1) Ollivier, C.; Renaud, P. *J. Am. Chem. Soc.* **2000**, *122*, 6496–6497. Ollivier, C.; Renaud, P. *J. Am. Chem. Soc.* **2001**, *123*, 4717–4727.

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(3) Panchaud, P.; Ollivier, C.; Renaud, P.; Zigmantas, S. *J. Org. Chem.* **2004**, *69*, 2755–2759.

(4) Chabaud, L.; Landais, Y.; Renaud, P. *Org. Lett.* **2005**, *7*, 2587–2590.

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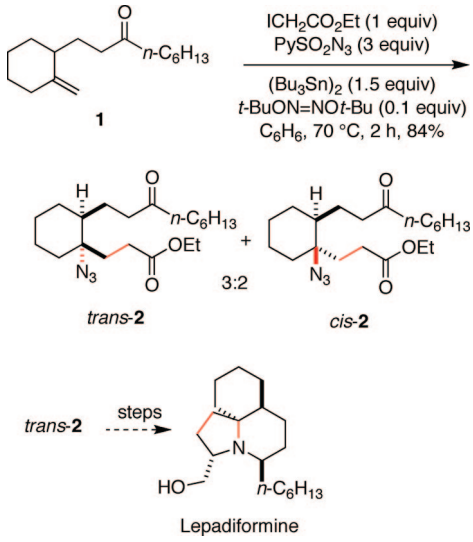
SCHEME 2. Radical Carboazidation As a Key Step for the Synthesis of Lepadiformine

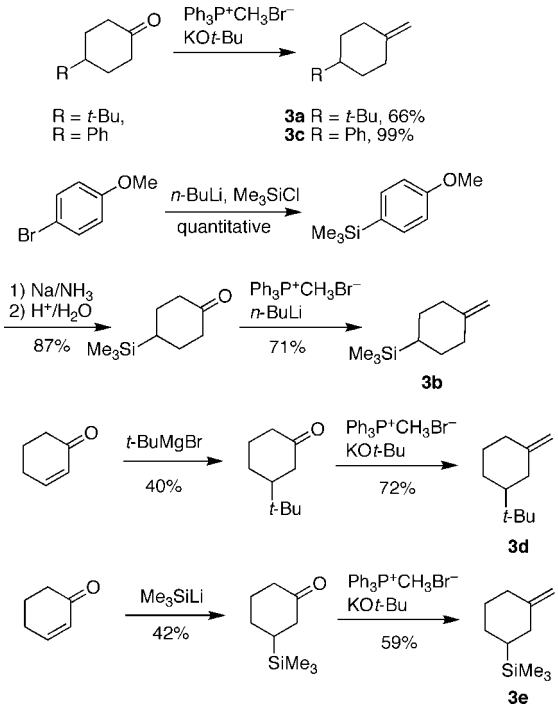


of the carboazidation reaction to natural product synthesis as demonstrated by our recent synthesis of the marine alkaloid lepadiformine.[6] Indeed, these alkenes undergo carboazidation in high yield and are easily available in racemic and enantiomerically pure form.[7] However, the level of diastereoselectivity reached in the carboazidation of methylenecyclohexane derivatives is not satisfactory. For example, in our synthesis of lepadiformine, the radical carboazidation of alkene **1** resulted in the formation of azidoesters **2** as a 3:2 *trans*/*cis* mixture (Scheme 2).[6] All attempts to increase the stereoselectivity of this process by changing the reaction temperature and the solvent failed to give a significant enhancement. A better understanding of the factors governing the stereoselectivity of the carboazidation of methylenecyclohexanes is needed. Herein, we report a systematic study of the diastereoselectivity of the radical carboazidation of methylenecyclohexanes. Several substitution patterns leading to high level of stereocontrol have been identified.[8]

Results and Discussion

Preparation of Substituted Methylenecyclohexanes. The methylenecyclohexane derivatives **3a**−**e** were prepared according to Scheme 3 using Wittig olefination of the corresponding ketones. The 4-silylated cyclohexanone was prepared from 4-bromoanisole by a bromine−lithium exchange reaction followed by silylation. The 4-trimethylsilylanisole was then converted into the desired ketone via Birch reduction and hydrolysis. The 3-*tert*-butyl- and 3-trimethylsilylcyclohexanone were prepared by conjugate addition of *tert*-butylmagnesium bromide and trimethylsilyllithium to cyclohexenone.

