organics

MDPI

Article

Acid Catalyzed *N*-Alkylation of Pyrazoles with Trichloroacetimidates

Rowan I. L. Meador, Nilamber A. Mate and John D. Chisholm *

Department of Chemistry, 1-014 Center for Science and Technology, Syracuse University, Syracuse, NY 13244, USA; rimeador@syr.edu (R.I.L.M.); namate@syr.edu (N.A.M.)
* Correspondence: jdchisho@syr.com

Abstract: *N*-Alkyl pyrazoles are important heterocycles in organic and medicinal chemistry, demonstrating a wide range of biological activity. A new method for the *N*-alkylation of pyrazoles has been developed using trichloroacetimidate electrophiles and a Brønsted acid catalyst. These reactions provide ready access to *N*-alkyl pyrazoles which are present in a variety of medicinally relevant lead structures. Benzylic, phenethyl and benzhydryl trichloroacetimidates provide good yields of the *N*-alkyl pyrazole products. Unsymmetrical pyrazoles provide a mixture of the two possible regioisomers, with the major product being controlled by sterics. This methodology provides an alternative to other alkylation methods that require strong base or high temperature.

Keywords: pyrazole; trichloroacetimidate; alkylation; acid; catalysis

check for updates

Citation: Meador, R.I.L.; Mate, N.A.; Chisholm, J.D. Acid Catalyzed *N*-Alkylation of Pyrazoles with Trichloroacetimidates. *Organics* **2022**, *3*, 111–121. https://doi.org/10.3390/org3020009

Academic Editors: Wim Dehaen, Michal Szostak and Huaping Xu

Received: 21 March 2022
Accepted: 28 April 2022
Published: 24 May 2022

1. Introduction

Pyrazoles are aromatic 5-membered carbocyclic rings with two adjacent nitrogen atoms. These heterocycles play an important role in organic and medicinal chemistry. For example, pyrazoles have been utilized as directing groups for C-H bond functionalization [1–3]. Recently it was shown that pyrazoles may be converted to amides via ozonolysis [1], further expanding the utility of the heterocycle. Pyrazoles are often incorporated into biologically active systems as a bioisostere for amides [4–6], phenols [7] or other aromatic rings [8]. Derivatives of pyrazole also show significant biological activity, with the heterocycle being the basis of molecules that have anti-infective, anti-oxidant and anti-dementia properties [9–12]. Pyrazoles are especially common in anti-tumor agents, such as the ones shown in Figure 1 [13]. Substituted pyrazoles also have found applications in many other fields including new energetic materials [14,15], sensors [16,17] and batteries [18].

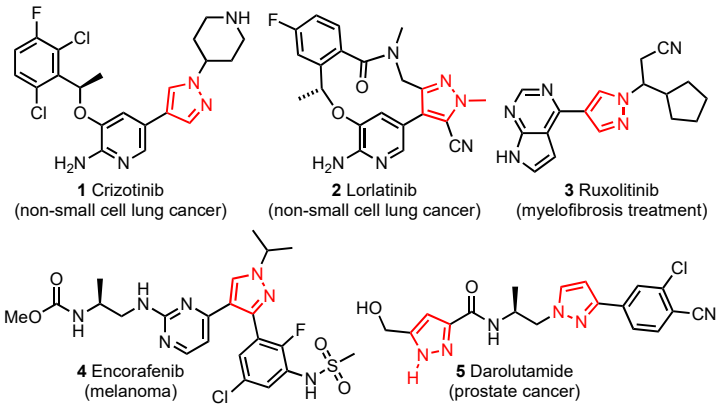


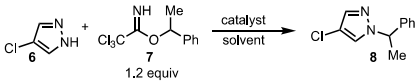
Figure 1. Examples of Anti-Tumor *N*-Alkyl Pyrazoles.

Given the common nature of pyrazole-based structures researchers have been active in defining new methods for the synthesis and modification of this heterocycle. Typically, in the case of *N*-alkyl pyrazoles, the substituent at the nitrogen is installed under basic conditions which deprotonate the nitrogen followed by the addition of an electrophile such as an alkyl halide [19–21]. Alternative methods based on the Mitsunobu reaction [22,23], transition metal catalysis [24–28] and enzymes [29] have also been advanced. Trichloroacetimidates have recently been recognized as excellent participants in a number of amination reactions [30–34]. Our recent studies on the substitution reactions of anilines [35], sulfonamides [36] and isatins [37] with trichloroacetimidate electrophiles led us to speculate that imidates may be efficient electrophiles for use in pyrazole alkylation.

2. Results and Discussion

Initially, we explored the alkylation of pyrazoles under promoter free conditions. Heating 4-choropyrazole **6** and phenethyl trichloroacetimidate **7** in refluxing 1,2-DCE for 24 h showed only a trace of alkylation product, so the use of acid catalysts was investigated (Table 1). Of the Lewis and Brønsted acids evaluated, camphorsulfonic acid (CSA) gave the best yield of *N*-alkylated product (77%). Other solvents were then evaluated, but did not show improved yields. The reaction time could be shortened to 4 h with little loss in yield, so these conditions were adopted for further studies on the reaction scope.

Table 1. Optimization of pyrazole *N*-alkylation conditions.



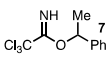
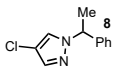
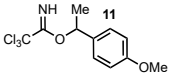
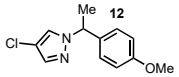
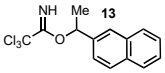
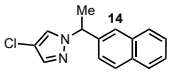
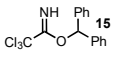
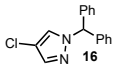
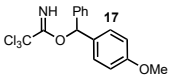
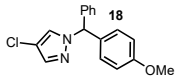
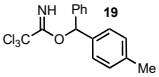
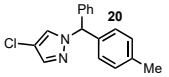
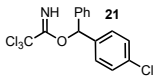
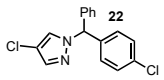
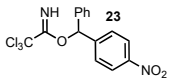
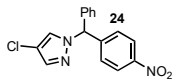
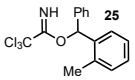
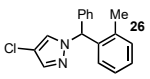
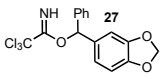
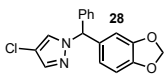
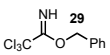
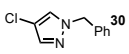
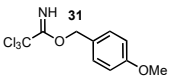
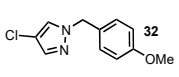
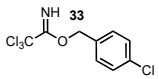
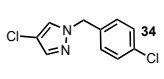
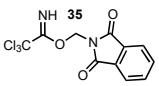
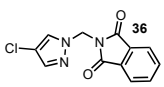
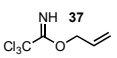
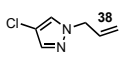
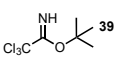
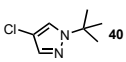
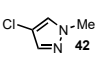
Entry	Catalyst	Solvent	Temp. (°C)	Time	Yield
1	none	1,2-DCE	rt	24	0
2	none	1,2-DCE	reflux	24	3
3	20 mol% TMSOTf	1,2-DCE	23	24	61
4	20 mol% BF_3•OEt_2	1,2-DCE	23	24	68
5	20 mol% CSA [1]	1,2-DCE	23	24	76
6	20 mol% CSA	toluene	23	24	69
7	20 mol% CSA	DCM	23	24	70
8	20 mol% CSA	MeCN	23	24	29
9	10 mol% CSA	1,2-DCE	23	24	62
10	20 mol% CSA	1,2-DCE	23	18	77
11	20 mol% CSA	1,2-DCE	23	8	75
12	20 mol% CSA	1,2-DCE	23	6	70
13	20 mol% CSA	1,2-DCE	23	4	71
14	20 mol% CSA	1,2-DCE	23	2	45
15	20 mol% CSA	1,2-DCE	reflux	4	71
16	50 mol% CSA	1,2-DCE	23	24	54

[1] CSA = camphorsulfonic acid.

