

Trans-Stereoselectivity in the Reaction between Homophthalic Anhydride and Imines

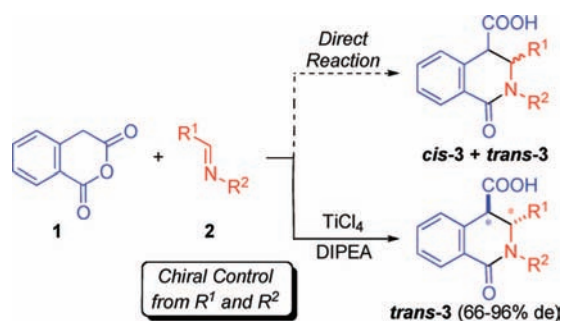
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ABSTRACT



The reaction between homophthalic anhydride and imines in the presence of TiCl_4 and diisopropyl ethyl amine is *trans*-selective. Under these conditions, the reaction using homochiral imines can be highly diastereoselective, thus allowing the synthesis of enantiopure 1,2,3,4-tetrahydro-1-oxoquinoline-4-carboxylic acids.

The reaction between cyclic anhydrides and imines¹ to yield lactams bearing a carboxylate functionality (Scheme 1) constitutes a convergent route to highly valuable compounds such as natural products² or topoisomerase I³ and HOXA13 inhibitors.⁴

The mechanism of this reaction has been controversial, and both concerted and stepwise mechanisms have been proposed.^{1b} Kaneti et al.⁵ have reported DFT and MO calculations on the reaction between succinic anhydride and imines. These authors concluded that the thermal reaction takes place via a concerted mechanism (Scheme 1, pathway A) involving the enolic form of the anhydride. Under these conditions, the *cis*-isomer is the major product when (*E*)-aldimines and homophthalic anhydride are used.⁶

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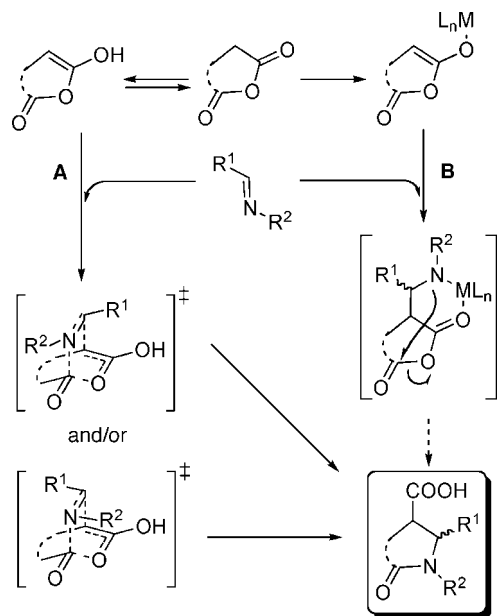
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Scheme 1. Possible Routes for the Reaction between Enolizable Anhydrides and Imines



^AEnol-based concerted pathway. ^BEnolate-based stepwise mechanism.

In view of these precedents, we decided to explore a hypothetical Perkin-Mannich route (Scheme 1, pathway B) in which an enolate derived from the enolizable anhydride would react with the imine to yield an intermediate containing the stereochemical information of the new C–C bond. Subsequent intramolecular cyclization would yield the corresponding cyclic amide, probably with a stereocontrol different to that obtained via pathway A.

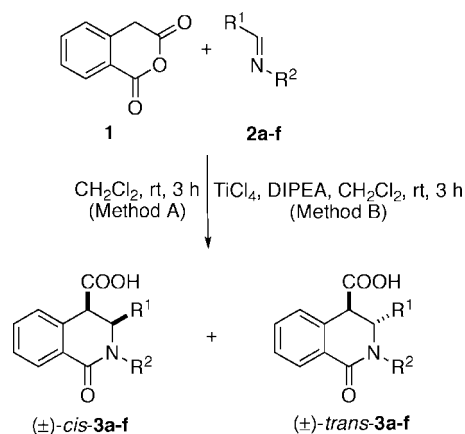
To test this hypothesis, we carried out the reaction between homophthalic anhydride **1** and aldimines **2a–f** to yield racemic 1,2,3,4-tetrahydroisoquinidine carboxylic acids **3a–f** (Scheme 2) in the presence⁷ of TiCl₄ and diisopropyl ethyl amine (DIPEA) as metal source and base, respectively.⁸ The results obtained, together with those observed for the direct reaction in the absence of the TiCl₄/DIPEA pair, are gathered in Table 1.