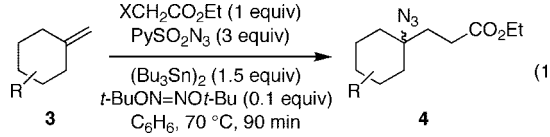
SCHEME 3. Preparation of 4- and 3-Substituted Methylenecyclohexanes 3a−e



2-Substituted methylenecyclohexanes **3f**−**j** were prepared according to Scheme 4. Compound **3f** was easily prepared from cyclohexanone by enamine-mediated conjugate addition to acrylonitrile followed by Wittig methylenation. A similar reaction sequence starting from 4-*tert*-butylcyclohexanone afforded the *cis*-methylenecyclohexane **3g**. The *trans* isomer **3h** was prepared by separation of the mixture of diastereomeric ketones followed by methylenation with in situ generated Kauffmann's tungsten carbene.[9] Under these conditions, the *trans* compound **3h** was contaminated with only 7% of the more stable *cis* isomer.

A last set of 2,2-disubstituted methylenecyclohexanes was prepared according to Scheme 5. The 4-*tert*-butyl-2,2-dimethylmethylenecyclohexane **3k** was obtained by direct alkylation of 4-*tert*-butylcyclohexanone and Wittig methylenation. The olefins **3l**−**n** were obtained via alkylation of the corresponding β-ketoesters with *n*-propyl iodide (**3l**) and formaldehyde followed by silylation (**3m** and **3n**) and subsequent methylenation.

Carboazidation Reactions. Methylenecyclohexane Derivatives Substituted at Position 4 or 3. A first series of experiments was performed with methylenecyclohexane derivatives **3a**−**e** bearing conformationally locking substituents at position 3 or 4 according to eq 1. Due to the absence of substituents at positions 2 and 5 and their locked conformation, these substrates are suitable to probe the axial vs equatorial selectivity of the radical azidation step.



Results are presented in Scheme 6. Under the standard conditions of the tin-mediated carboazidation, using 3-pyridinesulfonyl azide[10] as the azidating agent and ethyl iodoacetate or

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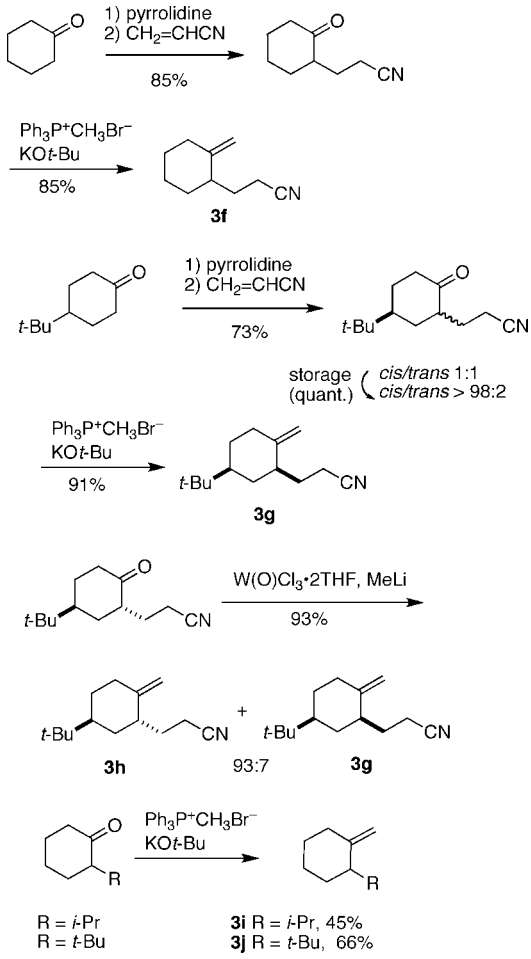
(8) Curran, D. P.; Porter, N. A.; Giese, B. *Stereochemistry of radical reactions: concepts, guidelines, and synthetic applications*; VCH: New York, 1996; p 280. Renaud, P. Stereoselectivity of Intermolecular Radical Reactions: Cyclic Systems. In *Radicals in Organic Synthesis*; Renaud, P.; Sibi, M. P., Eds.; Wiley-VCH: Weinheim, 2001; Vol. 1, pp 400−415.

