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Catalyzed Selective Direct α- and γ-Alkylation of Aldehydes with Cyclic Benzyl Ethers by Using $T^+BF_4^-$ in the Presence of an Inexpensive Organic Acid or Anhydride**

Heinrich Richter, Renate Rohlmann, and Olga García Mancheño*[a]

Abstract: The cross dehydrogenative coupling (CDC) of cyclic benzyl ethers with aliphatic and α,β-unsaturated aldehydes has been developed. The mild reaction conditions, in which an N-oxoammonium salt derived from TEMPO (2,2,6,6-tetramethyl-1-piperidinoxyl) is employed as the oxidant in combination with a Cu catalyst, allow the use of relatively redox-unstable aldehydes under oxidative CDC conditions. The addition of a catalytic amount of trifluoroacetic acid (TFA) or Ac_2O facilitates the reaction and increases the efficiency and selectivity. In contrast to the expected α-alkylation obtained with aliphatic aldehydes, α,β-unsaturated aldehydes led preferentially to the more challenging γ-alkylated products. The utility of the developed methodology was demonstrated by the synthesis of isochromane-derived bioactive compounds, such as the dopamine antagonist sonepiprazole.

Keywords: alkylation · C–H activation · copper · cross-coupling · oxoammonium salt

Introduction

The development of new environmentally friendly methods for the synthesis of C–C bonds is of great significance to chemists. Direct C–H functionalizations present an atom-economic approach towards the formation of new C–C bonds without prior installation of functional groups and are, therefore, especially attractive.[1] In this research area, cross dehydrogenative coupling is becoming firmly established[2] and allows diverse functionalizations of relatively unreactive $C(sp^3)$–H bonds. Typically, the oxidation of such C–H bonds by peroxides, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), or, more recently, dioxygen generates an electrophilic species such as an organic radical, a carbocation, and an oxonium or iminium ion, which can undergo a coupling reaction with a variety of nucleophiles.

Recently, we have presented a TEMPO oxoammonium salt (2,2,6,6-tetramethylpiperidine-1-oxoammonium tetrafluoroborate, $T^+BF_4^-$) as a nontoxic and mild hydrogen acceptor for the $Fe(OTf)_2$-catalyzed oxidative alkylation of benzylic $C(sp^3)$–H bonds next to a heteroatom by using activated enolizable C nucleophiles such as malonates, β-ketoesters, or β-nitroketones.[3] We thought that these mild reaction conditions might be compatible with other types of simple carbonyl-based nucleophilic reagents. Considering that TEMPO oxoammonium salts are generally used for the selective oxidation of primary alcohols to the corresponding aldehydes,[4] we envisioned the use of $T^+BF_4^-$ in the CDC of aldehydes.

In previous work reported by Li and co-workers, the dehydrogenative coupling of the related less problematic ketones with benzylic ethers was achieved by employing peroxides as oxidants.[5] More recently, Klussmann and co-workers have reported the α-alkylation of ketones with amines and diaryl methane derivatives by using *t*BuOOH or $MeSO_3H/O_2$, respectively.[6] N-substituted glycine esters and *N,N*-dialkyl anilines were also coupled with ketones by cooperative copper and an achiral pyrrolidine catalyst.[7] In addition, Cozzi and co-workers[8] have shown that the combination of MacMillan type organocatalysts with DDQ is indeed able to efficiently promote the asymmetric CDC reaction of aldehydes with suitable electrophiles[9] through enamine activation (Scheme 1). However, the substrate scope was restricted to activated 1,3,5-cycloheptatriene and diaryl methane derivatives such as xanthene, which led to very specific compounds. Moreover, the structurally interesting and pharmaceutically valuable cyclic benzylic ethers, such as isochromanes or 6*H*-benzochromenes, moieties present in a number of bioactive compounds, were not compatible with these reaction conditions. Therefore, we focused our attention upon the C–H functionalization of isochromanes[10] by selective direct alkylation of aldehydes (Scheme 1), because it would allow a modular and straightforward synthesis of interesting biologically active compounds.[11] Several illustrative examples of natural and synthetic bioactive α-functionalized isochromanes are shown in Scheme 2.

Herein, we report the selective α-alkylation of aliphatic aldehydes and ketones, as well as a novel γ-alkylation of

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[**] $T^+BF_4^-$: 2,2,6,6-Tetramethylpiperidine-1-oxoammonium tetrafluoroborate.

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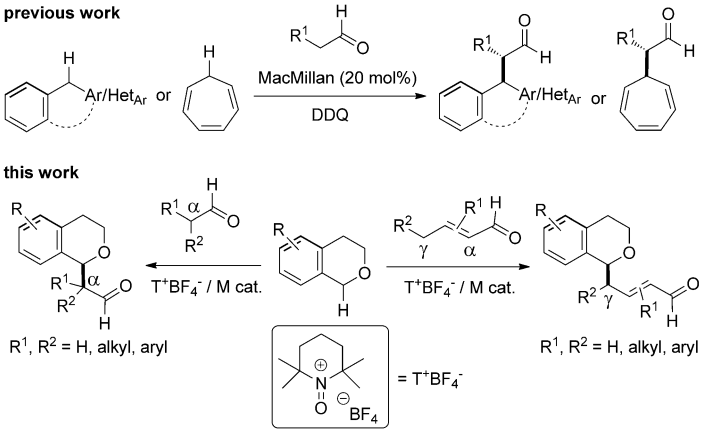
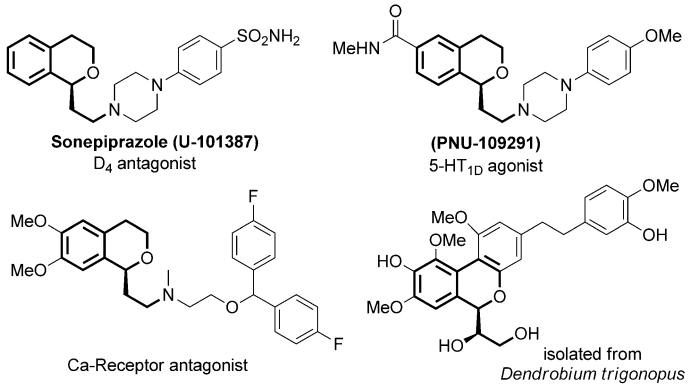