Our results indicate that the direct reaction between **1** and imines **2a,b** is not stereoselective (Table 1, entries 1 and 2), whereas the reaction with aldimines **2c,d** (Table 1, entries

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(8) Typical experimental procedure: To a stirred solution of homophthalic anhydride **1** (1 mmol, 0.162 g) in 2 mL of dichloromethane was added 1 M TiCl₄ in dichloromethane (1 mL) at 0 °C under argon atmosphere. After 5 min at 0 °C, DIPEA (1 mmol, 0.17 mL) was added at the same temperature. After stirring for 20 min, a solution of 1 mmol of the corresponding imine **2** in 2 mL of dichloromethane was added dropwise. The reaction mixture was stirred at room temperature for 3 h. The resulting mixture was washed three times with saturated solution of NH₄Cl (3 × 5 mL), dried with Na₂SO₄, evaporated, and purified by flash chromatography (Silicagel 60 230–400 mesh, ethyl acetate/hexane 1:1 and then 5:1) to yield the corresponding product *trans*-**3**.

Scheme 2. Reaction between Homophthalic Anhydride **1** and Aldimines **2a–e**



a: R¹ = 4-CH₃OC₆H₄; R² = CH₂COOCH₃
b: R¹ = C₆H₅; R² = CH₂COOCH₃
c: R¹ = C₆H₅; R² = 4-CH₃OC₆H₄
d: R¹ = 4-CH₃OC₆H₄; R² = CH₂C₆H₅
e: R¹ = C₆H₅; R² = CH₃
f: R¹ = C(CH₃)₃; R² = 4-CH₃OC₆H₄

3–5) takes place with high *cis*-stereocontrol. The reaction between **1** and (*E*)-benzylidenemethanamine **2e** is *trans*-selective (Table 1, entry 5). In contrast, the titanium assisted version of the reaction takes place with higher stereocontrol, the *trans*-derivative being the major one in all the cases studied. This stereocontrol did not vary significantly when the reaction between **1a** and **2a** was conducted at –20 and –80 °C. The structures of compounds *cis*-**3a** and *trans*-**3e** were confirmed by X-ray diffraction analysis (see the Supporting Information). The structures of the remaining products were established by comparison with these compounds and with other analogues reported in the literature.^{1–3} ¹H NMR analysis of acids **3a–f** showed coupling constants between the vicinal methine protons of ca. 5–6 and 1–2 Hz for the *cis* and *trans* stereoisomers, respectively.

To shed some light on the origins of the good stereocontrol observed in the Perkin-Mannich version of this reaction, we

Table 1. Formation of Compounds (±)-**3a–f** by Reaction between Homophthalic Anhydride **1** and Aldimines **2a–e**

entry	reaction	method A ^a		method B ^a	
		<i>cis:trans</i> ^b	yield (%) ^c	<i>cis:trans</i> ^b	yield (%) ^c
1	1 + 2a → 3a	50:50	31 ^d , 31 ^e	7:93	60 ^e
2	1 + 2b → 3b	50:50	31 ^d , 31 ^e	17:83	76 ^e
3	1 + 2c → 3c	94:6	91 ^d , 5 ^e	3:97	80 ^e
4	1 + 2d → 3d	82:18	47 ^d , 11 ^e	>2:98	63 ^e
5	1 + 2e → 3e	20:80	7 ^d , 63 ^e	>2:98	65 ^e
6	1 + 2f → 3f	27:73	23 ^d , 62 ^e	11:89	45 ^e

^a See Scheme 2 for details. ^b Determined by ¹H NMR on the crude reaction mixture. ^c Isolated yields of pure products. ^d Isolated yield of the *cis*-isomer. ^e Isolated yield of the *trans*-isomer.

carried out DFT^{9,10} calculations on the process indicated in Figure 1. This transformation corresponds to the C–C bond