SCHEME 4. Preparation of 2-Substituted Methylenecyclohexanes 3f−j



ethyl 2-ethoxythiocarbonylsulfanylethanoate as the radical precursor, alkenes **3a**−**e** are converted into the corresponding azidoesters **4a**−**e** in good yields (80−93%). The 4-substituted methylenecyclohexanes **3a**−**c** afford the *cis* azides **4a**−**c** with stereoselectivities ranging from *cis/trans* 75:25 to 84:16. The 3-susbtituted derivatives **3d** and **3e** give preferentially the *trans* azides **4d** and **4e** with similar levels of stereocontrol (*trans*/*cis* 79:21 and 75:25, respectively). The relative configuration of compounds **4a** and **4e** was deduced from NOE difference spectra (see the Supporting Information) of the corresponding spirolactams **5a** and **5e** easily prepared by hydrogenation of the azides followed by lactamization (Scheme 6).

From these results, a first trend can be deduced: axial attack is preferred for the reactions of cyclohexyl radicals with pyridinesulfonyl azide. Selectivities up to axial/equatorial 5:1

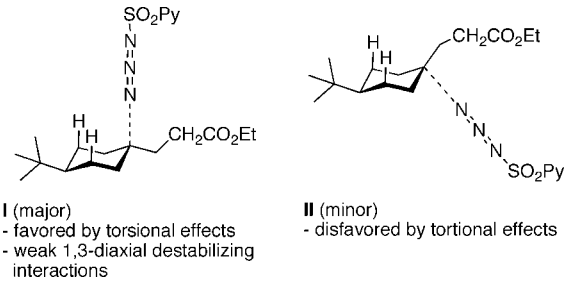
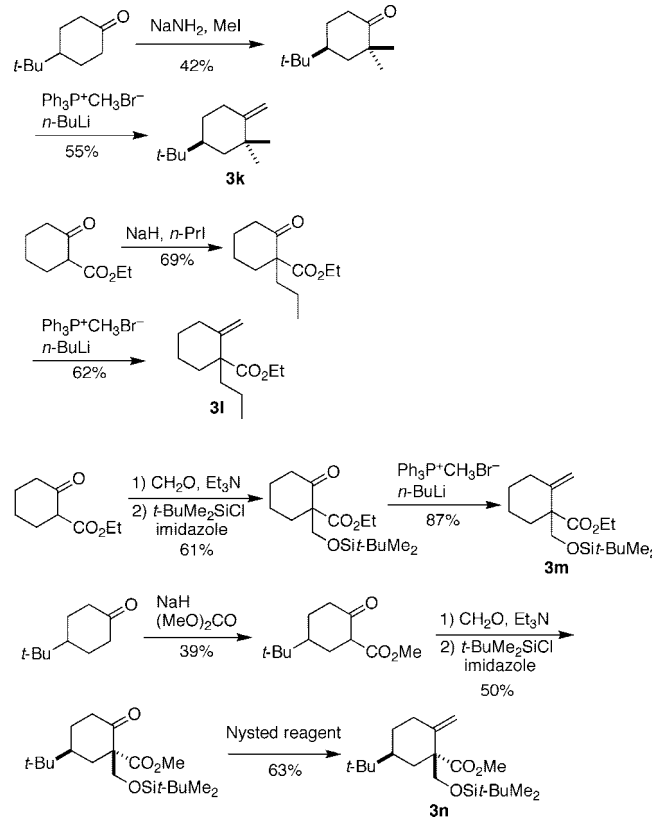
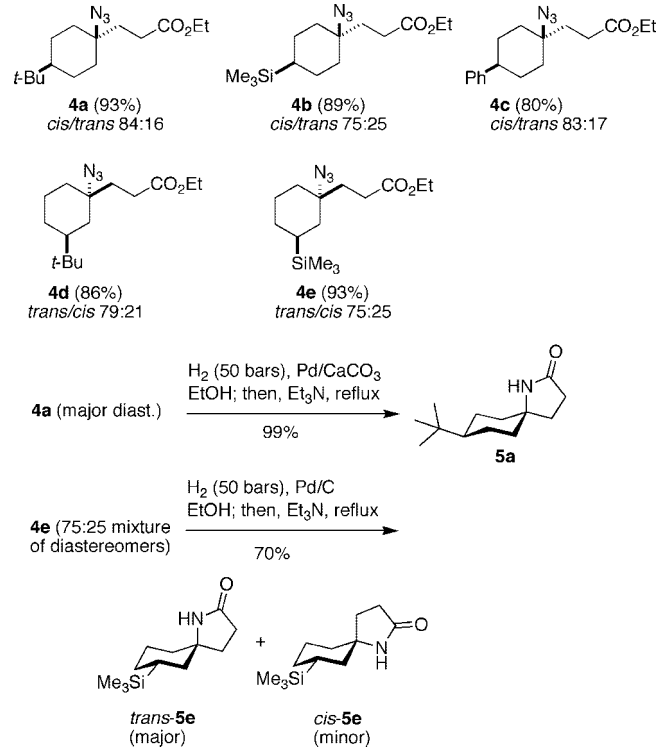


