

Communication

Trifluoroethanol Promoted Castagnoli–Cushman Cycloadditions of Imines with Homophthalic Anhydride

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Abstract: Lactams are essential compounds in medicinal chemistry and key intermediates in the synthesis of natural products. The Castagnoli–Cushman reaction (CCR) of homophthalic anhydride with imines is an exciting method for accessing cyclic densely substituted lactam products. Most CCRs need to be catalyzed or heated. Herein, we report a new, efficient, metal and catalyst-free CCR for the synthesis of poly-substituted 3,4-lactams utilizing the unique properties of trifluoroethanol (TFE). This procedure provides high-speed and smooth access to a broad range of densely substituted 3,4-lactams in good yields and a 100% atom-economical fashion.

Keywords: Castagnoli–Cushman reaction; homophthalic anhydride; imines; lactam; trifluoroethanol

1. Introduction

[4+2] Cycloadditions of enolizable anhydrides (succinic **IIa**, glutaric **IIb**, or homophthalic **IVa**) and imines formed in situ or prepared in a separate step were discovered by Castagnoli and Cushman and have attracted considerable attention from chemists for the preparation of substituted γ , δ , and ϵ -lactams (Scheme 1a) [1–3].



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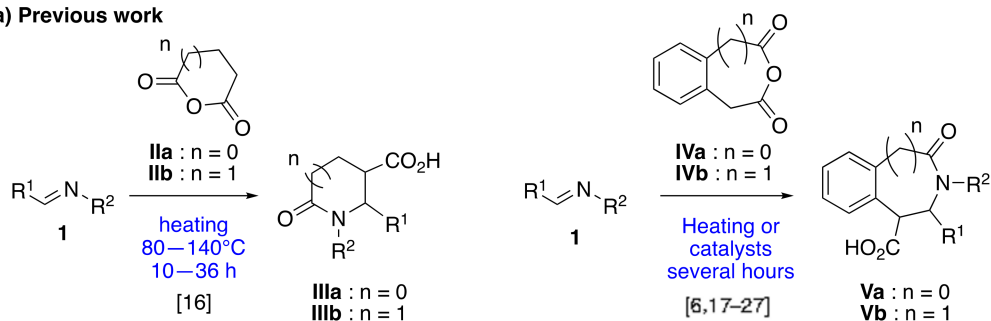
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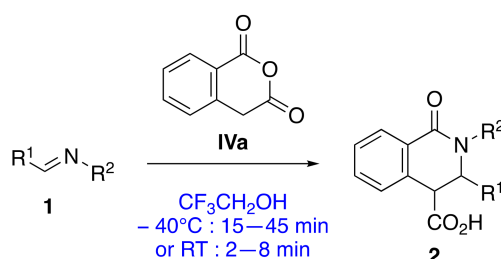


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a) Previous work



b) This work



Scheme 1. Castagnoli and Castagnoli–Cushman reactions.

Moreover, these cycloaddition reactions have seen wide applications in the synthesis of medicinal lead compounds piperidines and piperidinones derivatives [4,5], sting

antagonist [6], and antimalarial [7] or anticancer agents [8–10]. In addition, lactams obtained by these reactions, and their reduced nitrogen heterocycle analogs are found to be key intermediates in the synthesis of biologically significant natural products such as 13-methyltetrahydroprotoberbines (i.e., (+)-thalictricavine, (+)-canadine, (+) and (–)-cavidine [11–13], phenanthridine alkaloids and (–) and (+)-corynoline [14] possessing antitumor activity [15] (Figure 1).

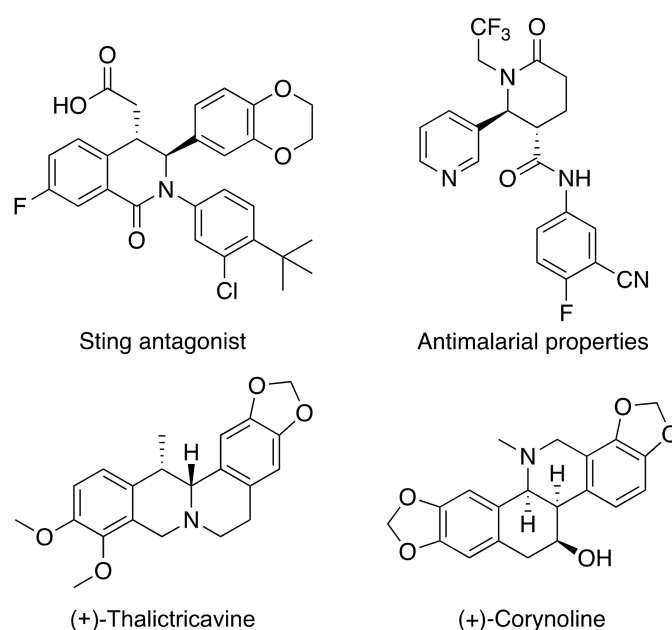


Figure 1. Bioactive compounds and natural products.

Surprisingly, despite the high interest in this transformation, the intrinsic drawbacks associated with the Castagnoli–Cushman reaction, including low reaction rates, moderate diastereoselectivity, catalyst-free, thermal-free, and limited substrate scope, have not been solved yet.

Generally, the reaction of succinic **IIa** and glutaric **Iib** anhydrides with imines requires forcing conditions such as reflux in benzene, toluene, or *p*-xylene (140 °C) during 12–36 h [16]. While the reaction conditions were less harsh when more enolizable anhydrides **Iva** and **IVb** were employed, catalysts or heating or long reactions time were necessary to isolate the CC products **Va** and **Vb** in decent yields.

In addition, depending on the nature of the imine and the reaction conditions, the cycloaddition of homophthalic anhydride (HPA) **IVa** with imines affords the 3,4-*cis* product **Va**, 3,4-*trans* product **Va**, or a mixture of both predominantly [3].

Mixtures of 3,4-*cis* and 3,4-*trans* isomers have been observed in the presence of catalytic amounts of bases (DIEA, TEA), Lewis acids (FeCl₃, AlCl₃, ZnCl₂), protic acid (HCl), or in the absence of catalyst [3]. BF₃·OEt₂ [17], TiCl₄ [18], InCl₃ [6], and aspartic acid [19] have been employed for the preparation of 3,4-*trans*-isoquinolonic acids. Recently, 3,4-*trans*-isoquinolonic acids have been prepared without catalyst by heating homophthalic anhydride **IVa** with different amines and aldehydes in the presence of Na₂SO₄ in refluxing toluene [20]. 3,4-*cis*-isoquinolonic acids have been prepared in the presence of ionic liquids [21], trimethyl orthoformate [22], Yb(OTf)₃ [23], silica sulfuric acid [24], sulfonic acid functionalized silica [25], KAl(SO₄)₂·12H₂O [26], or L-proline [27]. The formations of *cis*-isoquinolonic acids under the conditions described above took several hours at room temperature or reflux in different solvents (Scheme 1a).

Despite the considerable attention that CCRs have received over the past decades, the development of mild and practical methods is an ongoing challenge in organic synthesis. Therefore, further exploration of new catalyst-free, mild, efficient, and fast conditions is still desirable to access substituted γ , δ , and ϵ -lactams.

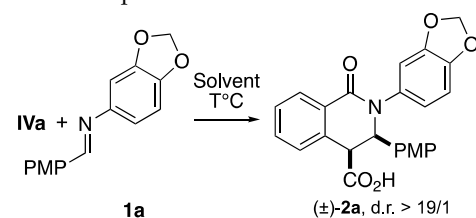
Fluorinated alcohols may be considered promising alternatives to address this synthetic challenge due to their unique properties such as high dielectric constant, polarity, high H-bond donor ability, and low nucleophilicity for cation stabilization [28,29].