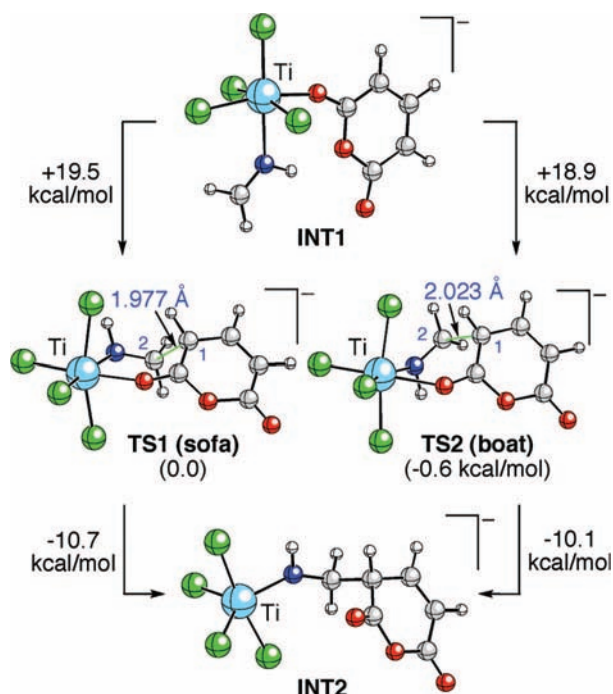


Figure 1. Transition structures **TS1** and **TS2** associated with the C–C bond forming step of the reaction of complex **INT1**. Energies include zero-point vibrational energy (ZPVE) corrections and have been calculated at the B3LYP/6–31G* & LANL2DZ level. Numbers in parentheses correspond to the relative energy differences.

forming step in the reaction between glutaconic anhydride and methanimine.

Many mechanistic studies dealing with the TiCl_4 /amine system assume that the active enolates are neutral ($\text{C}=\text{C}-\text{OTiCl}_3$) species¹¹ and/or anionic ($\text{C}=\text{C}-\text{OTiCl}_4^-$) complexes.¹² A recent paper¹³ has reported the presence of anionic titanium enolate complexes ($\text{C}=\text{C}-\text{OTiCl}_4^-$) in which the most stable form has significant biradical character. The corresponding triplet species was characterized by electron paramagnetic resonance. We carried out single point calculations on the optimized structure of **INT1** at the CASSCF(4,4) and CASSCF(8,10) levels to assess its hypo-

thetical biradical character. Our results indicated that the electronic structure of **INT1** is closed shell in nature. For instance, the natural occupancies of the four active MOs of the CASSCF(8,10) calculation were 1.945, 1.964, 1.969, and 1.944. In addition, the triplet state was found to be 32.1 kcal/mol higher in energy than the singlet. These results indicate that the more basic nitrogen atom of the iminic moiety in **INT1** does not favor the stabilization of biradicals.

We also located and characterized two different saddle points associated with the transformation depicted in Figure 1. For this model system **TS2**, which has a boat conformation, is more stable than the sofa transition structure **TS1**. CASSCF(8,10) single point calculations on both transition structures also resulted in closed shell electronic structures. The intermediate product of this C–C bond forming step is **INT2**, whose intramolecular cyclization must yield the corresponding cyclic amide, as is shown in Scheme 1.