FIGURE 1. Stereochemical outcome of the azidation of 1,4-disubstituted cyclohexyl radicals.

SCHEME 5. Preparation of 2,2-Disubstituted Methylenecyclohexanes 3k−n

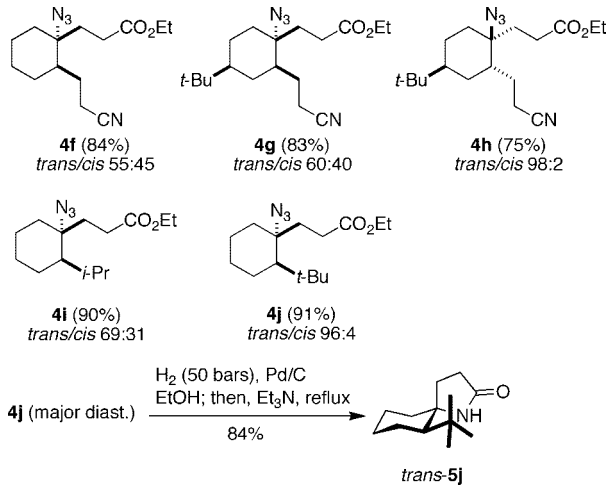


SCHEME 6. Carboazidation of 3- and 4-Substituted Methylenecyclohexanes



and 4:1 are observed when the conformation of the cyclohexyl ring is controlled by a *tert*-butyl group at positions 4 and 3, respectively. The observed stereoselectivity of 3−5:1 is consistently reproduced with different bulky substituents. This axial

SCHEME 7. Carboazidation of 2-Substituted Methylenecyclohexanes 3f−j



selectivity parallels nicely Giese's results on the stereoselectivity of cyclohexyl radical trapping.[11] In analogy to the reduction of cycloalkanones, Giese reported that axial reactions are favored by torsional effects and disfavored by 1,3-diaxial interactions.[11,12] The sulfonyl azide radical trap is nearly linear,[13] and the reaction is taking place at the γ-position of the azide residue.[14] As a consequence, the destabilizing 1,3-diaxial interactions are decreased, and the axial attack represents the major pathway (transition state model **I**, Figure 1). The equatorial attack is disfavored by torsional effects (model **II**, Figure 1). Similar results have been observed for hydrogen atom transfer from tributyltin deuteride and for halogen atom transfer.[11]