A number of different trichloroacetimidate electrophiles were then evaluated in the pyrazole ***N***-alkylation using 4-chloropyrazole as the nucleophile (Table 2). Replacement of the benzene ring of the phenethyl group with a 4-methoxyphenyl or a 2-naphthyl group gave good yields of the substitution products **12** and **14**. (entries 2 and 3). Diphenylmethyl imidates such as **15** were of special interest, as these systems have shown activity as opioid receptor ligands which can be used to treat addiction and other disorders [38]. Benzhydryl imidates provided the respective *N*-alkyl pyrazoles in good yields (entries 4–10) except for the nitro-substituted benzhydryl imidate **23** (entry 8). The poor reactivity of imidate **23** in the reaction appears to implicate a carbocation intermediate in the mechanism, as incorporation of a powerful electron withdrawing group such as the nitro group makes formation of a carbocation more difficult, and therefore this reaction did not provide any product. This trend was also apparent when benzyl imidates were investigated (entries 11–13), as the best yield was obtained with the 4-methoxybenzyl imidate **31** (92%), while the

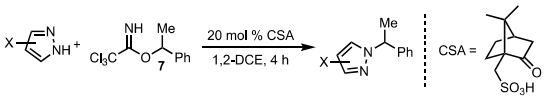
4-chlorobenzyl imidate **33** only gave 37% of the pyrazole product **34**. The methyl, allyl and *tert*-butyl imidates failed to provide any of the *N*-alkyl pyrazole products, only returning the starting materials under these reaction conditions. The methyl imidate cannot form a requisite carbocation, so its lack of reactivity is not unexpected. Allyl imidate **37** can rapidly rearrange to the acetamide via a [3,3]-sigmatropic process, which may compete with alkylation [39]. The *tert*-butyl imidate has been shown to undergo rapid elimination in the presence of acids, and special conditions are often needed for *N*-alkylation of this substrate [40].

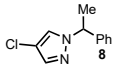
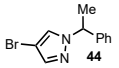
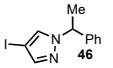
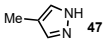
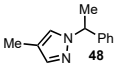
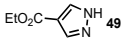
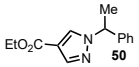
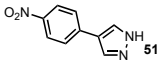
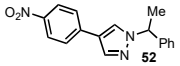
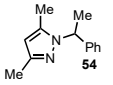
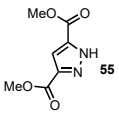
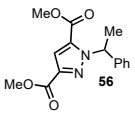
Table 2. *N*-Alkylation of 4-chloropyrazole **6** with trichloroacetimidates.

Entry	Imidate	Product	Yield (%)
1			71
2			97
3			67
4			59
5			71
6			98
7			76
8			0
9			85
10			98
11			73
12			92
13			37
14			62
15			0
16			0
17			0

The new alkylation conditions were also evaluated with regard to the pyrazole nucleophile (Table 3). A number of pyrazoles substituted at the 4-position with halogens, alkyl groups, aryl groups, and esters could be employed with good to moderate results (entries 1–5). The 3,5-disubstituted pyrazoles **53** and **55** were also successfully employed, although the yields for these reactions were generally lower than for 3-substituted pyrazoles. This may be due to steric effects with the groups next to the nitrogen slowing the alkylation. Unsubstituted pyrazole **57** was also utilized in the alkylation, providing a 45% yield. Indazole **59** also participated in the alkylation, providing the N1-alkyl product in 41% yield. None of the regioisomeric N2-alkyl indazole was detected.

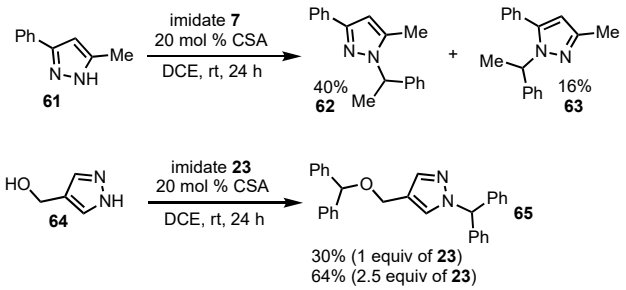
Table 3. Pyrazole alkylations with phenethyl imidate **7**.



Entry	Pyrazole	Product	Yield (%)
1			71
2			70
3			59
4			62
5			50
6			43
7			50
8			44
9			45
10			41

Unsymmetrical pyrazoles can provide two different regioisomers depending on which nitrogen reacts with the imidate. To evaluate the selectivity of the imidate alkylation, 3-methyl-5-phenyl-1H-pyrazole **61** was subjected to the transformation with phenethyl trichloroacetimidate (Scheme 1). This provided the two regioisomers, pyrazoles **62** and **63**, in 40% and 16% yield, respectively (a 2.5:1 ratio). The position of alkylation was verified by NOESY experiments on the two compounds, with compound **62** showing an interaction between the pyrazole methyl group and the phenethyl group, while isomer **63** lacked this signal. The position of alkylation appears to be the result of steric effects, which favor alkylation at the less hindered nitrogen of the pyrazole ring. We also attempted to determine the selectivity of the alkylation with regard to an alcohol functional group, as alcohols are common and imidates are known to react with them under similar conditions [41–44]. Using the commercially available 1H-pyrazole-4-methanol **64** as a substrate, treatment of this bifunctional compound with one equivalent of imidate **23** under the alkylation

conditions gave the dialkylated product **65** as the only product in 30% yield, with none of the monoalkylation products being detected. While puzzling at first, this result can be rationalized by the poor solubility of **64** in DCE, and the increase in solubility that occurs when the first alkylation takes place. Once the substrate is monoalkylated, it becomes significantly more soluble in the solvent, leading to the selective formation of the dialkylation product. The yield could be increased to 64% by increasing the amount of imidate to 2.5 equivalents. As the alkylation requires a nonpolar solvent to proceed in good yield (Table 1), conditions where selective monoprotection occurs will require further study.