Herein, we report a fast and powerful cycloaddition of imines **1** with HPA **IVa** in 2,2,2-trifluoroethanol (TFE), resulting in an efficient synthesis of lactams **2**. **2** are promising scaffolds for the design of biologically active compounds and key intermediates in the synthesis of natural products (Scheme 1b).

2. Results and Discussion

We initially investigated the reaction of HPA **IVa** with imine **1a** in different solvents (Table 1).

Table 1. Optimization of the reaction conditions ^{a,b}.



Entry	Solvent	Temp [°C]	Time	Yield ^c
1	CH ₂ Cl ₂	−40	24 h	37
2	CH ₂ Cl ₂	rt	16 h	72
3	toluene	−40	20 h	56
4	ACN	−40	20 h	50
5	MTBE	−40	48 h	78
6	TFE	−40	15 min	81
7	TFE	rt	2 min	72
8	CH ₂ Cl ₂ (+0.1 eq. TFE)	−40	3 h	61
9	HFIP	0	15 min	52

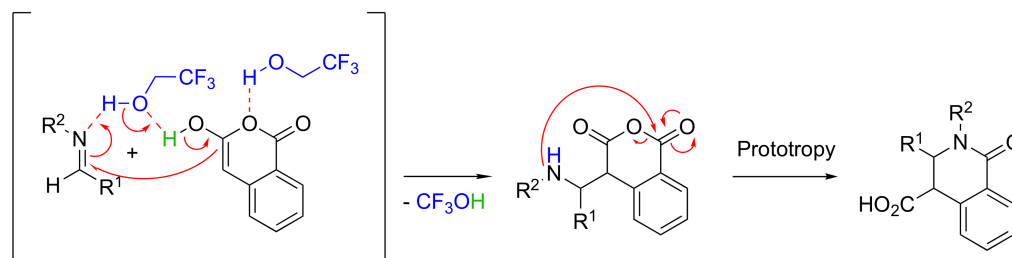
^a General conditions: homophthalic anhydride **IVa** (1.5 eq.) and imine **1a** (0.1 mmol). ^b PMP = 4-MeOC₆H₄. ^c Yield refer to chromatographically pure product.

This resulted in the formation of desired *cis*-lactam **2a** with excellent diastereoselectivity (d.r. > 19:1). Interestingly, the reaction rate varied noticeably depending on the solvent and the temperature. In CH₂Cl₂, toluene, and CH₃CN, the reaction takes several hours at −40 °C, even at room temperature. In polar solvents such as MTBE at −40 °C, the reaction also takes several hours, but the yield is higher (78%). To our delight, in TFE, the lactam **2a** was obtained in 81% yield in 15 min at −40 °C and in 72% yield in 2 min at room temperature (entries 6 and 7). Catalytic amounts of TFE in CH₂Cl₂ at −40 °C lead to an 8-fold decrease in reaction time (i.e., entries 1 and 8; 24 h vs. 3 h) and an increase in yield (i.e., entries 1 and 8; 37% vs. 61%). Another fluorinated alcohol, hexafluoro-2-propanol (HFIP), could also be used, although the yield was lower compared with the result of TFE (i.e., entry 9). The reaction could not be performed at −40 °C (solidifying of HFIP), and some degradation was observed at 0 °C. The diastereomeric excess remains unchanged whatever the solvent. The substituents of the starting imine induce diastereoselectivity.

Different mechanisms have been proposed for the CCR, including an iminolysis pathway and a concerted [4+2] cycloaddition [3,20]. The most plausible mechanism for the reaction of homophthalic anhydride **IVa** with simple imines **1** in TFE is shown in Scheme 2, proposal mechanism 1. The origin of the reaction's kinetic and yield increases in the presence of TFE might be attributed to a double activation of imine and carbonyl function of anhydride **IVa** via the H-bond network of TFE. The formation of hydrogen bonds between the anhydride and the TFE will decrease the pK_a of the enolizable proton. This will facilitate the attack of the **IVa** enol on the imine carbon. In this case, one molecule of TFE can bind to both imine and the **IVa** enol. A probable concerted hydrogen transfer

between activated imine and enol mediated by TFE could occur. This could explain the increase in reaction kinetics (Scheme 2). This scenario is supported by computational studies on closely related reactions of imines with α -cyanosuccinic anhydride [5] and is consistent with the relatively high acidity of **IVa** ($pK_a = 8.15$).

Proposal mechanism :



Intermediates in Perkin-type reaction

Scheme 2. Activation model via a putative transition state. pK_a values: **IVa** (8.15), imine (≈ 10), TFE (12.37).

Interested in expanding the scope of the optimal conditions in hand, we next examine carboxylic acid anhydrides other than homophthalic anhydride **IVa** and a variety of imines (Figure 2). Imine **1a** didn't react in TFE with glutaric anhydride, 3-methoxy-1H-isochromen-1-one, 1,4-dioxane-2,6-dione and (3*aR*,7*aS*)-hexahydroisobenzofuran-1,3-dione at $-40\text{ }^\circ\text{C}$ (24 h) or at reflux (24 h) or under microwave irradiations at $150\text{ }^\circ\text{C}$ (4 h).

The scope of the reaction was found to be relatively broad. Imines tolerated different N-aryl or N-alkyl groups well. Imines derived from aromatic aldehydes bearing aromatic rings (such as phenol, protected phenol, PMP, p-nitrobenzene) were converted into the corresponding cycloadducts **2b**, **2c**, **2d**, **2e**, **2i**, and **2h** in good yields (74–97%) with excellent diastereoselectivity except for **2h**. Imines bearing alkyl groups (such as N-tert-butyl or C-isopropyl) were also converted into the corresponding cycloadducts **2e** (79%) and **2f** (40%) with excellent diastereoselectivity. The yield of **2f** is lower because the imine **1f** is unstable. Imine **1g** derived from heterocyclic aldehyde (i.e., thiophene-2-carbaldehyde) also performed very well (i.e., **2g**, 90%), although the diastereoselectivity was reduced. The presence of an electron-withdrawing group such as a C-ethylcarboxylate on the imine (i.e., **1j**) led to **2j** but in lower yield (68%) with excellent diastereoselectivity.

The best yields have been obtained at room temperature. The diastereoselectivity was the same at $-40\text{ }^\circ\text{C}$ or room temperature for **2b**, **2c**, **2e**, and **2f**, whereas it changed for **2d**. The lower d.r. value for **2d** at room temperature may be due to the flexibility of the CH_2 -PMP group attached to the nitrogen atom of the imine. The formation of *cis*-diastereoisomer was observed in all cases except for **2h** and **2j**. The *trans*-diastereoisomer was major for **2h**. **2j** was obtained as *trans*-diastereoisomer solely.

The group's properties linked to the imine's carbon may explain these results. The presence of electron-rich groups promotes the formation of the *cis*-diastereoisomer, whereas electron-poor groups promote the synthesis of the *trans*-diastereoisomer. An ethylcarboxylate function being more electron-withdrawing than nitrobenzene may explain the exclusive formation of the *trans*-diastereoisomer **2j**.

The CCR usually leads to the kinetic *cis*-diastereoisomer product without catalyst or adduct. The thermodynamic *trans*-diastereoisomer can be obtained by epimerization in good yield upon exposure to DBU [30]. The *cis*-3,4-lactam **2a** was epimerized in *trans*-3,4-lactam **2a'** in 85% yield without loss of diastereoselectivity (Scheme 3).