Scheme 1. Cross dehydrogenative couplings with aldehydes.



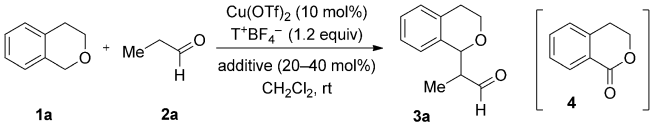
Scheme 2. Selected biologically active simple α-functionalized isochromanes.

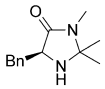
α,β-unsaturated aldehydes, with isochromane derivatives by using a CDC approach.

Results and Discussion

To the best of our knowledge, no literature precedence for the direct oxidative coupling of aldehydes with isochromane derivatives has been set to date. To explore the feasibility of this transformation, the coupling of isochromane (**1a**) with propanal (**2a**) was initially investigated as a model reaction (Table 1). We assumed that a MacMillan type catalyst could play a crucial role by allowing the activation of the aldehyde through enamine chemistry.[8,12] Thus, a test reaction in the presence of a transition-metal catalyst, a first-generation MacMillan catalyst (substituents: Bn/diMe; Macmillan I in Table 1), the TEMPO-derived oxoammonium salt (T$^+$BF$_4^-$),[13] and an excess of the aldehyde (5 equiv) was performed first. In contrast to our previous results with 1,3-dicarbonyl nucleophiles,[3] iron catalysis gave only traces of the coupling product. By switching from Fe(OTf)$_2$ to Cu(OTf)$_2$, the desired product **3a** was obtained in a promising 42% yield after 18 h (Table 1, entry 2), along with 20% of

Table 1. Optimization of the CDC of isochromane (**1a**) with propanal (**2a**).[a]



Entry	Additive (mol%)	pK_a of organic acid	[M]	d.r.[b]	Yield of **3a** [%][c,d]
1	–	–	0.2	n.d.[e]	18
2	2 				
	MacMillan I[f] (30)	–	0.2	1:1.1	42
3	L-proline (30)	2.0	0.2	1:3.3	52
4	AcOH (40)	4.8	0.2	n.d.[e]	45
5	TFA (40)	0.2	0.2	n.d.[e]	54
6	TFA (20)	0.2	0.2	n.d.[e]	56
7	TFA (20)	0.2	0.1	1:2.1	58
8	TFA (20)	0.2	0.05	n.d.[e]	53
9	malonic acid (20)	2.9	0.1	1:2.8	54
10	L-aspartic acid (20)	2.0	0.1	1:2	61
11	L-glutamic acid (20)	2.2	0.1	1:1.9	57
12	L-tartaric acid (20)	3.4	0.1	1:1.8	42
13	MeSO$_3$H (20)	−0.6	0.1	–	–
14	Ac$_2$O (20)	–	0.1	1:4.6	61[g]

[a] Reaction conditions: **1a** (0.2 mmol), Cu(OTf)$_2$ (10 mol%), **2a** (5 equiv), T$^+$BF$_4^-$ (1.2 equiv), and the corresponding additive in dry CH$_2$Cl$_2$ at room temperature. [b] Diastereomeric ratio determined by ^{1}H NMR spectroscopy. [c] Yield after column chromatography. [d] 1-Isochromanone (**4**) was also obtained in 10–20% yield. [e] n.d.: not determined. [f] Bn: benzyl. [g] Three equivalents of **2a** were used (same yield was obtained with five equivalents of aldehyde).

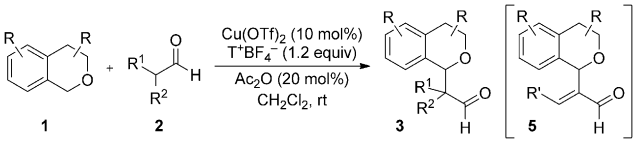
the over-oxidized compound 1-isochromanone (**4**). The combination of Cu(OTf)$_2$ and T$^+$BF$_4^-$ proved to be crucial for achieving this transformation. Other transition-metal catalysts,[14] as well as other oxidants like DDQ, *t*BuOOH, (*t*BuO)$_2$, and H$_2$O$_2$, were less efficient or gave no product at all. However, **3a** was obtained as a racemic mixture under these initial reaction conditions. In fact, without the MacMillan catalyst, the product **3a** was formed in 18% yield (Table 1, entry 1), which indicated that the aldehyde probably reacts through the enol/enolate form rather than the enamine.