Scheme 1. Selectivity Studies on the Alkylation.

These results may be rationalized by the mechanism presented in Figure 2 below. Initially, the imidate **7** is protonated by the CSA, which then ionizes to form the acetamide B and the carbocation C. The carbocation is then trapped with the pyrazole, resulting in the protonated pyrazole D. This intermediate can then react with another equivalent of imidate to provide alkylated pyrazole and regenerate the protonated imidate A.

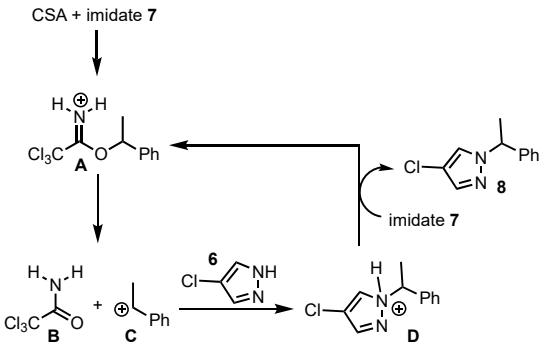


Figure 2. Proposed Reaction Mechanism.

3. Materials and Methods

3.1. General Experimental Information

All anhydrous reactions were run under a positive pressure of argon. Dichloromethane (DCM) was dried by passage through an alumina column [45]. 1,2-Dichloroethane (DCE) was freshly distilled from calcium hydride before use. Tetrahydrofuran (THF) was freshly distilled from Na/benzophenone still before use. Ethyl acetate (EA) and hexanes were used as received from the manufacturer. Silica gel column chromatography was performed using 60 Å silica gel (230−400 mesh). Melting points are uncorrected. Copies of spectra are available in the supplementary material.

3.2. Preparation of Trichloroacetimidates

Most of the trichloroacetimidates (**7** [46], **11** [47], **13** [36], **15** [43], **17** [48], **19** [49], **21** [48], **23** [47], **25** [48], **27** [37], **33** [50], and **35** [51]) were synthesized from the corresponding alcohols as reported previously. Trichloroacetimidates **29**, **31**, **37**, **39** and **41** were purchased from commercial sources.

3.3. General Procedure for the Synthesis of N-Alkyl Pyrazoles

A round-bottom flask was charged with imidate (1 equiv), pyrazole (1 equiv), and CSA (0.2 equiv) and put under an atmosphere of argon. Dry DCE was added to form a 0.25 M solution. The reaction was left to stir at room temperature for 4 h. After 4 h, the reaction mixture was diluted with EA, washed with sat. aq. $NaHCO_3$ and brine, dried (Na_2SO_4) and concentrated. The residue was purified by silica gel flash column chromatography to provide the *N*-alkyl pyrazole product. The alkylations were typically performed on a 1 mmol scale.

3.4. Tabulated Characterization Data for N-Alkyl Pyrazoles

4-Chloro-1-(1-phenylethyl)-1*H*-pyrazole (**8**). Yield 77%; TLC R_f = 0.37 (5% EA/95% hexanes); IR (ATR) 3129, 3030, 2936, 1493, 1310, 960, 696, 617 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.50 (s, 1H), 7.39–7.30 (m, 4H), 7.24 (d, J = 7.6 Hz, 2H), 5.48 (q, J = 7.0 Hz, 1H), 1.89 (d, J = 7.0 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 141.1, 137.5, 128.9, 128.2, 126.4, 126.0, 109.9, 61.9, 21.1; Anal Calcd for $C_{11}H_{11}ClN_2$: C, 63.93; H, 5.36; N, 13.55; Found: C, 63.86; H, 5.00; N, 13.57.

4-Chloro-1-[1-(*p*-methoxyphenyl)ethyl]-1*H*-pyrazole (**12**). Yield 97%; TLC R_f = 0.26 (5% EA/95% hexanes); ^1H NMR (400 MHz, $CDCl_3$) δ 7.33 (s, 1H), 7.20 (s, 1H), 7.05 (d, J = 8.4 Hz), 6.75 (d, J = 8.4 Hz, 2H), 5.27 (q, J = 7.4 Hz, 1H), 3.65 (s, 3H), 1.71 (d, J = 7.4 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 159.4, 137.3, 133.0, 127.8, 125.8, 114.2, 109.7, 61.4, 55.3, 21.1. This compound has been reported previously [52].

4-Chloro-1-[1-(2-naphthyl)ethyl]-1*H*-pyrazole (**14**). Yield 67%; mp = 92–94 °C; TLC R_f = 0.28 (5% EA/95% hexanes); IR (ATR) 3112, 3047, 2991, 2952, 1388, 1313, 838, 747 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, J = 7.2 Hz, 3H), 7.56 (s, 1H), 7.38–7.35 (m, 3H), 7.26 (s, 1H), 7.19 (d, J = 8.2 Hz, 1H), 5.48 (q, J = 7.2 Hz, 1H), 1.83 (d, J = 7.2 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 138.3, 137.6, 133.2, 133.0, 128.8, 128.1, 127.7, 126.5, 126.4, 126.1, 125.3, 124.3, 110.0, 62.0, 21.1; Anal Calcd for $C_{17}H_{13}ClN_2O_2$: C, 70.18; H, 5.10; N, 10.91; Found: C, 70.14; H, 5.05; N, 10.87.

1-Benzhydryl-4-chloro-1*H*-pyrazole (**16**). Yield 59%; mp = 100–103 °C; TLC R_f = 0.35 (5% EA/95% hexanes); IR (ATR) 3108, 3027, 2927, 1520, 726, 694 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.42 (s,1H), 7.26–7.22 (m, 6H), 7.13 (s, 1H), 7.00–6.99 (m, 4H), 6.61 (s, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 138.8, 138.2. 128.8, 128.4, 128.2, 127.6, 110.0, 70.3; Anal Calcd for $C_{16}H_{13}ClN_2$: C, 71.51; H, 4.88; N, 10.42; Found: C, 71.58; H, 4.82; N, 10.19.

4-Chloro-1-[(*p*-methoxyphenyl)phenylmethyl]-1*H*-pyrazole (**18**). Yield 71%; TLC R_f = 0.30 (5% EA/95% hexanes); IR (ATR) 3132, 3030, 2835, 1610, 1510, 1247, 730 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.41 (s, 1H), 7.24–7.22 (m, 3H), 7.13 (s, 1H), 6.97–6.95 (m, 4H), 6.79–6.77 (m, 2H), 6.55 (s, 1H), 3.69 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 159.6, 139.4, 138.2, 130.8, 129.7, 128.8, 128.2, 127.8, 127.5, 114.2, 109.9, 69.8, 55.3; Anal Calcd for $C_{17}H_{15}ClN_2O$: C, 68.34; H, 5.06; N, 9.38; Found: C, 68.39; H, 4.97; N, 9.41.