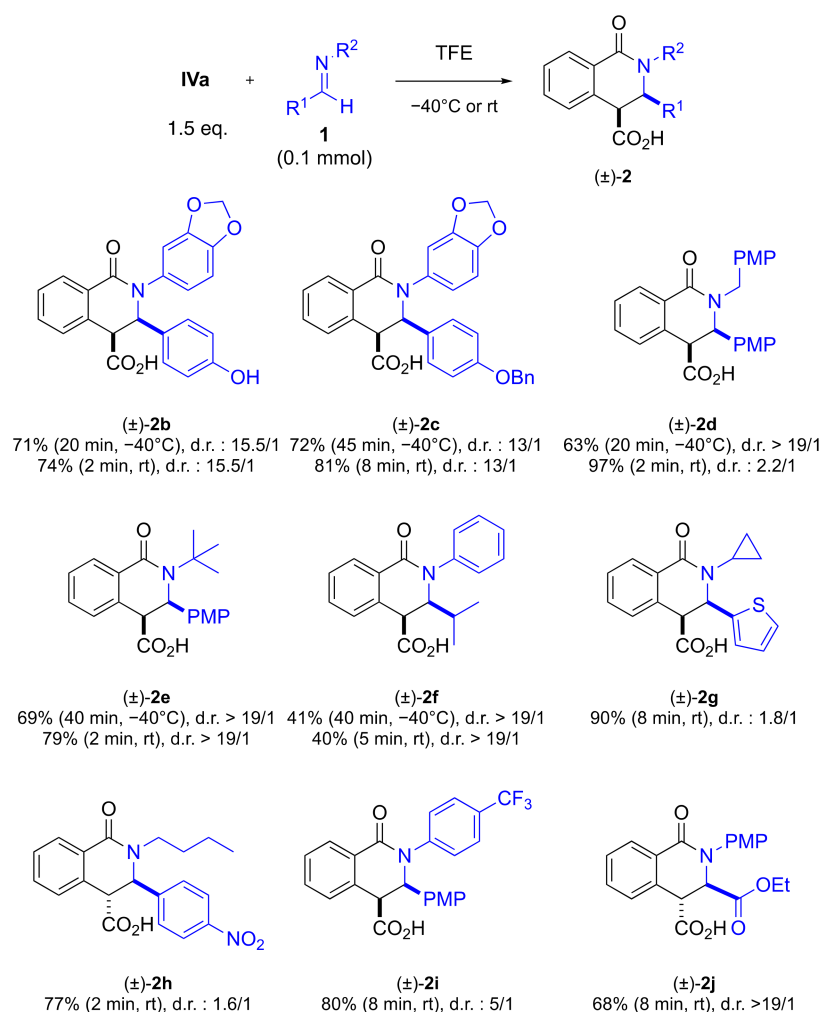
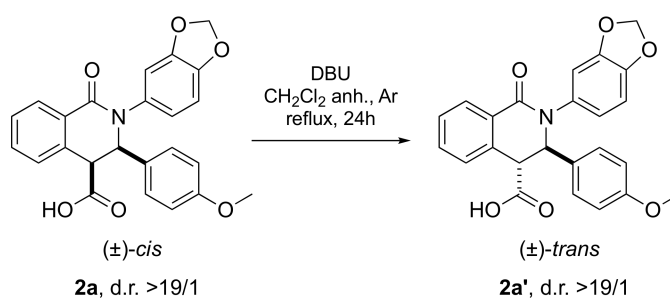


Figure 2. Substrate scope of imines **1**. d.r. was determined by $^1\text{H-NMR}$ Yields referred to pure products. The formation of **2g–2j** products was carried out only at room temperature.



Scheme 3. Epimerization of compound **2a** in **2a'**.

3. Materials and Methods

3.1. General Information

Reagents and solvents were purchased from commercial sources and were purified by distillation or recrystallization prior to use. Reactions were run under an argon atmosphere unless stated otherwise. The purification of reaction products was carried out by flash column chromatography using silica gel (60 F₂₅₄) packed Redisep or Interchim columns (230–400 mesh). Preparative thin-layer chromatography was performed on Macherey–Nagel 0.25 mm silica gel (60 F₂₅₄) glass plates. Melting points were recorded on a B540 Büchi melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin Elmer FT-IR 100 spectrum spectrometer. Proton nuclear magnetic resonance

spectra ($^1\text{H-NMR}$) were recorded on Bruker Advance-300 or Bruker AC-500 machines and are reported in parts per million (ppm) using solvent as an internal standard (CDCl_3 at 7.26 ppm, DMSO-d_6 at 2.50 ppm, or CD_3OD at 3.31 ppm). For $^1\text{H NMR}$, the NMR spectroscopic data are given in parts per million (ppm). Coupling constants, usually denoted J , are given in the unit of Hertz (Hz). Multiplicities are designed by abbreviation: singlet (s), broad singlet (bs), doublet (d), doublet of doublet (dd), doublet of doublet of doublet (ddd), triplet (t), doublet of triplet (d), quartet (q), quintet (quint.), multiplet (m), etc. Proton-decoupled carbon nuclear magnetic resonance spectra ($^{13}\text{C-NMR}$) were recorded on Bruker Advance-300 or Bruker AC-500 machines and are reported in parts per million (ppm) using solvent as an internal standard (CDCl_3 at 77.1 ppm, DMSO-d_6 at 39.5 ppm, or CD_3OD at 49.0 ppm). The d.r. was calculated with $^1\text{H NMR}$. Mass data were obtained on an AUTOMASS ThermoFinnigan spectrometer with electrospray or electronebullization ionization and quadrupole mass filter. HRMS data were recorded either by LCT spectrometer (Waters) or LCT Premier XE (Waters) with ESI ionization and TOF analyzer. Reactions under microwave irradiation were performed in an Anton Parr MCP300 reactor.

3.2. Synthesis

General Procedure for Castagnoli–Cushman reaction (2a–2f). A round-bottom flask under an argon atmosphere was charged with the corresponding imine **1** (0.100 mmol, 1.0 eq.) in TFE (3 mL) and then charged with homophthalic anhydride **IVa** (24.3 mg, 0.150 mmol, 1.5 eq.) at $-40\text{ }^\circ\text{C}$. The reaction mixture was stirred at $-40\text{ }^\circ\text{C}$ until the starting material was consumed, as indicated by TLC analysis. The mixture was concentrated in vacuo, and the residue was purified by preparative TLC to afford the pure product. Purification: $\text{CH}_2\text{Cl}_2/\text{MeOH}$ (95:5). Copies of ^1H and ^{13}C spectra for all prepared are available in the supplementary materials.

4-(benzyloxy)benzaldehyde (0c): The title compound was prepared following the literature procedure [31] using *p*-anisaldehyde (2.30 g, 18.846 mmol, 1.0 eq.) and benzyl bromide (3.36 mL, 28.269 mmol, 1.5 eq.). Product **0c** was isolated in 93% overall yield (3.74 g) in one step as a white powder. Mp: 68–70 $^\circ\text{C}$; IR (ν): 1738, 1604, 1507, 1451, 1266, 1061, 708, 617 cm^{-1} ; $^1\text{H NMR}$ (300 MHz, CDCl_3): d (ppm) 9.91 (s, 1H), 7.87 (d, $J = 8.9$ Hz, 2H), 7.48–7.37 (m, 5H), 7.10 (d, $J = 8.9$ Hz, 2H), 5.18 (s, 2H); $^{13}\text{C NMR}$ (125 MHz, CDCl_3): d (ppm) 190.8, 163.7, 136.0, 132.0, 130.1, 128.7, 128.3, 127.5, 115.1, 70.2; HRMS (E.S.I. $^+$, m/z) calcd for $\text{C}_{14}\text{H}_{13}\text{O}_2^+$ ($M + \text{H}$) $^+$: 213.0910, found: 213.0887.