Methylenecyclohexane Derivatives Substituted at Position 2. The influence of substituents at position 2 of the methylenecyclohexane was investigated next (Scheme 7). In agreement with the results obtained in the lepadiformine synthesis (Scheme 2), the presence of a primary alkyl substituent at position 2 is not sufficient to control the stereochemical outcome of the carboazidation process. For instance, the azide **4f** was obtained as a *trans/cis* 55:45 mixture of diastereomers. Locking the conformation of the 6-membered ring with a *tert*-butyl substituent at position 4 was then investigated. The *cis*-disubstituted methylenecyclohexane **3g** affords the azide **4g** with a low selectivity similar to the one observed for **4f**.[15] Interestingly, the *trans* alkene **3h** gives the azide **4h** with an excellent level of stereocontrol (*trans/cis* 98:2). The size of the α-substituent was investigated next by performing the carboazidation with 2-isopropyl and 2-*tert*-butylmethylenecyclohexane **3i** and **3j**. The isopropyl substituent induces only a moderate stereoselectivity (**4i**, *trans/cis* 69:31). However, a good level of *trans* selectivity was obtained for the 2-*tert*-butyl substituted azide **4j** (*trans/cis* 96:4). The relative configuration of **4j** was proved by X-ray structure analysis of the corresponding lactam **5j** (Scheme 7).

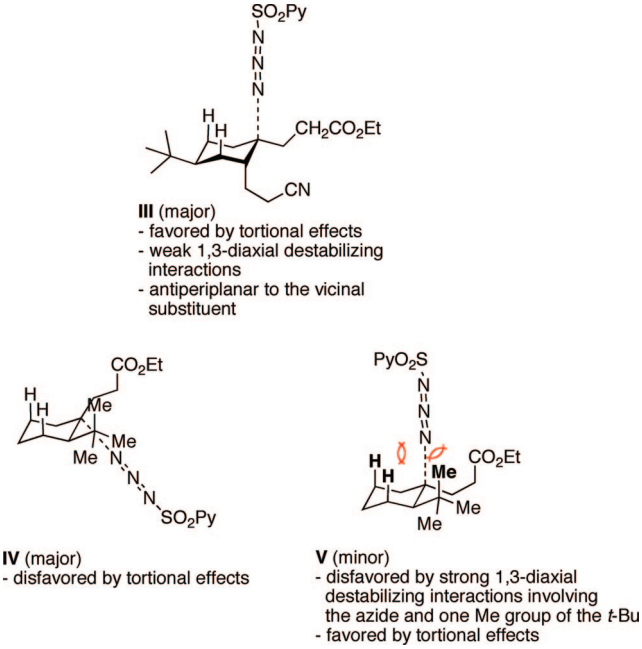


FIGURE 2. Stereochemical outcome of the azidation of 1,2-disubstituted cyclohexyl radicals.

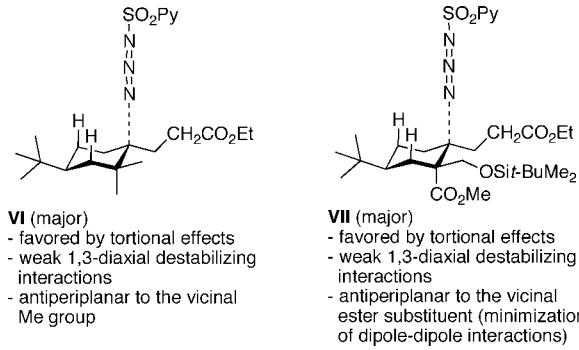


FIGURE 3. Stereochemical outcome for the azidation of 2,2,4-trisubstituted cyclohexyl radicals.