In our previous studies, the use of a catalytic amount of TFA had a beneficial effect on the reaction rate. Therefore, several organic acids were next screened as additives. Each of the acids used were competitive; however, methanesulfonic acid[6b] gave no product (Table 1, entry 13). TFA, aspartic acid, and, more interestingly, the nonacidic and inexpensive acetic anhydride (Ac$_2$O) gave the best results. Thus, the coupling compound **3a** was obtained in comparable good yields of 58–61% (Table 1, entries 7, 10, and 14). Additionally, the use of Ac$_2$O (20 mol%) allowed us to reduce the amount of aldehyde to three equivalents with the same good efficiency being maintained. Additionally, no formation of the oxidized byproduct **4** was observed if Ac$_2$O was used as the additive.

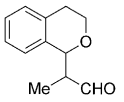
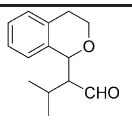
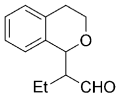
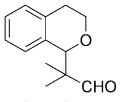
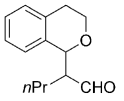
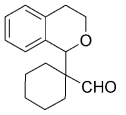
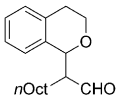
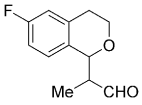
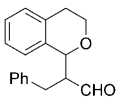
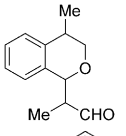
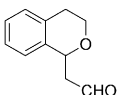
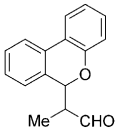
With the optimized conditions in hand (10 mol% $Cu(OTf)_2$, 20 mol% Ac_2O, 1.2 equiv of $T^+BF_4^-$, and 3 equiv of aldehyde in CH_2Cl_2 at room temperature), the substrate scope of the reaction was investigated (Table 2). Firstly, a variety of linear aliphatic aldehydes (R^1: H; R^2: Me, Et, *n*Pr, *n*Octyl, Bn) were treated with isochromane (Table 2, entries 1–5). The desired products **3a–e** were obtained in moderate to good yields (51–75%). Interestingly, the best result was obtained by scaling up the reaction from 0.2 mmol to 1.0 mmol. As a result, in the reaction of **1a** with **2a**, the α-functionalized aldehyde **3a** was obtained in a significantly improved 75% yield (Table 2, entry 1). The same effect was observed for **3c** and **3f** (Table 2, entries 3 and 6). The reaction with highly reactive and unstable acetaldehyde was also successfully accomplished, to provide the corresponding coupling product **3f** in 45–59% yield (Table 2, entry 6). However, the use of a larger amount of aldehyde (10 equiv) was required. A sterically hindered branched aliphatic aldehyde, isovaleraldehyde (R^1=H, R^2= *i*Pr), also proved to be a suitable partner, leading to the functionalized product **3g** in a good 52% yield (Table 2, entry 7). The more challenging formation of quaternary carbon centers was next explored. Consequently, five equivalents of α-disubstituted aldehydes **2h** (R^1, R^2=Me) and **2i** (R^1, R^2=cyclohexyl) were employed to furnish the desired products in 65 and 53% yields, respectively (Table 2, entries 8 and 9). Finally, substituted isochromanes **1b** and **1c**, and 6*H*-benzo[*c*]chromene **1d** were allowed to react with **2a**, to provide the corresponding α-functionalized aldehydes in similar yields (46–55%; Table 2, entries 10–12). Although the use of Ac_2O as an additive suppressed or minimized the oxidation to 1-oxo compounds, byproduct **5** was obtained in around 10% yield in a few cases (Table 2, entries 2 and 11). The formation of **5** can be explained by a further oxidation of **3** under the employed oxidative reaction conditions to form a conjugated system.

To generalize the procedure for the reaction with carbonyl compounds, ketones were next tested (Scheme 3). In this case, the use of TFA (20 mol%) and a catalytic amount of water (10 mol%) were crucial to achieve the desired transformation efficiently, although the exact role of water in this reaction is still unclear. Alkyl–alkyl and alkyl–aryl ketones underwent the CDC reaction to furnish the products in 43–54% yield.[15] When unsymmetrical 2-butanone was treated

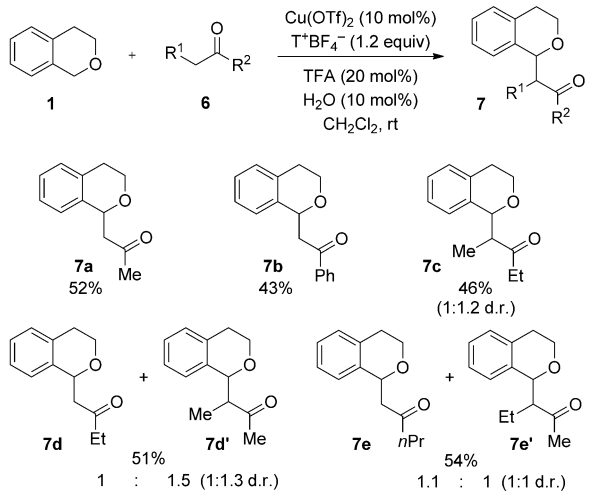
Table 2. Scope of the CDC reaction with aliphatic aldehydes.[a]