***N*-(benzo[*d*][1,3]dioxol-5-yl)-1-(4-methoxy phenyl)methanimine (1a):** To a stirred solution of benzo[*d*][1,3]dioxol-5-amine (1.28 g, 9.326 mmol, 1.0 eq.) in dry MeOH (40 mL) with molecular sieve 4Å were added *p*-anisaldehyde (1.13 mL, 9.326 mmol, 1.0 eq.) and glacial acetic acid (53.4 μL , 0.933 mmol, 0.1 eq.). The reaction mixture was stirred overnight at reflux. After cooling, the mixture was filtered on celite and concentrated under reduced pressure. The residue was purified by recrystallisation (heptane/AcOEt, 95:5) to afford the pure product **1a**. Brown crystals (1.71 g, 72%). Mp: 107–108 $^\circ\text{C}$; IR (ν): 2889, 1601, 1574, 1499, 1479, 1241, 1170, 1028, 924, 816 cm^{-1} ; $^1\text{H NMR}$ (500 MHz, CDCl_3): d (ppm) 8.30 (s, 1H), 7.75 (d, $J = 8.7$ Hz, 2H), 6.90 (d, $J = 8.7$ Hz, 2H), 6.74 (d, $J = 8.3$ Hz, 1H), 6.73 (d, $J = 2.1$ Hz, 1H), 6.65 (dd, $J = 8.3$ Hz, $J = 2.1$ Hz, 1H), 5.90 (s, 2H), 3.79 (s, 3H); $^{13}\text{C NMR}$ (125 MHz, CDCl_3): d (ppm) 162.1, 158.1, 148.2, 146.9, 145.8, 130.3 (2C), 129.3, 114.6, 114.2 (2C), 108.3, 101.9, 101.3, 55.4; HRMS (E.S.I. $^+$, m/z) calcd for $\text{C}_{15}\text{H}_{14}\text{NO}_3^+$ ($M + \text{H}$) $^+$: 256.0968, found: 256.0955.

4-((benzo[*d*][1,3]dioxol-5-ylimino)methyl) phenol (1b): To a stirred solution of benzo[*d*][1,3]dioxol-5-amine (13.7 mg, 0.100 mmol, 1.0 eq.) in dry MeOH (2 mL) with molecular sieve 4Å were added 4-hydroxybenzaldehyde (10.0 μL , 0.100 mmol, 1.0 eq.) and one drop of glacial acetic acid (0.010 mmol, 0.1 eq.). The reaction mixture was stirred overnight at reflux. After cooling, the mixture was concentrated under reduced pressure to afford the brut product **1b** without further purification. The imine was used in Castagnoli–Cushman reactions directly after preparation

N-(benzo[*d*][1,3]dioxol-5-yl)-1-(4-(benzyloxy) phenyl)methanimine (**1c**): To a stirred solution of benzo[*d*][1,3]dioxol-5-amine (193.0 mg, 1.407 mmol, 1.0 eq.) in dry MeOH (7 mL) with molecular sieve 4Å were added aldehyde **0c** (298.6 mg, 1.407 mmol, 1.0 eq.) and glacial acetic acid (8.1 μL, 0.141 mmol, 0.1 eq.). The reaction mixture was stirred for 1 h at reflux. After cooling, the mixture was filtered on celite and concentrated under reduced pressure to afford the pure product **1c**. Brown solid (462.8 mg, quant.). Mp: 102–104 °C; IR (ν): 2962, 2922, 1605, 1571, 1506, 1479, 1257, 1085, 1012, 791 cm⁻¹; ¹H NMR (500 MHz, DMSO-*d*₆): d (ppm) 8.53 (s, 1H), 7.85 (d, *J* = 8.7 Hz, 2H), 7.49–7.32 (m, 5H), 7.13 (d, *J* = 8.7 Hz, 2H), 6.96 (d, *J* = 2.1 Hz, 1H), 6.92 (d, *J* = 8.1 Hz, 1H), 6.76 (dd, *J* = 8.1 Hz, *J* = 2.1 Hz, 1H), 6.04 (s, 2H), 5.19 (s, 2H); ¹³C NMR (125 MHz, DMSO-*d*₆): d (ppm) 160.7, 158.1, 147.9, 146.0, 145.4, 136.7, 130.1 (2C), 129.2, 128.4 (2C), 127.9, 127.7 (2C), 115.2, 115.0 (2C), 108.4, 101.4, 101.2, 69.4; HRMS (E.S.I.⁺, *m/z*) calcd for C₂₁H₁₈NO₃⁺ (M + H)⁺: 332.1281, found: 322.0998.

N-(4-methoxybenzyl)-1-(4-methoxyphenyl) methanimine (**1d**): The title compound was prepared following the literature procedure [32] using (4-methoxyphenyl)methanamine (620.0 μL, 4.746 mmol, 1.0 eq.) and *p*-anisaldehyde (577.5 μL, 4.746 mmol, 1.0 eq.). Product **1d** was isolated in quant. overall yield (1.20 g) in one step as a brown solid. Mp: 36–37 °C; IR (ν): 2830, 2910, 1510, 1245, 1035, 810 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): d (ppm) 8.32 (s, 1H), 7.73 (d, *J* = 8.8 Hz, 2H), 7.27 (d, *J* = 8.8 Hz, 2H), 6.95 (d, *J* = 8.7 Hz, 2H), 6.91 (d, *J* = 8.7 Hz, 2H), 4.75 (s, 2H), 3.85 (s, 3H), 3.81 (s, 3H); ¹³C NMR (75 MHz, CDCl₃): d (ppm) 161.7, 160.9, 158.7, 131.7, 129.8 (2C), 129.2 (2C), 114.0 (2C), 113.9 (2C), 64.4, 55.3, 55.2; HRMS (E.S.I.⁺, *m/z*) calcd for C₁₆H₁₈NO₂⁺ (M + H)⁺: 256.1332, found: 256.1342.

N-*tert*-butyl-1-(4-methoxyphenyl)methanimine (**1e**): To a stirred solution of *tert*-butylamine (10.7 μL, 0.100 mmol, 1.0 eq.) in dry MTBE (2 mL) with molecular sieve 4Å was added *p*-anisaldehyde (12.2 μL, 0.100 mmol, 1.0 eq.). The reaction mixture was stirred for 24 h at room temperature. The mixture was concentrated under reduced pressure to afford the brut product **1e** without further purification. The imine was used in Castagnoli–Cushman reactions directly after preparation.

2-methyl-*N*-phenylpropan-1-imine (**1f**): To a stirred solution of aniline (9.1 μL, 0.100 mmol, 1.0 eq.) in dry CH₂Cl₂ (1 mL) with MgSO₄ (18.1 mg, 0.150 mmol, 1.5 eq) was added isobutyraldehyde (13.7 μL, 0.150 mmol, 1.5 eq.). The reaction mixture was stirred for 1 h at reflux. After cooling, the mixture was filtered and concentrated under reduced pressure to afford the brut product **1f** without further purification. The imine was used in Castagnoli–Cushman reactions directly after preparation.

N-cyclopropyl-1-(thiophen-2-yl)methanimine (**1g**): The title compound was prepared following the literature procedure [33] using cyclopropanamine (6.9 μL, 0.100 mmol, 1.0 eq.) and thiophene-2-carbaldehyde (9.4 μL, 0.100 mmol, 1.0 eq.). The brut product **1g** was used in Castagnoli–Cushman reactions without further purification directly after preparation. The imine was used in Castagnoli–Cushman reactions directly after preparation.

N-butyl-1-(4-nitrophenyl)methanimine (**1h**): To a stirred solution of butan-1-amine (9.9 μL, 0.100 mmol, 1.0 eq.) in dry toluene (1 mL) with MgSO₄ (18.1 mg, 0.150 mmol, 1.5 eq) was added 4-nitrobenzaldehyde (15.1 mg, 0.100 mmol, 1.0 eq.). The reaction mixture was stirred overnight at 80 °C. After cooling, the mixture was filtered and concentrated under reduced pressure to afford the brut product **1h** without further purification. The imine was used in Castagnoli–Cushman reactions directly after preparation.