4-Chloro-1-[phenyl(*p*-tolyl)methyl]-1*H*-pyrazole (**20**). Yield 98%; mp = 70–72 °C; TLC R_f = 0.35 (5% EA/95% hexanes); IR (ATR) 3129, 3055, 2919, 1512, 1293, 990, 735 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.41 (s, 1H), 7.24–7.22 (m, 3H), 7.13 (s, 1H), 7.06 (d, J = 7.6 Hz, 2H), 6.98 (d, J = 6.9 Hz, 2H), 6.91 (d, J = 7.6 Hz, 2H), 6.57 (s, 1H), 2.25 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 139.1, 138.3, 138.2, 135.8, 129.5, 128.8, 128.3, 128.2, 128.0, 127.5, 109.9, 70.1, 21.2; Anal Calcd for $C_{17}H_{15}ClN_2$: C, 72.21; H, 5.35; N, 9.91; Found: C, 71.20; H, 5.20; N, 9.74.

4-Chloro-1-[(*p*-chlorophenyl)phenylmethyl]-1*H*-pyrazole (**22**). Yield 76%; TLC R_f = 0.46 (5% EA/95% hexanes IR (ATR) 3133, 3096, 1490, 967, 735 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.42 (s, 1H), 7.27–7.21 (m, 5H), 7.14 (s, 1H), 7.01–6.99 (m, 2H), 6.92 (d, J = 8.8 Hz, 2H), 6.56 (s, 1H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 138.5, 138.3, 137.5, 134.3, 129.5, 129.0, 128.9, 128.7, 128.3, 127.6, 110.6, 69.6; Anal Calcd for $C_{16}H_{12}ClN_2$: C, 63.39; H, 3.99; N, 9.24; Found: C, 63.19; H, 3.94; N, 9.59.

4-Chloro-1-[phenyl(*o*-tolyl)methyl]-1*H*-pyrazole (**26**). Yield 85%; mp = 89–92 °C; TLC R_f = 0.36 (5% EA/95% hexanes); IR (ATR) 3099, 3029, 2920, 1488, 1299, 964, 708 cm^{-1}; ^1H

NMR (400 MHz, $CDCl_3$) δ 7.55 (s, 1H), 7.39–7.37 (m, 3H), 7.30–7.16 (m, 4H), 7.09–7.07 (m, 2H), 6.90 (s, 1H), 6.72 (d, J = 7.4 Hz, 1H), 2.23 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 138.3, 138.2, 137.2, 136.6, 130.9, 128.9, 128.4, 128.3, 128.1, 127.7, 126.4, 109.9, 67.6, 29.7, 19.2; Anal Calcd for $C_{17}H_{15}ClN_2$: C, 72.21; H, 5.35; N, 9.91; Found: C, 71.94; H, 5.44; N, 9.81.

1-[(2*H*-1,3-Benzodioxol-5-yl)phenylmethyl]-4-chloro-1*H*-pyrazole (**28**). Yield 98%; TLC R_f = 0.30 (5% EA/95% hexanes); IR (ATR) 3134, 3062, 2893, 1501, 1487, 1235, 1035 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.42 (s, 1H), 7.25–7.23 (m, 3H), 7.16 (s, 1H), 6.98 (d, J = 6.6 Hz, 2H), 6.67 (d, J = 7.7 Hz, 1H), 6.49 (m, 3H), 5.86 (s, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 148.1, 147.7, 139.0, 138.3, 132.6, 128.8, 128.3, 127.9, 127.5, 122.1, 109.9, 108.8, 108.4, 101.4, 69.9; Anal Calcd for $C_{17}H_{13}ClN_2O_2$: C, 65.29; H, 4.19; N, 8.96; Found: C, 65.27; H, 4.14; N, 8.63.

1-Benzyl-4-chloro-1*H*-pyrazole (**30**). Yield 73%; TLC R_f = 0.31 (10% EA/90% hexanes); ^1H NMR (400 MHz, $CDCl_3$) δ 7.49 (s, 1H), 7.37–7.33 (m, 4H), 7.24–7.22 (m, 2H), 5.23 (s, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 137.9, 135.8, 130.0, 128.4, 127.9, 127.3, 110.3, 56.7. This compound has been reported previously [53].

4-Chloro-1-[(*p*-methoxyphenyl)methyl]-1*H*-pyrazole (**32**). Yield: 92%; TLC R_f = 0.32 (10% EA/90% hexanes); IR (ATR) 3124, 2999, 2933, 2834, 1612, 1511, 1244 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.46 (s, 1H), 7.32 (s, 1H), 7.20 (d, J = 8.6 Hz, 2H), 6.90 (d, J = 8.6 Hz, 2H), 5.19 (s, 2H), 3.82 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 159.7, 137.7, 129.5, 127.6, 126.9, 114.3, 110.2, 56.3, 56.3; Anal Calcd for $C_{11}H_{11}ClN_2O$: C, 59.33; H, 4.98; N, 12.58; found: C, 59.44; H, 4.92; N, 12.83.

4-Chloro-1-[(*p*-chlorophenyl)methyl]-1*H*-pyrazole (**34**). Yield 37%; mp = 52–55 °C; TLC R_f = 0.27 (5% EA/95% hexanes); IR (ATR) 3129, 3045, 2943, 1492, 970, 755 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.37 (s, 1H), 7.25–7.22 (m, 4H), 7.05 (d, J = 8.3 Hz, 2H), 5.11 (s, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 138.2, 134.4, 134.3, 129.1, 128.9, 127.2, 110.6, 55.9; Anal Calcd for $C_{10}H_8Cl_2N_2$: C, 52.89; H, 3.55; N, 12.34; found: C, 52.81; H, 3.54; N, 12.17.

2-[(4-Chloro-1*H*-pyrazol-1-yl)methyl]-1,3-isoindolinedione (**36**). Yield 62%; mp = 164–168 °C; TLC R_f = 0.30 (30% EA/70% hexanes); IR (ATR) 3135, 2963, 1771, 1717, 1401, 1323 cm^{-1}; ^1H NMR (400 MHz, $(CD_3)_2SO$) δ 8.13 (s, 1H), 7.95–7.88 (m, 4H), 7.58 (s, 1H), 5.85 (s, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $(CD_3)_2SO$) δ 167.2, 138.7, 135.5, 131.6, 129.5, 124.1, 109.2, 52.8; Anal Calcd for $C_{12}H_8ClN_3O_2$: C, 55.08; H, 3.08; N, 16.06; Found: C, 54.73; H, 2.88; N, 16.40.

4-Bromo-1-(1-phenylethyl)-1*H*-pyrazole (**44**). Yield: 70%. IR (ATR) 3124, 3028, 2980, 2933, 1304, 987, 696 cm^{-1}; TLC R_f = 0.37 (5% EA/95% hexanes); ^1H NMR (400 MHz, $CDCl_3$) δ 7.38 (s, 1H), 7.25–7.17 (m, 4H), 7.10 (d, J = 6.7 Hz, 2H), 5.35 (q, J = 7.0 Hz, 1H), 1.75 (d, J = 7.0 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 141.1, 139.6, 128.9, 128.2, 128.1, 126.4, 93.1, 61.9, 21.2; Anal Calcd for $C_{11}H_{11}BrN_2$: C, 52.61; H, 4.42; N, 11.16; Found: C, 52.51; H, 4.46; N, 11.28.