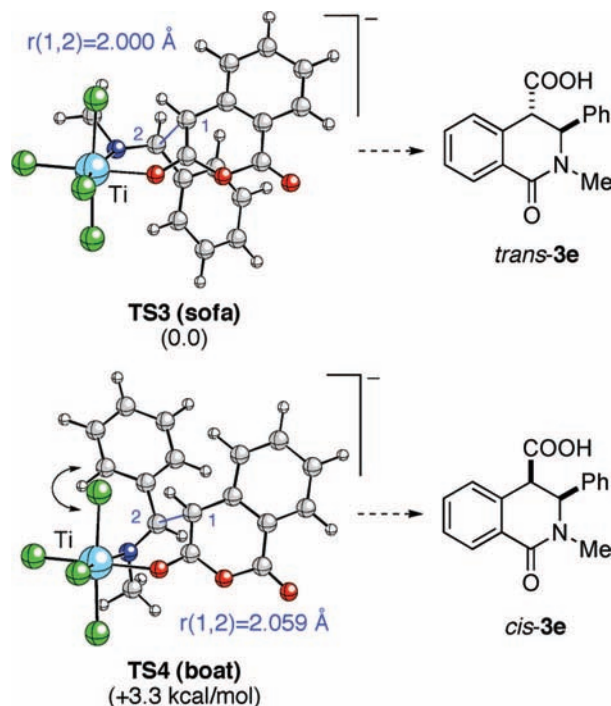


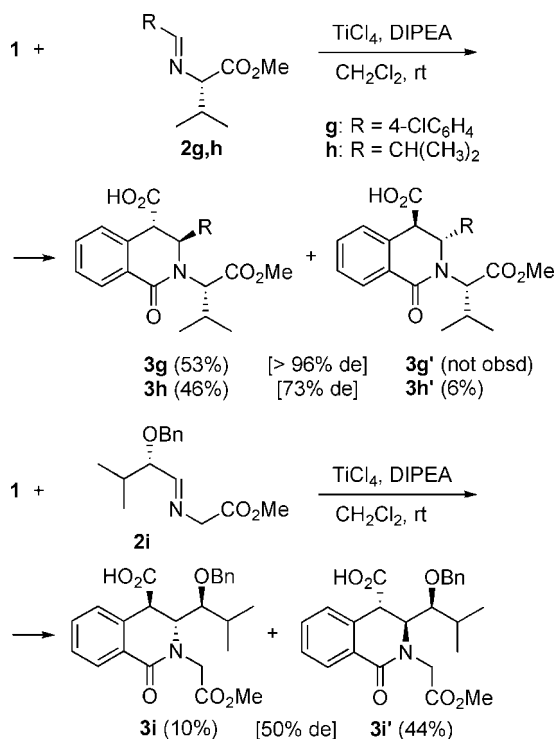
Figure 2. Transition structures **TS1a** and **TS2a** associated with the C–C bond forming step leading to *cis*- and *trans*-**3e** from **1** and imine **2e**. See the caption of Figure 1 for additional details.

(9) Density-functional theory (DFT) calculations were carried out using the B3LYP hybrid functional. See: (a) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648. (b) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1998**, *37*, 785. (c) Vosko, S. H.; Wilk, L.; Nusair, M. *Can. J. Phys.* **1980**, *58*, 1200. The 6–31G* basis set was used for all atoms except for titanium, which was computed using the LANL2DZ effective core potential and basis set. See: (d) Hay, P. J.; Wadt, W. R. *J. Chem. Phys.* **1985**, *82*, 299.

(10) All the calculations reported in this work were carried out using the Gaussian03 (Rev. D.02) suite of programs: Frisch, M. J. *Gaussian03*, revision D.02; Gaussian, Inc.: Wallingford, CT, 2004 (full reference is given in the Supporting Information).

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Scheme 3. Reaction between Homophthalic Anhydride **1** and Enantiopure Imines **2g–i**^a



^aNumbers in parenthesis correspond to yields of isolated pure products. The diastereomeric excess (de, in brackets) was determined by ¹H NMR on the crude reaction mixture.

Our next step in this preliminary study was to extend the *trans*-stereocontrol observed in the titanium route to homo-chiral imines. We observed that enantiopure imine **2g** in the presence of the TiCl₄/DIPEA system at room temperature yielded a single diastereomer **3g** (Scheme 3), whose structure

was determined by X-ray diffraction analysis (see the Supporting Information). This stereocontrol was observed to be lower when the reaction was carried out between **1** and imines **2h,i** (Scheme 3). In these cases, compounds **3h'** and **3i'** were also obtained, although the *trans*-stereoselectivity was kept. The stereochemistry of **3i'** was also confirmed by X-Ray diffraction analysis (see the Supporting Information).

In summary, we have shown that *trans*-stereoselectivity can be obtained in the reaction between homophthalic anhydride and imines. This stereocontrol is achieved by means of the TiCl₄/DIPEA pair. If enantiopure imines are used, the corresponding homochiral derivatives can be obtained, especially when the *N*-substituent is the source of chirality.

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Supporting Information Available: Full characterization of all novel compounds. Energies, zero-point vibrational energies (ZPVE), imaginary frequencies, and Cartesian coordinates of the transition structures reported in Figures 1 and 2. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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