1-(4-methoxyphenyl)-*N*-(4-(trifluoromethyl) phenyl)methanimine (**1i**): To a stirred solution of 4-(trifluoromethyl)aniline (12.6 μL, 0.100 mmol, 1.0 eq.) in dry MeOH (1 mL) with molecular sieve 4Å were added 4-methoxybenzaldehyde (12.2 μL, 0.100 mmol, 1.0 eq.) and one drop of glacial acetic acid (0.010 mmol, 0.1 eq.). The reaction mixture was stirred overnight at reflux. After cooling, the mixture was filtered and concentrated under reduced pressure to afford the brut product **1i** without further purification. The imine was used in Castagnoli–Cushman reactions directly after preparation.

Ethyl 2-((4-methoxyphenyl)imino)acetate (**1j**): The title compound was prepared following the literature procedure [34] using 4-methoxyaniline (12.3 mg, 0.100 mmol, 1.0 eq.) and ethyl 2-oxoacetate (20.4 μL, 0.100 mmol, 1.0 eq., 50% in toluene). The brut product **1j** was

used without further purification. The imine was used in Castagnoli–Cushman reactions directly after preparation.

Cis-2-(benzo[d][1,3]dioxol-5-yl)-3-(4-methoxyphenyl)-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxylic acid (**2a**): The title compound was prepared following the general procedure described above using **1a** (25.5 mg, 0.100 mmol, 1.0 eq.) and **IVa** (24.3 mg, 0.150 mmol, 1.5 eq.) in 15 min of reaction time. The product **2a** was isolated in 81% yield (33.8 mg, d.r. (*cis/trans*): >19/1) as a brown powder. When the reaction was performed at room temperature in 2 min of reaction time: 30.1 mg, 72%, d.r. (*cis/trans*): >19/1. Mp: 158–159 °C; IR (ν): 3321, 2902, 1717, 1609, 1485, 1246, 1175, 1032, 926, 796, 731 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3): d (ppm) 8.30 (dd, $J = 7.0$ Hz, $J = 1.2$ Hz, 1H), 7.60–7.48 (m, 3H), 6.97 (dd, $J = 6.7$ Hz, $J = 2.0$ Hz, 2H), 6.75 (d, $J = 8.0$ Hz, 1H), 6.70 (dd, $J = 6.8$ Hz, $J = 2.0$ Hz, 2H), 6.63 (d, $J = 2.0$ Hz, 1H), 6.59 (dd, $J = 8.0$ Hz, $J = 2.0$ Hz, 1H), 5.96 (s, 2H), 5.28 (d, $J = 6.0$ Hz, 1H), 4.92 (d, $J = 6.0$ Hz, 1H), 3.74 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3): d (ppm) 172.0, 163.9, 159.7, 147.8, 146.7, 135.4, 132.6, 132.5, 129.2, 129.1 (2C), 128.8, 128.3, 128.1, 127.7, 120.6, 113.9 (2C), 108.8, 108.2, 101.5, 65.3, 55.1, 49.5; HRMS (E.S.I.⁺, m/z) calcd for $\text{C}_{24}\text{H}_{20}\text{NO}_6^+$ ($M + \text{H}$)⁺: 418.1285, found: 418.1352.

Trans-2-(benzo[d][1,3]dioxol-5-yl)-3-(4-methoxyphenyl)-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxylic acid (**2a'**): A round-bottom flask under an argon atmosphere was charged with **2a** (41.7 mg, 0.100 mmol, 1 eq) in dry CH_2Cl_2 (2 mL), and DBU (5.6 μL , 0.050 mmol, 0.5 eq) was added. The reaction mixture was stirred for 24 h at reflux. The resultant solution was concentrated under reduced pressure, and the residue was purified by preparative TLC to afford the pure product **2a'**. Purification: $\text{CH}_2\text{Cl}_2/\text{MeOH}$ (95/5). White amorphous solid (35.5 mg, 85%), d.r. (*trans/cis*) >19/1. IR (ν): 3321, 2902, 1717, 1609, 1485, 1246, 1175, 1032, 926, 796, 731 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3): δ (ppm) 8.18 (dd, $J = 6.5$ Hz, $J = 2.7$ Hz, 1H), 7.42 (dd, $J = 6.5$ Hz, $J = 5.4$ Hz, 2H), 7.22 (dd, $J = 5.4$ Hz, $J = 2.7$ Hz, 1H), 7.00 (d, $J = 8.6$ Hz, 2H), 6.84 (d, $J = 1.7$ Hz, 1H), 6.76 (dd, $J = 8.3$ Hz, $J = 1.7$ Hz, 1H), 6.72 (d, $J = 8.6$ Hz, 2H), 6.69 (d, $J = 8.3$ Hz, 1H), 5.90 (d, $J = 1.4$ Hz, 2H), 5.49 (s, 1H), 3.94 (s, 1H), 3.72 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3): δ (ppm) 173.2, 163.6, 159.3, 147.7, 146.5, 136.1, 132.5, 132.4, 130.8, 129.6, 129.3, 128.5, 128.4, 127.6 (2C), 120.3, 114.1 (2C), 108.6, 108.2, 101.4, 64.7, 55.2, 53.4; (E.S.I.⁺, m/z) calcd for $\text{C}_{24}\text{H}_{20}\text{NO}_6^+$ ($M + \text{H}$)⁺: 418.1285, found: 418.1352.

Cis-2-(benzo[d][1,3]dioxol-5-yl)-3-(4-hydroxyphenyl)-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxylic acid (**2b**): The title compound was prepared following the general procedure described above using the brut **1b** (0.100 mmol, 1.0 eq.) and **IVa** (24.3 mg, 0.150 mmol, 1.5 eq.) in 20 min of reaction time. The product **2b** was isolated in 71% yield (28.6 mg, d.r. (*cis/trans*): 15.5/1) as a beige powder. When the reaction was performed at room temperature in 2 min of reaction time: 29.9 mg, 74%, d.r. (*cis/trans*): 15.5/1. Mp: 205–206 °C; IR (ν): 3389, 2904, 1717, 1591, 1557, 1513, 1483, 1433, 1249, 1197, 1175, 1034, 927, 786, 703 cm^{-1} ; ^1H NMR (300 MHz, CD_3OD): d (ppm) 8.14 (dd, $J = 7.6$ Hz, $J = 1.1$ Hz, 1H), 7.68 (d, $J = 7.6$ Hz, 1H), 7.58 (td, $J = 7.5$ Hz, $J = 1.1$ Hz, 1H), 7.49 (t, $J = 7.5$ Hz, 1H), 6.88 (d, $J = 8.5$ Hz, 2H), 6.75 (d, $J = 8.9$ Hz, 1H), 6.62 (d, $J = 8.9$ Hz, 2H), 6.57 (d, $J = 8.5$ Hz, 2H), 5.94 (d, $J = 2.8$ Hz, 2H), 5.31 (d, $J = 5.9$ Hz, 1H), 4.82 (d, $J = 5.9$ Hz, 1H); ^{13}C NMR (75 MHz, CD_3OD): d (ppm) 172.7, 166.3, 158.7, 149.2, 148.2, 136.6, 136.2, 133.8, 130.7 (2C), 130.3, 129.3, 129.2, 128.8, 122.2, 116.4, 116.0 (2C), 109.9, 108.9, 102.9, 67.0, 51.0; HRMS (E.S.I.⁺, m/z) calcd for $\text{C}_{23}\text{H}_{18}\text{NO}_6^+$ ($M + \text{H}$)⁺: 404.1129, found: 404.1090.