1 2 3 5

Entry	1	R^1/R^2	Product 3		d.r.[b]	Yield of 3 [%][c]	Entry	1	R^1/R^2	Product 3		d.r.[b]	Yield of 3 [%][c]
1	**1a**	Me/H		**3a**	1:4.6	61 (75)[d]	7	**1a**	*i*Pr/H		**3g**	1:4.3	52
2	**1a**	Et/H		**3b**	1:1.6	55[e]	8	**1a**	Me/Me		**3h**	–	65[g]
3	**1a**	*n*Pr/H		**3c**	1:1.6	64 (73)[d]	9	**1a**	Cy[h]		**3i**	–	53[g,i]
4	**1a**	*n*Octyl/H		**3d**	1:1.4	51	10	**1b**	Me/H		**3j**	1:3.6	55
5	**1a**	Bn/H		**3e**	1:1.9	53	11	**1c**	Me/H		**3k**	1:2:3:5.3	52[j]
6	**1a**	H/H		**3f**	–	45[f] (59)[d]	12	**1d**	Me/H		**3l**	1:1	46[k]

[a] Reaction conditions: **1** (0.2 mmol), $Cu(OTf)_2$ (10 mol%), Ac_2O (20 mol%), **2** (3 equiv), and $T^+BF_4^-$ (1.2 equiv) in dry CH_2Cl_2 at room temperature. [b] Diastereomeric ratio determined by ^1H NMR spectroscopy. [c] Yield after column chromatography. [d] Yield from the 1 mmol scale reaction in brackets. [e] 12% of **5c** was isolated. [f] Ten equivalents of **2b** were used. [g] Five equivalents of **2h** were used. [h] Cy: cyclohexyl. [i] TFA (20 mol%) was used instead of Ac_2O. [j] 12% of **5k** was isolated. [k] Significant amounts of the corresponding 1-oxo compound were detected by GC-MS.



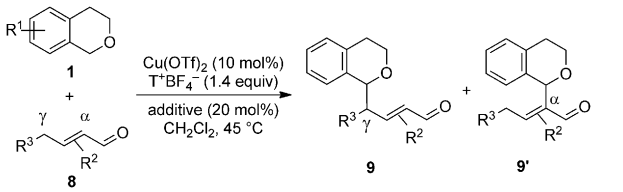
Scheme 3. $T^+BF_4^-$-mediated CDC reaction with ketones.

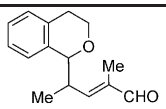
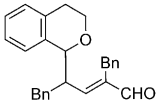
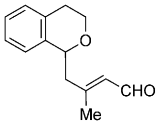
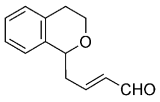
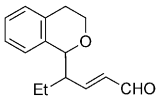
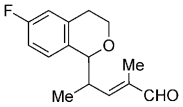
with isochromane, a 1:1.5 mixture of regioisomers was obtained, in which the major isomer was the coupling product at the more substituted carbon atom. On the other hand, 2-pentanone gave a 1.1:1 mixture of regioisomers.

The more appealing reaction with α,β-unsaturated aldehydes was next explored. Although enals, which are in equilibrium with their dienol forms, can be alkylated by the in situ formed oxonium ion of isochromanes at both the α and γ positions, we explored an unprecedented CDC γ alkylation under the given reaction conditions for the aliphatic aldehydes.[16] Therefore, 2-methyl-2-pentenal (**8a**) was initially submitted to the reaction with isochromane. To our delight, under slightly modified conditions, the desired γ-alkylation product was selectively formed. Thus, **9a** was obtained in a satisfying 47% yield by increasing the amount of oxidant $T^+BF_4^-$ to 1.4 equivalents and carrying out the reaction at 45°C in the presence of 20 mol% of Ac_2O (Table 3, entry 1). Selected α,β-unsaturated aldehydes were then tested and gave the corresponding alkylated compounds in moderate yields. In some cases, the use of TFA as an additive instead of Ac_2O gave slightly better results. Remarkably, α-branched (R^2 = Me, Bn) and β-substituted (R^2 = Me) enals gave exclusively the γ-alkylation products **9** (Table 3, entries 1–3 and 6). Good to excellent selectivities in favor of γ- rather than α-alkylation were obtained for enals lacking a substituent at the double bond (Table 3, entries 4 and 5). Additionally, in the case of the α-alkylated products, the conjugated compounds **9′** were obtained as the only detectable isomers.

The application of the methodology to the synthesis of potential bioactive compounds was next accomplished (Scheme 4). A two-step approach consisting of a CDC reaction and a reductive amination sequence was utilized. The second step was carried out by using $NaBH_3CN$ (2 equiv) as a reducing agent with an excess of cyclic amines such as morpholine or piperidine.[17] This methodology allows the easy structural variation of this class of compounds. Consequently, a small family of aminoisochromanes (**10**–**12**) was

Table 3. CDC reaction with α,β-unsaturated aldehydes.[a]



Entry	1	R^2/R^3	Product 9		d.r. 9[b]	9/9′[b]	Yield [%][c]
1	**1a**	α-Me/Me		**9a**	1:1.1	–	47[d,e]
2	**1a**	α-Bn/Bn		**9b**	1:1.2	–	44[f]
3	**1a**	β-Me/H		**9c**	1:1.4	–[g]	39[d]
4	**1a**	H/H		**9d**	–	(6.7:1)	35[f,h]
5	**1a**	H/Et		**9e**	1:1.1	(12:1)	36[f]
6	**1a**	α-Me/Me		**9f**	1:1.2	–	40[d]