This second set of experiments demonstrates that high stereoselectivities are reached when the substituent at position 2 is forced into an axial position (see formation of **4h**) or is very bulky (tertiary alkyl group, see **4j**). The high stereoselectivity observed for the formation of *trans*-**4h** is easily explained by transition state model **III** (Figure 2) where the preferential axial attack described in Figure 1 (model **I**) is reinforced by the presence of a vicinal axial substituent. The preferential formation of **4j** results from an equatorial attack according to model **IV** (Figure 2). This equatorial attack represents the major pathway since the axial attack (model **V**, Figure 2) suffers from strong destabilizing interactions between the incoming sulfonyl azide and one of the methyl group from the *tert*-butyl substituent (1,3-diaxial-like interactions).

Methylenecyclohexane Derivatives Disubstituted at Position 2. A series of experiments was performed in order to check if the carboazidation can be stereoselective when the vicinal center is a quaternary center (Scheme 8). Starting from the 2,2-dimethyl-4-*tert*-butylmethylenecyclohexane **3k**, the *cis* azide **4k** is obtained with a moderate level of stereocontrol (*cis*/*trans* 85:15). The conformationally labile substrate **3l** bearing at position 2 a propyl and an ethoxycarbonyl substituent gives **4l** as a 1:1 mixture of diastereomers. Interestingly, substrate **3m** gives **4m**

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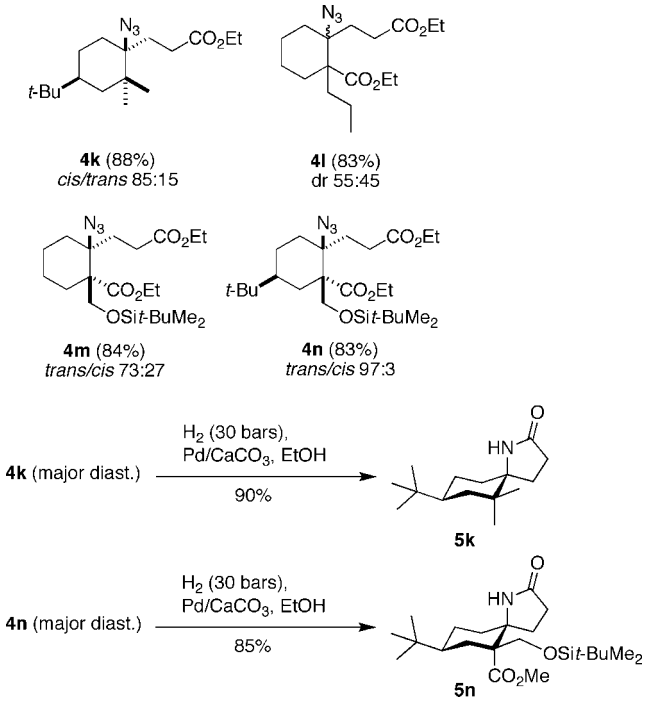
(12) Wu, Y. D.; Houk, K. N. *J. Am. Chem. Soc.* **1987**, *109*, 908–910. Wu, Y. D.; Houk, K. N.; Trost, B. M. *J. Am. Chem. Soc.* **1987**, *109*, 5560–5561.
(13) Parkanyi, L.; Besenyei, G. *J. Mol. Struct.* **2004**, *691*, 97–106.
(14) Masterson, D. S.; Shackleford, J. P. *Synlett* **2007**, 1302–1304.
(15) For simplicity reasons, the *cis*/*trans* nomenclature has been also used for 2,5-disubstitued cyclohexyl azides and takes into account only the relative configuration of the newly formed center and the substituent at position 2.

SCHEME 8. Carboazidation of 2,2-Disubstituted Methylenecyclohexanes 3k−n



with a moderate stereoselectivity. This selectivity could be increased by introducing a *tert*-butyl group at postion 4. Indeed, carboazidation of **3n** affords **4n** with excellent stereocontrol (*trans*/*cis* 97:3). By comparison with **3m**, the carboazidation of **3n** represents a case of matched asymmetric induction. Unfortunately, the diastereomeric methylenecyclohexane could not be synthesized, and the level of stereoselectivity for the expected mismatched case could not be determined. The relative stereochemistry of azides **4k** and **4n** was determined after conversion into the γ-lactams **5k** and **5n** by X-ray crystal structure analysis (Scheme 8).