4-Iodo-1-(1-phenylethyl)-1*H*-pyrazole (**46**). Yield: 70%. IR (ATR) 3109, 2978, 1493, 960, 696 cm^{-1}; TLC R_f = 0.37 (5% EA/95% hexanes); ^1H NMR (400 MHz, $CDCl_3$) δ 7.58 (s, 1H), 7.44 (s, 1H), 7.39–7.23 (m, 5H), 5.53 (q, J = 7.0 Hz, 1H), 1.90 (d, J = 6.9 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 144.2, 141.1, 132.4, 128.9, 128.2, 126.4, 61.7, 56.2, 21.3; Anal Calcd for $C_{11}H_{11}IN_2$: C, 44.32; H, 3.72; N, 9.40; Found: C, 44.02; H, 3.44; N, 9.03.

4-Methyl-1-(1-phenylethyl)-1*H*-pyrazole (**48**). Yield: 62% IR (ATR) 3085, 2980, 1493, 1340, 1156, 990 cm^{-1}; TLC = R_f 0.63 (30% EA/70% hexanes); ^1H NMR (400 MHz, $CDCl_3$) δ 7.36–7.27 (m, 4H), 7.21–7.18 (m, 3H), 5.48 (q, J = 7.3 Hz, 1H), 2.07 (s, 3H), 1.88 (d, J = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 142.1, 139.2, 128.7, 127.7, 126.7, 126.3, 116.0, 60.9, 21.4, 8.9; Anal Calcd for $C_{12}H_{14}N_2$: C, 77.38; H, 7.58; N, 15.04; Found: C, 77.28; H, 7.55; N, 14.92.

Ethyl 1-(1-phenylethyl)-1*H*-pyrazole-4-carboxylate (**50**). Yield: 50%. IR (ATR) 2981, 1708, 1551, 1408, 1217, 1024 cm^{-1}; TLC R_f = 0.34 (20% EA/80% hexanes); ^1H NMR (400 MHz, $CDCl_3$) δ 7.94 (s, 1H), 7.89 (s, 1H), 7.37–7.30 (m, 3H), 7.22 (d, J = 7.2 Hz, 2H), 5.52 (q, J = 7.0 Hz, 1H), 4.27 (q, J = 7.1 Hz, 2H), 1.90 (d, J = 7.1 Hz, 3H), 1.32 (t, J = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 163.1, 140.8, 140.6, 131.2, 128.9, 128.3, 126.4, 115.0, 61.7,

60.1, 21.3, 14.4; Anal Calcd for $C_{14}H_{16}N_2O_2$: C, 68.83; H, 6.60; N, 11.47; Found: C, 68.80; H, 6.56; N, 11.58.

4-(*p*-Nitrophenyl)-1-(1-phenylethyl)-1*H*-pyrazole (**52**). Yield: 43%. mp = 119–123 °C; IR (ATR) 3068, 2943, 1597, 1500, 1333, 1112 cm^{-1}; TLC R_f = 0.35 (25% EA/75% hexanes); ^1H NMR (400 MHz, $CDCl_3$) δ 8.19 (d, J = 8.7 Hz, 2H), 7.90 (s, 1H), 7.74 (s, 1H), 7.58 (d, J = 8.7 Hz, 2H), 7.39–7.34 (m, 3H), 7.29–7.27 (m, 2H), 5.57 (q, J = 7.1 Hz, 1H), 1.96 (d, J = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 146.0, 141.0, 139.4, 137.1, 128.9, 128.2, 126.4, 125.9, 125.5, 124.4, 121, 61.7, 21.3; Anal Calcd for $C_{17}H_{15}N_3O_2$: C, 69.61; H, 5.15; N, 14.33; Found: C, 69.66; H, 5.25; N, 14.42.

3,5-Dimethyl-1-(1-phenylethyl)-1*H*-pyrazole (**54**). Yield: 52%. TLC R_f = 0.22 (5% EA/95% hexanes); ^1H NMR (400 MHz, $CDCl_3$) δ 7.20–7.15 (m, 2H), 7.13–7.09 (m 1H), 6.99 (d, J = 7.4 Hz, 2H), 5.73 (s, 1H), 5.24 (q, J = 7.0 Hz, 1H), 2.18 (s, 3H), 1.99 (s, 3H), 1.81 (d, J = 7.0 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 146.9, 143.0, 138.9, 138.6, 127.2, 125.9, 105.6, 57.3, 21.8, 13.8, 11.2. This compound has been reported previously [1].

Dimethyl 1-(1-phenylethyl)-1*H*-pyrazole-3,5-dicarboxylate (**56**). Yield: 44%. mp = 74–77 °C; IR (ATR) 3141, 2988, 1719, 1456, 1218, 1086 cm^{-1}; TLC R_f = 0.69 (20% EA/80% hexanes); ^1H NMR (400 MHz, acetone-d_6) δ 7.32–7.24 (m, 6H), 6.67 (q, J = 7.0 Hz, 1H), 3.86 (d, J = 3.8 Hz, 6H), 1.91 (d, J = 7.0 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, acetone-d_6) δ 161.5, 159.3, 142.0, 141.9, 133.4, 128.5, 127.7, 126.4, 113.8, 59.8, 51.7, 51.2, 21.8; Anal Calcd for $C_{15}H_{16}N_2O_4$: C, 62.49; H, 5.59; N, 9.72; Found: C, 62.42; H, 5.60; N, 9.79.

1-(1-Phenylethyl)-1*H*-pyrazole (**58**). Yield: 45%; TLC R_f = 0.33 (20% EA/80% hexanes); ^1H NMR (400 MHz, $CDCl_3$) δ 7.56–7.55 (s, 1H), 7.41 (d, J = 2.1 Hz, 1H), 7.35–7.27 (m, 3H), 7.20–7.18 (m, 2H), 6.27 (t, = 2.0 Hz, 1H), 5.55 (q, = 7.1 Hz, 1H), 1.90 (d, J = 7.1 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 141.9, 139.0, 128.7, 127.8, 127.7, 126.3, 105.4, 61.0, 21.5. This compound has been previously reported [54].