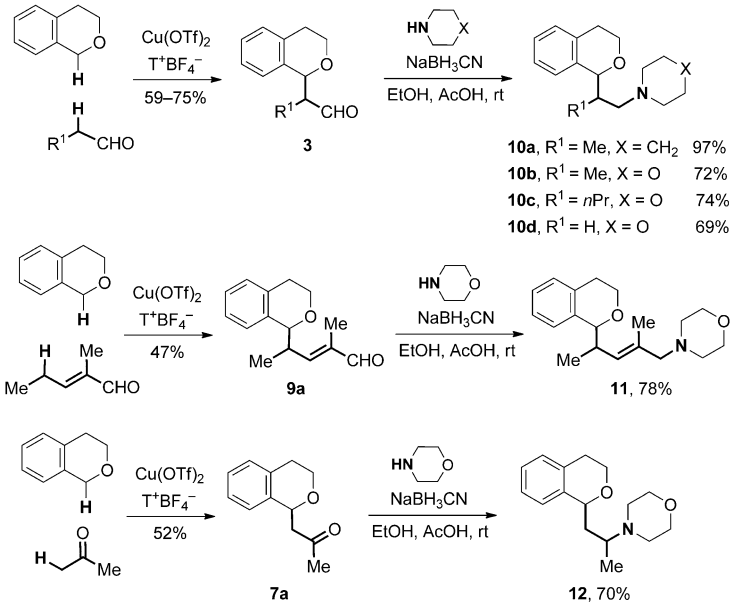
[a] Reaction conditions: **1** (0.2 mmol), $Cu(OTf)_2$ (10 mol%), additive (20 mol%), **8** (5 equiv), and $T^+BF_4^-$ (1.4 equiv) in dry CH_2Cl_2 at 45°C. [b] Diasteriomeric ratios and **9**/**9′** ratios determined by ^1H NMR spectroscopy. [c] Yield after column chromatography. [d] Ac_2O was used as the additive. [e] The reaction on the 1 mmol scale gave the same yield. [f] TFA was used as the additive. [g] The formation of the α-alkylation product was not observed. [h] Ten equivalents of aldehyde were used.

prepared from simple and commercially available isochromane and alkyl or α,β-unsaturated aldehydes and ketones such as acetone.

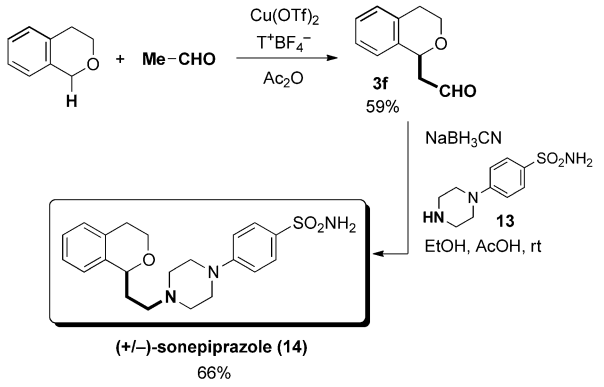
Finally, the racemic synthesis of the dopamine antagonist sonepiprazole was carried out (Scheme 5). The CDC product of acetaldehyde with isochromane, **3f**, was subjected to the reductive amination reaction with the appropriate substituted piperazine **13**.[18] In this case, we were able to reduce the amount of amine to 1.5 equivalents and obtain sonepiprazole (**14**) in a good 66% yield.

Conclusion

In summary, we have developed a general procedure that allows the CDC reaction of cyclic benzyl ethers with a variety of simple carbonyl compounds like aliphatic aldehydes, enals, and ketones. The use of an oxoammonium salt as the formal hydrogen acceptor in combination with $Cu(OTf)_2$ as



Scheme 4. Modular synthesis of aminoisochromane derivatives.



Scheme 5. Synthesis of (+/−)-sonepiprazole by a CDC/reductive-amination sequence.

the catalyst is key for the success of this transformation. Moreover, additives, such as organic acids like TFA or anhydrides such Ac_2O, facilitate the reaction in terms of efficiency and selectivity. Remarkably, in the case of α,β-unsaturated aldehydes, good to excellent selectivities were obtained in the challenging γ-alkylation reaction. Lastly, we applied this methodology for the modular and straightforward preparation of a family of aminoisochromane derivatives, including the known bioactive compound sonepiprazole, by a CDC/reductive-amination sequence.

Experimental Section

General methods and materials: All reactions were carried out in heat-gun-dried glassware under an argon atmosphere. Dichloromethane was distilled over CaH_2. ^1H, ^{13}C, and ^{19}F NMR spectra were recorded in $CDCl_3$ (reference signals: $\delta(^1H)=7.26$ ppm, $\delta(^{13}C)=77.16$ ppm) on Bruker ARX-300 and Varian AV-300 or AV-400 MHz spectrometers. Chemical shifts (δ) are given in ppm and spin–spin coupling constants (J) are given in Hz. Analytical thin-layer chromatography was performed by using silica gel 60 F_{254}, and a solution of $KMnO_4$ served as staining agent. Column chromatography was performed on silica gel 60 (0.040–0.063 mm) or ALOX N (neutral). Exact masses (HRMS) were recorded on a Bruker Daltonics MicroTof spectrometer (CH_3OH as the sample solvent). Reactions were conducted under an argon atmosphere, and aldehydes were freshly distilled before use. Analytical grade solvents and other commercially available reagents were used without further purification. $TEMPO^+BF_4^-$,[13] isochromanes **1b** and **1c**,[19] 6H-benzochromene **1d**,[20] α,β-unsaturated aldehyde **9b**,[21] and piperazine **13**[18] were prepared following literature procedures.