The preferential axial selectivity leading to the formation of *cis*-**4k** is rationalized by transition-state model **VI** (Figure 3) closely related to **III** (Figure 2). For **4l** and **4m**, the observed stereoselectivities depend on the conformation equilibrium of the radical intermediate and the axial/equatorial selectivity for each radical conformer. The higher selectivity for **4m** may results from dipole−dipole interactions between the sulfonyl azide and the ester group. The good level of stereocontrol for the formation of **4n** is explained by model **VII** where selectivity of the axial attack is reinforced by the presence of an *anti* ester group.

Conclusions

This study of the model system has shown that control of the selectivity of the carboazidation reaction of methylenecyclohexanes is possible when the substrate is properly designed. A high level of equatorial attack can only be obtained with very bulky substituents at position 2. Axial attack is the preferred reaction pathway for cyclohexyl radicals, and excellent stereoselectivities can be obtained by introducing an axial substituent at position 2. In this case, a second equatorial substituent at position 2 may be tolerated without a large detrimental effect on the diastereoselectivity. Application of these results for the stereoselective synthesis of naturally occurring alkaloids is underway and will be reported in due course.

Experimental Section

General Procedure for the Radical Carboazidation of Alkenes. To a mixture of the olefin (2.0 equiv), ethyl 2-iodoacetate or ethyl 2-ethoxythiocarbonylsulfanylethanoate (1.0 equiv), and 3-pyridinesulfonyl azide (3.0 equiv) in benzene (4 mL/mmol) were added hexabutyldistannane (1.5 equiv) and di-*tert*-butylhyponitrite (0.1 equiv). The reaction mixture was stirred at 70−80 °C for 90 min. The solvent was then removed under reduced pressure and the yellow residue purified by flash chromatography (FC). The diastereomeric ratio was determined by integration of the ^{1}H and/or ^{13}C NMR signals.

Ethyl 3-(1-Azido-4-*tert*-butylcyclohexyl)propanoate (4a). Prepared according to the general procedure from olefin **3a** and ethyl 2-iodoacetate. FC (silica gel containing 10% KF, cyclohexane/*t*-BuOMe 98:2) gave **4a** (262 mg, 0.93 mmol, 93%, dr 84:16) as a colorless liquid.

Mixture of diastereoisomers: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.15 (q, J = 7.1 Hz, 2H), 2.50−2.28 (m, 2H), 1.95−0.77 (m, 11H), 1.27 (t, J = 7.1 Hz, 3H), 0.86 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.5 (minor), 173.3 (major), 63.2 (minor), 63.1 (major), 60.6 (major + minor), 47.6 (major), 47.5 (minor), 36.2 (major), 34.7 (2C, minor), 35.0 (2C, major), 32.5 (major), 32.3 (minor), 29.1 (minor), 28.9 (major), 28.7 (minor), 27.6 (3C, major + minor), 23.6 (2C, minor), 22.9 (2C, major), 14.3 (major + minor); IR (ATR) ν 2943, 2867, 2095, 1734, 1254, 1181 cm^{-1}; MS (EI) *m*/*z* 239 (11), 193 (14), 180 (13), 152 (15), 136 (20), 110 (13), 96 (22), 69 (17), 57 (100), 41 (34); HRMS (EI) calcd for $C_{15}H_{27}O_2$ ([M − N_3]$^+$) 239.2011, found 239.2001. Anal. Calcd for $C_{15}H_{27}N_3O_2$: C, 64.03; H, 9.67; N, 14.93; O, 11.37. Found: C, 64.00; H, 9.61; N, 14.90; O, 11.37.

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Supporting Information Available: Experimental procedures and characterization data of compounds **3a**−**n**, **4b**−**n**, **5a**,**e**,**j**−**n** and copies of ^{1}H and ^{13}C NMR spectra of compounds **3b**,**f**−**h**,**l**−**n**, **4a**−**n**, **5a**,**e**,**j**−**n**. X-ray crystallographic data for **5j**, **5k**, and **5n**. This material is available free of charge via the Internet at http://pubs.acs.org.

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