1-(1-Phenylethyl)-1*H*-indazole (**60**). Yield: 41%. mp = 91–93 °C; IR (ATR) 3067, 2983, 1626, 1513, 1448, 1167, 1010 cm^{-1}; TLC R_f = 0.65 (25% EA/75% hexanes); ^1H NMR (400 MHz, $CDCl_3$) δ 7.91 (s, 1H), 7.75 (d, J = 8.8 Hz, 1H), 7.62 (d, J = 8.4 Hz, 1H), 7.36–7.27 (m, 6H), 7.07 (t, J = 7.5 Hz, 1H), 5.86 (q, J = 7.0 Hz, 1H), 2.06 (d, J = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 148.1, 140.8, 128.9, 128.2, 126.6, 126.2, 121.8, 121.6, 121.5, 120.2, 117.4, 62.7, 21.6; Anal Calcd for $C_{15}H_{14}N_2$: C, 81.05; H, 6.35; N, 12.60; Found: C, 81.07; H, 6.12; N, 12.46.

5-Methyl-3-phenyl-1-(1-phenylethyl)-1*H*-pyrazole (**62**). Yield: 16%. IR (ATR) 3060, 2981, 2932, 1603, 1453, 1260, 764 cm^{-1}; TLC R_f = 0.41 (10% EA/90% hexanes); ^1H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, J = 7.4 Hz, 2H), 7.39 (d, J = 7.5 Hz, 2H), 7.31–7.28 (m, 3H), 7.25–7.21 (m, 1H), 7.18 (d, J = 7.3 Hz, 2H), 6.36 (s, 1H), 5.47 (q, J = 7.0 Hz, 1H), 2.17 (s, 3H), 1.98 (d, J = 7.0 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 149.5, 142.6, 139.6, 133.9, 128.6, 128.5, 127.3, 126.2, 126.0, 125.6, 103.2, 58.1, 21.9, 11.3; Anal Calcd for $C_{18}H_{18}N_2$: C, 84.41; H, 6.92; N, 10.68; Found: C, 82.37; H, 6.88; N, 10.70.

3-Methyl-5-phenyl-1-(1-phenylethyl)-1*H*-pyrazole (**63**). Yield: 40%. IR (ATR) 3060, 2978, 1494, 1444, 1256 759 cm^{-1}; TLC R_f = 0.34 (10% EA/90% hexanes); ^1H NMR (400 MHz, $CDCl_3$) δ 7.38–7.36 (m, 3H), 7.29–7.27 (m, 2H), 7.24–7.20 (m, 3H), 7.13 (d, J = 7.7 Hz, 2H), 6.09 (s, 1H), 5.45 (q, J = 7.0 Hz, 1H), 2.37 (s, 3H), 1.89 (d, J = 7.0 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 147.8, 144.6, 143.1, 131.2, 129.1, 128.5, 128.4, 128.3, 127.1, 126.1, 106, 57.2, 22.1, 13.8; Anal Calcd for $C_{18}H_{18}N_2$: C, 84.41; H, 6.92; N, 10.68; Found: C, 82.36; H, 6.86; N, 10.64.

1-Benzhydryl-4-[(benzhydryloxy)methyl]-1*H*-pyrazole (**65**). Yield: 61%. IR (ATR): 3060, 3027, 2866, 1493, 1451, 1060, 694 cm^{-1}; TLC R_f = 0.47 (30% EA/70% hexanes); ^1H NMR (400 MHz, $CDCl_3$) δ 7.60 (s, 1H), 7.35–7.29 (m, 15H), 7.23 (bs, 2H), 7.12–7.10 (m, 4H), 6.77 (s, 1H), 5.40 (s, 1H), 4.43 (s, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 141.9, 139.6, 139.3, 129.4, 128.7, 128.4, 128.3, 128.1, 127.5, 127.1, 118, 82.1, 69.6, 61.6; Anal Calcd for $C_{18}H_{18}N_2$: C, 83.69; H, 6.09; N, 6.51; Found: C, 83.59; H, 6.19; N, 6.49.

4. Conclusions

In conclusion, a new method for the *N*-alkylation of pyrazoles has been developed utilizing trichloroacetimidates and camphorsulfonic acid as a Brønsted acid catalyst. This method provides ready access to *N*-alkyl pyrazoles which are present in a variety of medicinally relevant structures. Benzylic, phenethyl and benzhydryl trichloroacetimidates provide moderate to good yields of the *N*-alkyl pyrazole products. Unsymmetrical pyrazoles provide a mixture of the two possible regioisomers, with sterics controlling the which isomer is the major product. This method is differentiated from past *N*-alkylations in that it does not depend on transition metal catalysts or the use of strong base, instead proceeding under mild acid-catalyzed conditions.

Supplementary Materials: Supporting information (copies of ^{1}H NMR, ^{13}C NMR and NOESY spectra) can be downloaded at: https://www.mdpi.com/article/10.3390/org3020009/s1.

Author Contributions: Conceptualization, J.D.C., R.I.L.M. and N.A.M.; investigation, R.I.L.M. and N.A.M.; formal analysis, R.I.L.M., N.A.M. and J.D.C.; writing—original draft preparation, J.D.C., R.I.L.M. and N.A.M.; writing—review and editing, J.D.C., R.I.L.M. and N.A.M.; supervision, J.D.C. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Gulia, N.; Daugulis, O. Palladium-Catalyzed Pyrazole-Directed sp3 C-H Bond Arylation for the Synthesis of β-Phenethylamines. *Angew. Chem. Int. Ed.* **2017**, *56*, 3630–3634. [CrossRef]
2. Li, T.; Liu, C.; Wu, S.; Chen, C.; Zhu, B. Rhodium(III)-catalyzed unreactive C(sp3)-H alkenylation of N-alkyl-1H-pyrazoles with alkynes. *Org. Biomol. Chem.* **2019**, *17*, 7679–7683. [CrossRef] [PubMed]
3. Du, R.; Liu, L.; Xu, S. Iridium-catalyzed regio- and enantioselective borylation of unbiased methylene C(sp3)-H bonds at the position β to a nitrogen center. *Angew. Chem. Int. Ed.* **2021**, *60*, 5843–5847. [CrossRef] [PubMed]
4. Papageorgiou, C.; Albert, R.; Floersheim, P.; Lemaire, M.; Bitch, F.; Weber, H.-P.; Andersen, E.; Hungerford, V.; Schreier, M.H. Pyrazole Bioisosteres of Leflunomide as B-Cell Immunosuppressants for Xenotransplantation and Chronic Rejection: Scope and Limitations. *J. Med. Chem.* **1998**, *41*, 3530–3538. [CrossRef] [PubMed]
5. Kumari, S.; Carmona, A.V.; Tiwari, A.K.; Trippier, P.C. Amide Bond Bioisosteres: Strategies, Synthesis, and Successes. *J. Med. Chem.* **2020**, *63*, 12290–12358. [CrossRef]
6. Graham, T.H.; Shu, M.; Verras, A.; Chen, Q.; Garcia-Calvo, M.; Li, X.; Lisnock, J.; Tong, X.; Tung, E.C.; Wiltsie, J.; et al. Pyrazoles as non-classical bioisosteres in prolylcarboxypeptidase (PrCP) inhibitors. *Bioorg. Med. Chem. Lett.* **2014**, *24*, 1657–1660. [CrossRef]
7. Wilkening, R.R.; Ratcliffe, R.W.; Fried, A.K.; Meng, D.; Sun, W.; Colwell, L.; Lambert, S.; Greenlee, M.; Nilsson, S.; Thorsell, A.; et al. Estrogen receptor β-subtype selective tetrahydrofluorenones: Use of a fused pyrazole as a phenol bioisostere. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 3896–3901. [CrossRef]
8. Schwärzer, K.; Rout, S.K.; Bessinger, D.; Lima, F.; Brocklehurst, C.E.; Karaghiosoff, K.; Bein, T.; Knochel, P. Selective functionalization of the 1H-imidazo[1,2-b]pyrazole scaffold. A new potential non-classical isostere of indole and a precursor of push-pull dyes. *Chem. Sci.* **2021**, *12*, 12993–13000. [CrossRef]
9. Kucukguzel, S.G.; Senkardes, S. Recent advances in bioactive pyrazoles. *Eur. J. Med. Chem.* **2015**, *97*, 786–815. [CrossRef]
10. Faria, J.V.; Vegi, P.F.; Miguita, A.G.C.; dos Santos, M.S.; Boechat, N.; Bernardino, A.M.R. Recently reported biological activities of pyrazole compounds. *Bioorg. Med. Chem.* **2017**, *25*, 5891–5903. [CrossRef]
11. Li, X.; Yu, Y.; Tu, Z. Pyrazole scaffold synthesis, functionalization, and applications in Alzheimer's disease and Parkinson's disease treatment (2011–2020). *Molecules* **2021**, *26*, 1202. [CrossRef] [PubMed]
12. Mykhailiuk, P.K. Fluorinated Pyrazoles: From Synthesis to Applications. *Chem. Rev.* **2021**, *121*, 1670–1715. [CrossRef] [PubMed]
13. Santos, N.E.; Carreira, A.R.F.; Silva, V.L.M.; Braga, S.S. Natural and biomimetic antitumor pyrazoles, a perspective. *Molecules* **2020**, *25*, 1364. [CrossRef]
14. Yin, P.; Jean'ne, M.S. Nitrogen-rich azoles as high density energy materials: Reviewing the energetic footprints of heterocycles. *Adv. Heterocycl. Chem.* **2017**, *121*, 89–131. [CrossRef]