General procedure for the alkylation of aldehydes: $T^+BF_4^-$ (0.24–0.28 mmol) was added to a mixture of **1** (0.2 mmol), aldehyde **2** or **8** (0.6–2.0 mmol), $Cu(OTf)_2$ (7.2 mg, 0.02 mmol), and TFA or Ac_2O (0.04 mmol) in dry CH_2Cl_2 (2.0 mL). The reaction mixture was stirred for 16–32 h at room temperature (aliphatic aldehydes) or 45 °C (α,β-unsaturated aldehydes). After the starting material had been consumed (monitored by GC-MS or TLC), the solvent was concentrated under reduced pressure and the residue was purified by column chromatography on silica gel.

Alkylation of ketones 6: A slightly modification of the above-described procedure was used for the alkylation of ketones **6**. The reaction mixture comprised **1** (0.20 mmol), ketone **6** (0.6–1.0 mmol), $Cu(OTf)_2$ (0.02 mmol), TFA (0.04 mmol), H_2O (0.02 mmol), and $T^+BF_4^-$ (0.24 mmol) in dry CH_2Cl_2 (2.0 mL) at room temperature.

2-(Isochroman-1-yl)propanal (3a): Following the general procedure, the reaction of **1a** (25 μL, 0.2 mmol) with **2a** (44 μL, 0.6 mmol) in the presence of $Cu(OTf)_2$ and Ac_2O gave **3a** as a colorless oil with a 1:4.6 mixture of diastereoisomers (23 mg, 61%). The reaction on the 1 mmol scale gave **3a** in 75% yield: Chromatography eluent: pentane/ethyl acetate (30:1); ^1H NMR (300 MHz, $CDCl_3$): $\delta=9.90$ (d, $J=0.4$ Hz, 1H major), 9.53 (d, $J=1.1$ Hz, 1H minor), 7.25–7.10 (m, 3H major and 3H minor), 7.07–7.02 (m, 1H major and 1H minor), 5.43 (d, $J=1.1$ Hz, 1H major), 5.01 (d, $J=1.1$ Hz, 1H minor), 4.18 (ddd, $J=11.2$, 5.7, 1.9 Hz, 1H minor), 4.15 (ddd, $J=11.1$, 5.7, 1.4 Hz, 1H major), 3.76–3.69 (m, 1H minor), 3.73 (td, $J=11.5$, 2.9 Hz, 1H major), 3.11–2.97 (m, 1H major and 1H minor), 2.88 (qd, $J=6.9$, 2.7 Hz, 1H major), 2.65 (d, $J=16.3$ Hz, 1H minor), 2.59 (d, $J=16.3$ Hz, 1H major), 1.30 (d, $J=7.0$ Hz, 3H minor), 0.95 ppm (d, $J=6.9$ Hz, 3H major); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=204.2$, 204.0, 135.8, 135.3, 135.2, 134.8, 129.4, 129.3, 127.0, 126.8, 126.7, 126.6, 124.9, 124.3, 75.6, 64.6, 51.7, 51.6, 29.3, 29.1, 11.5, 7.0 ppm; HRMS (ESI): calcd for $C_{12}H_{14}O_2{\cdot}Na^+$: 213.0886 $[M+Na]^+$; found: 213.0883.

General procedure for the reductive amination:[17] The appropriate secondary amine (1.5–10 equiv) and $NaBH_3CN$ (2 equiv) were added to a solution of the corresponding aldehyde **3**, **7**, or **9** (0.2 mmol, 1 equiv) in ethanol (1.0 mL) at room temperature. The pH value was maintained at 6 with dropwise addition of acetic acid while the mixture was stirred. The reaction was monitored by TLC until completion (typically after 2 h). NaOMe (0.1 equiv) was added, and the reaction mixture was stirred at room temperature overnight. The mixture was concentrated and was basified with a 2 M NaOH solution. The aqueous layer was extracted with CH_2Cl_2, and the organic phase was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography on ALOX N (neutral).

***rac*-Sonepiprazole (4-(4-(2-(Isochroman-1-yl)ethyl)piperazin-1-yl)benzenesulfonamide; 14)**:[11e] Following the general procedure, the reaction of **3f** (20 mg, 0.11 mmol) with **13** (1.5 equiv, 41.1 mg, 1.7 mmol) gave **14** as a white solid (29.1 mg, 66%); Chromatography on silica gel with ethyl acetate as the eluent; ^1H NMR (300 MHz, $[D_6]$DMSO): $\delta=7.61$ (d, $J=9.0$ Hz, 2H), 7.24–7.07 (m, 4H), 7.05 (s, 2H), 7.01 (d, $J=9.1$ Hz, 2H), 4.76 (dd, $J=8.3$, 2.0 Hz, 1H), 4.04 (ddd, $J=11.2$, 5.2, 4.0 Hz, 1H), 3.66 (ddd, $J=11.3$, 9.2, 4.0 Hz, 1H), 3.26 (t, $J=4.6$ Hz, 4H), 2.86 (ddd, $J=14.9$, 9.1, 5.4 Hz, 1H), 2.65 (dt, $J=16.4$, 3.8 Hz, 1H), 2.60–2.45 (m, 5H), 2.44–2.32 (m, 1H), 2.18–2.03 (m, 1H), 1.96–1.79 ppm (m, 1H); ^{13}C NMR (75 MHz, $[D_6]$DMSO): $\delta=152.8$, 138.1, 133.6, 132.8, 128.7, 127.1, 126.1,

126.0, 124.8, 113.6, 73.6, 62.3, 54.2, 52.6, 47.1, 32.6, 28.5 ppm; HRMS (ESI$^+$): calcd for $C_{21}H_{27}N_3O_3S{\cdot}H^+$: 402.1846; found: 402.1856.