Cis-2-(benzo[d][1,3]dioxol-5-yl)-3-(4-(benzyloxy)phenyl)-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxylic acid (**2c**): The title compound was prepared following the general procedure described above using **1c** (33.1 mg, 0.100 mmol, 1.0 eq.) and **IVa** (24.3 mg, 0.150 mmol, 1.5 eq.) in 45 min of reaction time. The product **2c** was isolated in 72% yield (35.5 mg, d.r. (*cis/trans*): 13/1) as a brown powder. When the reaction was performed at room temperature in 8 min of reaction time: 40.0 mg, 81%, d.r. (*cis/trans*): 13/1. Mp: 177–178 °C; IR (ν): 3289, 3059, 1715, 1644, 1600, 1504, 1487, 1384, 1246, 1036, 1007, 792, 733, 699 cm^{-1} ; ^1H NMR (300 MHz, CD_3OD): d (ppm) 8.08 (dd, $J = 7.7$ Hz, $J = 1.3$ Hz, 1H), 7.78 (d, $J = 7.7$ Hz, 1H), 7.52 (td, $J = 7.5$ Hz, $J = 1.4$ Hz, 1H), 7.42–7.26 (m, 6H), 7.01 (d, $J = 8.8$ Hz, 2H), 6.75 (d, $J = 8.8$ Hz, 2H), 6.72 (d, $J = 7.7$ Hz, 1H), 6.66 (s, 1H), 6.63 (d, $J = 2.2$ Hz, 1H),

5.93 (d, $J = 4.9$ Hz, 2H), 5.33 (d, $J = 5.9$ Hz, 1H), 4.97 (s, 2H), 4.61 (d, $J = 5.9$ Hz, 1H); ^{13}C NMR (75 MHz, CD_3OD): d (ppm) 174.2, 165.3, 158.4, 147.6, 146.5, 137.6, 137.3, 135.6, 135.5, 134.6, 132.0, 129.9, 129.4 (2C), 128.8, 128.6, 128.0, 127.3, 127.2, 127.1, 126.4, 120.5, 113.9 (2C), 108.5, 107.4, 101.4, 69.5, 66.5, 52.8; HRMS (E.S.I.⁺, m/z) calcd for $\text{C}_{30}\text{H}_{24}\text{NO}_6^+$ ($\text{M} + \text{H}$)⁺: 494.1598, found: 494.1574.

2-(4-methoxybenzyl)-3-(4-methoxyphenyl)-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxylic acid (2d): The title compound was prepared following the general procedure described above using **1d** (25.5 mg, 0.100 mmol, 1.0 eq.) and **IVa** (24.3 mg, 0.150 mmol, 1.5 eq.) in 20 min of reaction time. The product **2d** was isolated in 63% yield (26.3 mg, d.r. (*cis/trans*): >19/1) as a light amorphous solid. When the reaction was performed at room temperature in 2 min of reaction time: 40.5 mg, 97%, d.r. (*cis/trans*): 2.2/1 with separation. *Cis* product (**2d**): light amorphous solid (27.8 mg, 67%). *Trans* product (**2d'**): light amorphous solid (12.5 mg, 30%). *Cis* product **2d**: IR (ν): 2928, 1726, 1613, 1572, 1511, 1470, 1249, 1176, 1031, 832, 735 cm^{-1} ; ^1H NMR (300 MHz, CD_3OD): d (ppm) 8.00 (dd, $J = 7.8$ Hz, $J = 1.5$ Hz, 1H), 7.58 (d, $J = 7.8$ Hz, 1H), 7.41–7.20 (m, 3H), 7.11 (d, $J = 8.7$ Hz, 2H), 6.86 (d, $J = 8.7$ Hz, 2H), 6.77 (d, $J = 8.7$ Hz, 2H), 6.59 (d, $J = 8.7$ Hz, 2H), 5.31 (d, $J = 14.5$ Hz, 1H), 4.88 (d, $J = 6.4$ Hz, 1H) 4.21 (d, $J = 6.4$ Hz, 1H), 3.67 (s, 3H), 3.60 (s, 3H), 3.56 (d, $J = 14.5$ Hz, 1H); ^{13}C NMR (75 MHz, CD_3OD): d (ppm) 166.6, 160.9, 160.7, 138.2, 136.1, 133.3, 131.8, 130.6 (2C), 130.5 (2C), 130.2, 129.9, 128.8, 128.4, 127.8, 115.1 (2C), 114.6 (2C), 62.5, 55.7, 55.6, 53.5, 48.9; HRMS (E.S.I.⁺, m/z) calcd for $\text{C}_{25}\text{H}_{24}\text{NO}_5^+$ ($\text{M} + \text{H}$)⁺: 418.1649, found: 418.1667. *Trans* product **2d'**: IR (ν): 2960, 2926, 1728, 1611, 1574, 1510, 1466, 1246, 1174, 1029, 799, 733 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3): d (ppm) 8.16 (dd, $J = 6.9$ Hz, $J = 2.2$ Hz, 1H), 7.41–7.31 (m, 3H), 7.10 (d, $J = 8.6$ Hz, 2H), 7.01 (dd, $J = 6.5$ Hz, $J = 1.8$ Hz, 1H), 6.87 (d, $J = 8.6$ Hz, 2H), 6.67 (d, $J = 8.7$ Hz, 2H), 6.65 (d, $J = 8.7$ Hz, 2H), 5.50 (d, $J = 14.5$ Hz, 1H), 4.98 (s, 1H), 3.75 (s, 1H), 3.66 (s, 3H), 3.63 (s, 3H), 3.56 (d, $J = 14.5$ Hz, 1H); ^{13}C NMR (75 MHz, CDCl_3): d (ppm) 175.0, 163.7, 159.3, 159.1, 132.1, 131.5, 130.2 (2C), 129.4, 129.1, 128.8, 128.6, 128.3, 127.5 (2C), 114.2 (2C), 113.7 (2C), 59.5, 55.2, 55.1, 51.1, 48.2; HRMS (E.S.I.⁺, m/z) calcd for $\text{C}_{25}\text{H}_{24}\text{NO}_5^+$ ($\text{M} + \text{H}$)⁺: 418.1649, found: 418.1609.

Cis-2-(tert-butyl)-3-(4-methoxyphenyl)-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxylic acid (2e): The title compound was prepared following the general procedure described above using the brut **1e** (0.100 mmol, 1.0 eq.) and **IVa** (24.3 mg, 0.150 mmol, 1.5 eq.) in 40 min of reaction time. The product **2e** was isolated in 69% yield (24.4 mg, d.r. (*cis/trans*): >19/1) as a white powder. When the reaction was performed at room temperature in 2 min of reaction time: 27.9 mg, 79%, d.r. (*cis/trans*): >19/1. Mp: 60–62 °C; IR (ν): 2923, 2510, 1716, 1653, 1603, 1511, 1390, 1254, 1161, 1025, 788, 756 cm^{-1} ; ^1H NMR (500 MHz, CD_3OD): d (ppm) 8.03 (d, $J = 7.7$ Hz, 1H), 7.72 (d, $J = 7.7$ Hz, 1H), 7.41 (dd, $J = 7.7$ Hz, $J = 7.7$ Hz, 1H), 7.34 (dd, $J = 7.7$ Hz, $J = 7.7$ Hz, 1H), 6.99 (d, $J = 8.6$ Hz, 2H), 6.67 (d, $J = 8.6$ Hz, 2H), 5.58 (d, $J = 5.6$ Hz, 1H), 4.43 (d, $J = 5.6$ Hz, 1H), 3.70 (s, 3H), 1.52 (s, 9H); ^{13}C NMR (125 MHz, CDCl_3): d (ppm) 170.8, 162.3, 144.4, 132.7, 132.0, 130.6 (2C), 130.1, 129.7, 128.0, 127.7, 114.7, 114.3 (2C), 60.7, 60.3, 55.6, 54.6, 29.2 (3C); HRMS (E.S.I.⁺, m/z) calcd for $\text{C}_{21}\text{H}_{24}\text{NO}_4^+$ ($\text{M} + \text{H}$)⁺: 354.1700, found: 354.1745.