15. Zhang, S.; Gao, Z.; Lan, D.; Jia, Q.; Liu, N.; Zhang, J.; Kou, K. Recent advances in synthesis and properties of nitrated-pyrazoles based energetic compounds. *Molecules* **2020**, *25*, 3475. [CrossRef]
16. Kashyap, S.; Singh, R.; Singh, U.P. Inorganic and organic anion sensing by azole family members. *Coord. Chem. Rev.* **2020**, *417*, 213369. [CrossRef]
17. Tigreros, A.; Portilla, J. Recent progress in chemosensors based on pyrazole derivatives. *RSC Adv.* **2020**, *10*, 19693–19712. [CrossRef]
18. El Boutaybi, M.; Taleb, A.; Touzani, R.; Bahari, Z. Metal-organic frameworks based on pyrazole subunit for batteries applications: A systematic review. *Mater. Today Proc.* **2020**, *31*, S96–S102. [CrossRef]
19. Matos, I.; Perez-Mayoral, E.; Soriano, E.; Zukal, A.; Martin-Aranda, R.M.; Lopez-Peinado, A.J.; Fonseca, I.; Cejka, J. Experimental and theoretical study of pyrazole N-alkylation catalyzed by basic modified molecular sieves. *Chem. Eng. J.* **2010**, *161*, 377–383. [CrossRef]
20. Almena, I.; Diez-Barra, E.; De La Hoz, A.; Ruiz, J.; Sanchez-Migallon, A.; Elguero, J. Alkylation and arylation of pyrazoles under solvent-free conditions: Conventional heating versus microwave irradiation. *J. Heterocycl. Chem.* **1998**, *35*, 1263–1268. [CrossRef]
21. Diez-Barra, E.; De la Hoz, A.; Sanchez-Migallon, A.; Tejeda, J. Synthesis of N-alkylpyrazoles by phase transfer catalysis without solvent. *Synth. Commun.* **1990**, *20*, 2849–2853. [CrossRef]
22. Wang, R.; Chen, Y.; Zhao, X.; Yu, S.; Yang, B.; Wu, T.; Guo, J.; Hao, C.; Zhao, D.; Cheng, M. Design, synthesis and biological evaluation of novel 7H-pyrrolo[2,3-d]pyrimidine derivatives as potential FAK inhibitors and anticancer agents. *Eur. J. Med. Chem.* **2019**, *183*, 111716. [CrossRef] [PubMed]
23. Mosallanejad, A.; Lorthioir, O. Application of Tsunoda reagent to the convenient synthesis of drug-like pyrazoles. *Tetrahedron Lett.* **2018**, *59*, 1708–1710. [CrossRef]
24. Gill, A.; Werz, U.R.; Maas, G. N-vinylation and N-allylation of 3,5-disubstituted pyrazoles by N-H insertion of vinylcarbenoids. *Z. Naturforsch. B J. Chem. Sci.* **2015**, *70*, 747–756. [CrossRef]
25. Beattie, D.; Brearley, A.; Brown, Z.; Charlton, S.J.; Cox, B.; Fairhurst, R.A.; Fozard, J.R.; Gedeck, P.; Kirkham, P.; Meja, K.; et al. Synthesis and evaluation of two series of 4′-aza-carbocyclic nucleosides as adenosine A2A receptor agonists. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 1219–1224. [CrossRef] [PubMed]
26. Haydl, A.M.; Xu, K.; Breit, B. Regio- and Enantioselective Synthesis of N-Substituted Pyrazoles by Rhodium-Catalyzed Asymmetric Addition to Allenes. *Angew. Chem. Int. Ed.* **2015**, *54*, 7149–7153. [CrossRef]
27. Arredondo, V.; Hiew, S.C.; Gutman, E.S.; Premachandra, I.D.U.A.; Van Vranken, D.L. Enantioselective Palladium-Catalyzed Carbene Insertion into the N-H Bonds of Aromatic Heterocycles. *Angew. Chem. Int. Ed.* **2017**, *56*, 4156–4159. [CrossRef]
28. Wang, H.; Guo, C. Enantioselective γ-Addition of Pyrazole and Imidazole Heterocycles to Allenoates Catalyzed by Chiral Phosphine. *Angew. Chem. Int. Ed.* **2019**, *58*, 2854–2858. [CrossRef] [PubMed]
29. Bengel, L.L.; Aberle, B.; Egler-Kemmerer, A.-N.; Kienzle, S.; Hauer, B.; Hammer, S.C. Engineered Enzymes Enable Selective N-Alkylation of Pyrazoles With Simple Haloalkanes. *Angew. Chem. Int. Ed.* **2021**, *60*, 5554–5560. [CrossRef]
30. Arachchi, M.K.; Nguyen, H.M. Iridium-Catalyzed Enantioselective Allylic Substitutions of Racemic, Branched Trichloroacetimidates with Heteroatom Nucleophiles: Formation of Allylic C-O, C-N, and C-S Bonds. *Adv. Synth. Catal.* **2021**, *363*, 4239–4246. [CrossRef]
31. Arnold, J.S.; Nguyen, H.M. Rhodium-catalyzed asymmetric amination of allylic trichloroacetimidates. *Synthesis* **2013**, *45*, 2101–2108. [CrossRef]
32. Wong, V.H.L.; Hor, T.S.; Hii, K.K. Silver-catalysed intramolecular hydroamination of alkynes with trichloroacetimidates. *Chem. Commun.* **2013**, *49*, 9272–9274. [CrossRef] [PubMed]
33. Maleckis, A.; Klimovica, K.; Jirgensons, A. Catalytic Enantioselective Synthesis of 4-Vinyl-2-trichloromethyloxazoline: An Access to Enantioenriched Vinylglycinol Surrogate. *J. Org. Chem.* **2010**, *75*, 7897–7900. [CrossRef]
34. Anderson, C.E.; Donde, Y.; Douglas, C.J.; Overman, L.E. Catalytic Asymmetric Synthesis of Chiral Allylic Amines. Evaluation of Ferrocenyloxazoline Palladacycle Catalysts and Imidate Motifs. *J. Org. Chem.* **2005**, *70*, 648–657. [CrossRef]
35. Wallach, D.R.; Stege, P.C.; Shah, J.P.; Chisholm, J.D. Brønsted Acid Catalyzed Monoalkylation of Anilines with Trichloroacetimidates. *J. Org. Chem.* **2015**, *80*, 1993–2000. [CrossRef] [PubMed]
36. Wallach, D.R.; Chisholm, J.D. Alkylation of Sulfonamides with Trichloroacetimidates under Thermal Conditions. *J. Org. Chem.* **2016**, *81*, 8035–8042. [CrossRef]
37. Mate, N.A.; Meador, R.I.L.; Joshi, B.D.; Chisholm, J.D. Alkylation of isatins with trichloroacetimidates. *Org. Biomol. Chem.* **2022**, *20*, 2131–2136. [CrossRef]
38. McHardy, S.F.; Vetelino, M.G. Preparation of 1-diphenylmethylpyrazoles as Opioid Receptor Ligands. U.S. Patent 6960609B2, 1 November 2005.
39. Overman, L.E.; Carpenter, N.E. The allylic trihaloacetimidate rearrangement. *Org. React.* **2005**, *66*, 1–107.
40. Cran, J.; Vidhani, D.; Krafft, M. Copper-Catalyzed N-tert-Butylation of Aromatic Amines under Mild Conditions Using tert-Butyl 2,2,2-Trichloroacetimidate. *Synlett* **2014**, *25*, 1550–1554. [CrossRef]
41. Iversen, T.; Bundle, D.R. Benzyl trichloroacetimidate, a versatile reagent for acid-catalyzed benzylation of hydroxy-groups. *J. Chem. Soc. Chem. Commun.* **1981**, 1240–1241. [CrossRef]
42. Nakajima, N.; Horita, K.; Abe, R.; Yonemitsu, O. MPM (4-methoxybenzyl)-protection of hydroxy functions under mild acidic conditions. *Tetrahedron Lett.* **1988**, *29*, 4139–4142. [CrossRef]