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[1] a) *Handbook of C–H Transformations* (Ed.: G. Dyker), Wiley-VCH, Weinheim, **2005**; b) A. R. Dick, M. S. Sanford, *Tetrahedron* **2006**, *62*, 2439–2463; c) *Topics in Current Chemistry, Vol. 292: C–H Activation* (Eds.: J.-Q. Yu, Z. J. Shi), Springer, Heidelberg, **2010**; d) H. M. L. Davies, J. Du Bois, J.-Q. Yu, *Chem. Soc. Rev.* **2011**, *40*, 1855–1856; e) L. Ackermann, *Chem. Rev.* **2011**, *111*, 1315–1345.

[2] For selected reviews on CDC, see: a) C.-J. Li, Z. Li, *Pure Appl. Chem.* **2006**, *78*, 935–945; b) C. J. Li, *Acc. Chem. Res.* **2009**, *42*, 335–344; c) C. J. Scheuermann, *Chem. Asian J.* **2010**, *5*, 436–451; d) M. Klussmann, D. Sureshkumar, *Synthesis* **2011**, 353–369; e) C. Liu, H. Zhang, W. Shi, A. Lei, *Chem. Rev.* **2011**, *111*, 1780–1824; f) C. S. Yeung, V. M. Dong, *Chem. Rev.* **2011**, *111*, 1215–1292. For the seminal work of C.-J. Li, see: g) Z. Li, C.-J. Li, *J. Am. Chem. Soc.* **2005**, *127*, 3672–3673; h) Z. Li, C.-J. Li, *J. Am. Chem. Soc.* **2006**, *128*, 56–57.

[3] H. Richter, O. García Mancheño, *Eur. J. Org. Chem.* **2010**, 4460–4467.

[4] For a comprehensive review on oxoammonium chemistry, see: a) J. M. Bobbitt, C. Brückner, N. Merbouh in *Organic Reactions, Vol. 74* (Ed.: S. E. Denmark), Wiley, New York, **2009**, pp. 103–424. For some recent examples, see: b) W. F. Bailey, J. M. Bobbitt, K. B. Wiberg, *J. Org. Chem.* **2007**, *72*, 4504–4509; c) T. Vogler, A. Studer, *Synthesis* **2008**, 1979–1993; d) C.-X. Miao, L.-N. He, J.-Q. Wang, J.-L. Wang, *Adv. Synth. Catal.* **2009**, *351*, 2209–2216; e) S.-M. Ma, J.-X. Liu, S.-H. Li, B. Chen, J.-J. Cheng, J.-Q. Kuang, Y. Liu, B.-Q. Wan, Y. Wang, J.-T. Ye, Q. Yu, W.-M. Yuan, S.-C. Yu, *Adv. Synth. Catal.* **2011**, *353*, 1005–1017, and references therein.

[5] a) Y. Zhang, C. J. Li, *J. Am. Chem. Soc.* **2006**, *128*, 4242–4243; b) W. J. Yoo, C. A. Correia, Y. H. Zhang, C. J. Li, *Synlett* **2009**, 138–142.

[6] a) A. Sud, D. Sureshkumar, M. Klussmann, *Chem. Commun.* **2009**, *21*, 3169–3171; b) Á. Pintér, A. Sud, D. Sureshkumar, M. Klussmann, *Angew. Chem.* **2010**, *122*, 5124–5128; *Angew. Chem. Int. Ed.* **2010**, *49*, 5004–5007.

[7] a) J. Xie, Z.-Z. Huang, *Angew. Chem. Int. Ed.* **2010**, *49*, 10181–10185; b) F. Yang, J. Li, J. Xie, Z.-Z. Huang, *Org. Lett.* **2010**, *12*, 5214–5217.

[8] F. Benfatti, M. Guiteras Capdevila, L. Zoli, E. Benedetto, P. G. Cozzi, *Chem. Commun.* **2009**, 5919–5921.

[9] For methodic kinetic studies with carbocations, see, for example: a) H. Mayr, B. Kempf, A. R. Ofial, *Acc. Chem. Res.* **2003**, *36*, 66–77; b) R. Kempf, N. Hampel, A. R. Ofial, H. Mayr, *Chem. Eur. J.* **2003**, *9*, 2209–2218; c) T. B. Phan, C. Nolte, S. Kobayashi, A. R. Ofial, H. Mayr, *J. Am. Chem. Soc.* **2009**, *131*, 11392–11401.