Cis-3-isopropyl-1-oxo-2-phenyl-1,2,3,4-tetrahydroisoquinoline-4-carboxylic acid (2f): The title compound was prepared following the general procedure described above using the brut **1f** (0.100 mmol, 1.0 eq.) and **IVa** (24.3 mg, 0.150 mmol, 1.5 eq.) in 40 min of reaction time. The product **2f** was isolated in 41% yield (12.8 mg, d.r. (*cis/trans*): >19/1) as a light amorphous solid. When the reaction was performed at room temperature in 5 min of reaction time: 12.4 mg, 40%, d.r. (*cis/trans*): >19/1. IR (ν): 3398, 2963, 1710, 1599, 1580, 1552, 1497, 1381, 1261, 1027, 799, 755 cm^{-1} ; ^1H NMR (300 MHz, CD_3OD): d (ppm) 7.96 (dd, $J = 7.5$ Hz, $J = 1.5$ Hz, 2H), 7.58 (dd, $J = 8.1$ Hz, $J = 1.5$ Hz, 2H), 7.52 (dd, $J = 7.5$ Hz, $J = 1.3$ Hz, 1H), 7.5 (t, $J = 7.5$ Hz, 2H), 7.37 (dd, $J = 8.1$ Hz, $J = 1.3$ Hz, 1H), 7.30 (d, $J = 7.5$ Hz, 1H), 4.55 (dd, $J = 5.6$ Hz, $J = 3.3$ Hz, 1H), 4.50 (d, $J = 5.6$ Hz, 1H), 3.66 (b-s, 1H, OH), 2.27 (ddd, $J = 7.1$ Hz, $J = 7.1$ Hz, $J = 3.3$ Hz, 1H), 0.73 (d, $J = 7.1$ Hz, 3H), 0.68 (d, $J = 7.1$ Hz, 3H); ^{13}C NMR (125 MHz, CD_3OD): d (ppm) 176.6, 166.6, 144.8, 140.0, 133.2, 130.9, 129.7 (2C),

129.2, 128.8 (2C), 128.5, 127.7, 127.6, 68.6, 52.5, 32.5, 23.0, 19.8; HRMS (E.S.I.⁺, m/z) calcd for C₁₉H₂₀NO₃⁺ (M + H)⁺: 310.1438, found: 310.1452.

Cis-2-cyclopropyl-1-oxo-3-(thiophen-2-yl)-1,2,3,4-tetrahydroisoquinoline-4-carboxylic acid (2g): A round-bottom flask under an argon atmosphere was charged with the brut **1g** (0.100 mmol, 1.0 eq.) in TFE (3 mL) and then charged with homophthalic anhydride **IVa** (24.3 mg, 0.150 mmol, 1.5 eq.). The reaction mixture was stirred for 8 min at room temperature. The mixture was concentrated in vacuo, and the residue was purified by preparative TLC to afford the pure products **2g** and **2g'**. Purification: CH₂Cl₂/MeOH (93:7). The product **2g** (*cis* product) was isolated in 58% yield (18.2 mg, white powder). The product **2g'** (*trans* product) was isolated in 32% yield (10.1 mg, white powder). *Cis* product **2g**: Mp: 228–229 °C; IR (ν): 3428, 3075, 3011, 1714, 1642, 1598, 1462, 1423, 1359, 1301, 1244, 1226, 1027, 907, 827, 697 cm⁻¹; ¹H NMR (500 MHz, CD₃OD): d (ppm) 8.09 (d, J = 7.6 Hz, 1H), 7.88 (d, J = 7.6 Hz, 1H), 7.55 (t, J = 7.6 Hz, 1H), 7.43 (t, J = 7.6 Hz, 1H), 7.14 (d, J = 4.7 Hz, 1H), 6.89 (d, J = 2.7 Hz, 1H), 6.83 (dd, J = 4.7 Hz, J = 2.7 Hz, 1H), 5.50 (d, J = 5.7 Hz, 1H), 4.55 (d, J = 5.7 Hz, 1H), 2.68–2.63 (m, 1H), 1.06–1.01 (m, 1H), 0.91–0.85 (m, 2H), 0.85–0.80 (m, 1H); ¹³C NMR (125 MHz, CD₃OD): d (ppm) 173.6, 168.2, 141.6, 136.7, 133.6, 130.2, 130.0, 128.7, 128.4, 128.3, 126.9, 126.4, 61.6, 51.7, 30.8, 9.7, 6.4; HRMS (E.S.I.⁺, m/z) calcd for C₁₇H₁₆NO₃⁺ (M + H)⁺: 314.0845, found: 314.0853. *Trans* product **2g'**: Mp: 238–239 °C; IR (ν): 3395, 3076, 3011, 1709, 1638, 1598, 1580, 1465, 1432, 1359, 1245, 1156, 1028, 966, 826, 728, 698 cm⁻¹; ¹H NMR (500 MHz, CD₃OD): d (ppm) 8.00 (d, J = 7.6 Hz, 1H), 7.47 (t, J = 7.6 Hz, 1H), 7.37 (t, J = 7.6 Hz, 1H), 7.29 (d, J = 7.6 Hz, 1H), 7.15 (d, J = 4.8 Hz, 1H), 6.87 (d, J = 2.8 Hz, 1H), 6.85 (dd, J = 4.8 Hz, J = 2.8 Hz, 1H), 5.68 (s, 1H), 3.93 (s, 1H), 2.83–2.78 (m, 1H), 1.05–0.97 (m, 1H), 0.88–0.82 (m, 2H), 0.82–0.76 (m, 1H); ¹³C NMR (125 MHz, CD₃OD): d (ppm) 176.0, 167.9, 145.8, 138.2, 133.4, 131.1, 130.0, 128.3 (2C), 127.4, 126.1, 125.5, 62.2, 55.5, 31.0, 9.6, 6.5; HRMS (E.S.I.⁺, m/z) calcd for C₁₇H₁₆NO₃⁺ (M + H)⁺: 314.0845, found: 314.0839.