43. Ali, I.A.I.; El Ashry, E.S.H.; Schmidt, R.R. Protection of Hydroxy Groups with Diphenylmethyl and 9-Fluorenyl Trichloroacetimidates—Effect on Anomeric Stereocontrol. *Eur. J. Org. Chem.* **2003**, *2003*, 4121–4131. [CrossRef]
44. Howard, K.T.; Duffy, B.C.; Linaburg, M.R.; Chisholm, J.D. Formation of DPM ethers using O-diphenylmethyl trichloroacetimidate under thermal conditions. *Org. Biomol. Chem.* **2016**, *14*, 1623–1628. [CrossRef] [PubMed]
45. Pangborn, A.B.; Giardello, M.A.; Grubbs, R.H.; Rosen, R.K.; Timmers, F.J. Safe and Convenient Procedure for Solvent Purification. *Organometallics* **1996**, *15*, 1518–1520. [CrossRef]
46. Zhao, C.; Toste, F.D.; Raymond, K.N.; Bergman, R.G. Nucleophilic Substitution Catalyzed by a Supramolecular Cavity Proceeds with Retention of Absolute Stereochemistry. *J. Am. Chem. Soc.* **2014**, *136*, 14409–14412. [CrossRef]
47. Adhikari, A.A.; Suzuki, T.; Gilbert, R.T.; Linaburg, M.R.; Chisholm, J.D. Rearrangement of Benzylic Trichloroacetimidates to Benzylic Trichloroacetamides. *J. Org. Chem.* **2017**, *82*, 3982–3989. [CrossRef]
48. Zhang, Q.; Mixdorft, J.C.; Reynders, G.J.; Nguyen, H.M. Rhodium-catalyzed benzylic fluorination of trichloroacetimidates. *Tetrahedron* **2015**, *71*, 5932–5938. [CrossRef]
49. Mahajani, N.S.; Chisholm, J.D. Synthesis of 1,1′-Diarylethanes and Related Systems by Displacement of Trichloroacetimidates with Trimethylaluminum. *J. Org. Chem.* **2018**, *83*, 4131–4139. [CrossRef]
50. Li, C.K.; Li, W.B.; Wang, J.B. Gold(I)-catalyzed arylmethylation of terminal alkynes. *Tetrahedron Lett.* **2009**, *50*, 2533–2535. [CrossRef]
51. Ali, I.A.I.; El Ashry, E.S.H.; Schmidt, R.R. Imidomethylation of C-nucleophiles using O-phthalimidomethyl trichloroacetimidate and catalytic amounts of TMSOTf. *Tetrahedron* **2004**, *60*, 4773–4780. [CrossRef]
52. Song, C.; Dong, X.; Yi, H.; Chiang, C.-W.; Lei, A. DDQ-Catalyzed Direct C(sp3)-H Amination of Alkylheteroarenes: Synthesis of Biheteroarenes under Aerobic and Metal-Free Conditions. *ACS Catal.* **2018**, *8*, 2195–2199. [CrossRef]
53. Olsen, K.L.; Jensen, M.R.; MacKay, J.A. A mild halogenation of pyrazoles using sodium halide salts and Oxone. *Tetrahedron Lett.* **2017**, *58*, 4111–4114. [CrossRef]
54. Shi, J.; Yuan, T.; Wang, R.; Zheng, M.; Wang, X. Boron carbonitride photocatalysts for direct decarboxylation: The construction of C(sp3)-N or C(sp3)-C(sp2) bonds with visible light. *Green Chem.* **2021**, *23*, 3945–3949. [CrossRef]