[10] For CDC in α C–H bond functionalization of isochromanes, see, for example: a) Y.-C. Xu, C. Roy, E. Lebeau, *Tetrahedron Lett.* **1993**, *34*, 8189–8192; b) Y.-C. Xu, D. T. Kohlman, S. X. Liang, C. Erikkson, *Org. Lett.* **1999**, *1*, 1599–1602; c) Y. Zhang, C.-J. Li, *Angew. Chem.* **2006**, *118*, 1983–1986; *Angew. Chem. Int. Ed.* **2006**, *45*, 1949–1952. See also references [2, 3, 5].

[11] See, for example: a) K. M. Merchant, G. S. Gill, D. W. Harris, R. M. Huff, M. J. Eaton, K. Lookingland, B. S. Lutzke, R. B. Mccall, M. F. Piercey, P. J. Schreur, V. H. Sethy, M. W. Smith, K. A. Svensson, A. H. Tang, P. F. Vonvoigtlander, R. E. Tenbrink, *J. Pharm. Exp. Therap.* **1996**, *279*, 1392–1403; b) M. D. Ennis, N. B. Ghazal, R. L. Hoffman, M. W. Smith, S. K. Schlachter, C. F. Lawson, W. B. Im, J. F. Pregenzer, K. A. Svensson, R. A. Lewis, E. D. Hall, D. M. Sutter, L. T. Harris, R. B. McCall, *J. Med. Chem.* **1998**, *41*, 2180–2183; c) M. Combourieu, J. C. Laigle (AkzoNobel), Eur. Pat. Appl., EP 450689A1 19911009, **1991**; d) J. Hu, W. Fan, L. Zhou, Y. Zhao, J. Zhou, *Bull. Korean Chem. Soc.* **2010**, *31*, 3025–3026. See also: e) R. E. TenBrink, C. L. Bergh, J. N. Duncan, D. W. Harris, R. M. Huff, R. A. Lahti, C. F. Lawson, B. S. Lutzke, I. J. Martin, S. A. Rees, S. K. Schlachter, J. C. Sih, M. W. Smith, *J. Med. Chem.* **1996**, *39*, 2435–2437; f) E. L. Larghi, T. S. Kaufman, *Synthesis* **2006**, 187–220; g) G. Kerti, T. Kurtán, K. E. Kövér, S. Sólyom, I. Greiner, S. Antus, *Tetrahedron: Asymmetry* **2010**, *21*, 2356–2360.

[12] For a recent review on enamine catalysis, see: S. Mukherjee, J. W. Yang, S. Hoffmann, B. List, *Chem. Rev.* **2007**, *107*, 5471–5569.

[13] Oxoammonium salt $T^+BF_4^-$ was prepared from TEMPO and BF_4H according to the literature reports: Y. Yonekuta, K. Oyaizu, H. Nishide, *Chem. Lett.* **2007**, *36*, 866–867. See also references [3, 4a].

[14] Lewis acid metal catalysts like $Fe(OTf)_2$, $Al(OTf)_3$, $Sm(OTf)_3$, $Zn(OTf)_2$, and $Yb(OTf)_3$ provided the desired product **3a** in relatively lower yields. CuBr, CuCl, $CuCl_2$, $CuOTf{\cdot}1/2\,C_6H_6$, and $FeCl_3$ were not active or gave only traces of the desired product.

[15] Due to the required presence of water in the reaction mixture, 1-isochromanone (**4**) was formed as the major byproduct in 10–20% yield. For related alternative reactions of benzyl ethers with H_2O by using TEMPO salts as oxidants, see: P. P. Pradhan, J. M. Bobbitt, W. F. Bailey, *J. Org. Chem.* **2009**, *74*, 9524–9527.

[16] According to the vinylogy principle, γ-enolizable α,β-unsaturated carbonyl compounds can act as nucleophilic dienolates: a) R. C. Fuson, *Chem. Rev.* **1935**, *16*, 1–27. For recent examples on organocatalyzed S_N1-type γ alkylation of α,β-unsaturated aldehydes by using secondary alcohols, see: b) G. Bergonzini, S. Vera, P. Melchiorre, *Angew. Chem.* **2010**, *122*, 9879–9882; *Angew. Chem. Int. Ed.* **2010**, *49*, 9685–9688; c) J. Stiller, E. Marqués-López, R. P. Herrera, R. Fröhlich, C. Strohmann, M. Christmann, *Org. Lett.* **2011**, *13*, 70–73.

[17] See, for example: P. E. Persons, J. P. Mayer, D. E. Nichols, J. M. Cassady, E. B. Smalstig, J. A. Clemens, *Eur. J. Med. Chem.* **1991**, *26*, 473–475.

[18] 4-(1-Piperazinyl)benzenesulfonamide (**13**) was prepared following the literature procedure: a) I. Miyazaki, S. Simizu, K. Ishida, H. Osada, *ChemBioChem* **2009**, *10*, 838–843. Alternatively, the coupling of 4-bromobenzenesulfonamide with piperazine in boiling dimethoxyethane was performed; however, low conversion values were observed (17% of **13** and quantitative reisolation of the bromide).

[19] D. L. Mohler, D. W. Thompson, *Tetrahedron Lett.* **1987**, *28*, 2567–2570.

[20] L.-C. Campeau, M. Parisien, A. Jean, K. Fagnou, *J. Am. Chem. Soc.* **2006**, *128*, 581–590.

[21] A. Erkkilä, P. M. Pihko, *Eur. J. Org. Chem.* **2007**, 4205–4216.

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