Trans-2-butyl-3-(4-nitrophenyl)-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxylic acid (2h): A round-bottom flask under an argon atmosphere was charged with the brut **1h** (0.100 mmol, 1.0 eq.) in TFE (3 mL) and then charged with homophthalic anhydride **IVa** (24.3 mg, 0.150 mmol, 1.5 eq.). The reaction mixture was stirred for 2 min at room temperature. The mixture was concentrated in vacuo, and residue was purified by preparative TLC to afford the pure products **2h** and **2h'**. Purification: CH₂Cl₂/MeOH (93:7). The product **2h** (*trans* product) was isolated in 48% yield (17.5 mg, white powder). The product **2h'** (*cis* product) was isolated in 29% yield (10.8 mg, white powder). *Trans* product **2h**: Mp: 223–224 °C; IR (ν): 3415, 2959, 2932, 2871, 1708, 1636, 1599, 1518, 1472, 1344, 1263, 1164, 1109, 908, 853, 712 cm⁻¹; ¹H NMR (300 MHz, CD₃OD): d (ppm) 8.09 (d, J = 8.8 Hz, 2H), 8.00 (dd, J = 7.1 Hz, J = 2.1 Hz, 1H), 7.42–7.32 (m, 2H), 7.38 (d, J = 8.8 Hz, 2H), 7.11 (dd, J = 6.5 Hz, J = 2.1 Hz, 1H), 5.59 (d, J = 1.0 Hz, 1H), 4.04 (dt, J = 13.3 Hz, J = 8.0 Hz, 1H), 3.86 (d, J = 1.0 Hz, 1H), 2.96 (ddd, J = 13.3 Hz, J = 8.0 Hz, J = 6.5 Hz, 1H), 1.72–1.61 (m, 2H), 1.41–1.33 (m, 2H), 0.94 (t, J = 7.3 Hz, 3H); ¹³C NMR (75 MHz, CD₃OD): d (ppm) 174.4, 165.0, 148.0, 147.2, 135.5, 131.7, 129.1, 128.6, 127.0 (3C), 126.6, 123.1 (2C), 62.5, 53.8, 46.6, 29.4, 19.8, 12.6; HRMS (E.S.I.⁺, m/z) calcd for C₂₀H₂₁N₂O₅⁺ (M + H)⁺: 369.1445, found: 369.1440. *Cis* product **2h'**: Mp: 232–233 °C; IR (ν): 3386, 2958, 2931, 2872, 1727, 1633, 1598, 1519, 1471, 1377, 1345, 1313, 1255, 1163, 1110, 1014, 909, 855, 799, 729, 715 cm⁻¹; ¹H NMR (500 MHz, CD₃OD): d (ppm) 8.08 (d, J = 7.4 Hz, 1H), 8.03 (d, J = 8.3 Hz, 2H), 7.72 (d, J = 7.4 Hz, 1H), 7.49 (dd, J = 7.4 Hz, J = 7.4 Hz, 1H), 7.41 (dd, J = 7.4 Hz, J = 7.4 Hz, 1H), 7.32 (d, J = 8.3 Hz, 2H), 5.29 (d, J = 6.2 Hz, 1H), 4.55 (d, J = 6.2 Hz, 1H), 4.02 (ddd, J = 14.4 Hz, J = 8.0 Hz, J = 8.0 Hz, 1H), 2.91 (ddd, J = 14.4 Hz, J = 8.0 Hz, J = 5.5 Hz, 1H), 1.71–1.59 (m, 2H), 1.44–1.35 (m, 2H), 0.95 (t, J = 7.3 Hz, 3H); ¹³C NMR (125 MHz, CD₃OD): d (ppm) 175.5, 166.4, 149.0, 146.9, 137.3, 133.4, 130.5 (2C), 130.1, 130.0, 128.4, 128.1, 124.0 (2C), 63.6, 53.6, 47.6, 31.2, 21.2, 14.1; HRMS (E.S.I.⁺, m/z) C₂₀H₂₁N₂O₅⁺ (M + H)⁺: 369.1445, found: 369.1447.

Cis-3-(4-methoxyphenyl)-1-oxo-2-(4-(trifluoromethyl)phenyl)-1,2,3,4-tetrahydroisoquinoline-4-carboxylic acid (2i): A round-bottom flask under an argon atmosphere was charged with the brut **1i** (0.100 mmol, 1.0 eq.) in TFE (3 mL) and then charged with homophthalic

anhydride **IVa** (24.3 mg, 0.150 mmol, 1.5 eq.). The reaction mixture was stirred for 8 min at room temperature. The mixture was concentrated in vacuo, and the residue was purified by preparative TLC to afford the pure product **2i**. Purification: CH₂Cl₂/MeOH (93:7). The product **2i** was isolated in 80% yield (28.3 mg, d.r. (*cis/trans*): 5/1) as a white powder. Mp: 238–239 °C; IR (ν): 3427, 3075, 2935, 2839, 1719, 1648, 1603, 1513, 1460, 1391, 1322, 1249, 1162, 1115, 1060, 1018, 930, 734, 693 cm⁻¹; ¹H NMR (300 MHz, CD₃OD): d (ppm) 8.13 (dd, *J* = 7.7 Hz, *J* = 1.1 Hz, 1H), 7.75 (d, *J* = 7.7 Hz, 1H), 7.60 (d, *J* = 8.3 Hz, 2H), 7.57 (ddd, *J* = 7.7 Hz, *J* = 7.7 Hz, *J* = 1.1 Hz, 1H), 7.45 (dd, *J* = 7.7 Hz, *J* = 7.7 Hz, 1H), 7.42 (d, *J* = 8.3 Hz, 2H), 7.05 (d, *J* = 8.8 Hz, 2H), 6.69 (d, *J* = 8.8 Hz, 2H), 5.52 (d, *J* = 5.6 Hz, 2H), 4.64 (d, *J* = 5.6 Hz, 1H), 3.69 (s, 3H); ¹³C NMR (75 MHz, CD₃OD): d (ppm) 174.6, 160.9, 146.6, 138.3, 136.2, 133.8, 132.4, 131.5, 130.8 (2C), 130.4, 130.0, 129.6 (2C), 129.0, 128.3, 126.8, 126.7, 114.6 (2C), 66.8, 55.6, 53.4; ¹⁹F NMR (280 MHz, CD₃OD): d (ppm) -63.96 (s, CF₃); HRMS (E.S.I.⁺, *m/z*) calcd for C₂₄H₁₉F₃NO₄⁺ (*M* + *H*)⁺: 442.1261, found: 442.1253.

Trans-3-(ethoxycarbonyl)-2-(4-methoxyphenyl)-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxylic acid (**2j**): A round-bottom flask under an argon atmosphere was charged with the brut **1j** (0.100 mmol, 1.0 eq.) in TFE (3 mL) and then charged with homophthalic anhydride **IVa** (24.3 mg, 0.150 mmol, 1.5 eq.). The reaction mixture was stirred 8 min at room temperature. The mixture was concentrated in vacuo, and residue was purified by preparative TLC to afford the pure product **2j**. Purification: CH₂Cl₂/MeOH (93:7). The product **2j** was isolated in 68% yield (25.0 mg, d.r. (*trans/cis*): >19/1) as a brown powder. Mp: 224–225 °C; IR (ν): 3386, 2960, 2936, 1738, 1634, 1599, 1509, 1462, 1429, 1364, 1299, 1241, 1178, 1026, 912, 834, 711 cm⁻¹; ¹H NMR (300 MHz, CD₃OD): d (ppm) 8.00 (dd, *J* = 7.5 Hz, *J* = 1.2 Hz, 1H), 7.75 (ddd, *J* = 7.5 Hz, *J* = 7.5 Hz, *J* = 1.4 Hz, 1H), 7.44 (d, *J* = 8.9 Hz, 2H), 7.46–7.40 (m, 2H), 6.98 (d, *J* = 8.9 Hz, 2H), 5.20 (d, *J* = 1.7 Hz, 1H), 4.24 (d, *J* = 1.7 Hz, 1H), 4.08 (q, *J* = 7.1 Hz, 2H), 3.83 (s, 3H), 1.11 (t, *J* = 7.1 Hz, 3H); ¹³C NMR (175 MHz, CD₃OD): d (ppm) 175.8, 172.7, 166.6, 160.2, 138.6, 136.6, 133.2, 130.5, 129.9, 129.7 (2C), 128.6, 128.2, 115.1 (2C), 67.8, 62.7, 55.9, 51.7, 14.3; HRMS (E.S.I.⁺, *m/z*) calcd for C₂₀H₂₀NO₆⁺ (*M* + *H*)⁺: 370.1285, found: 370.1283.

4. Conclusions

In summary, an efficient, simple, and rapid cycloaddition of homophthalic anhydride with imines has been described to enable access to a variety of densely substituted 3,4-lactams. This reaction typically proceeds with high diastereoselectivity for *cis*-kinetic or *trans*-thermodynamic diastereoisomers, depending on the substituent's properties attached to the starting imine's carbon. We demonstrated for the first time that TFE could act simultaneously as a solvent and as a powerful catalyst for CCR without generating by-products.

Supplementary Materials: The following are available online, copies of ¹H and ¹³C spectra for all prepared.

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