Nucleophilic Reactions

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Trichloromethyl Ketones as Synthetically Versatile Donors: Application in Direct Catalytic Mannich-Type Reactions and the Stereoselective Synthesis of Azetidines**

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The catalytic generation of metal enolates in situ and their use in stereoselective carbon–carbon bond-forming reactions are subjects of vigorous current research.[1] This strategy is superior in terms of atom economy to conventional methods that employ stoichiometric amounts of strong base.[2] Although various metal catalysts have proven effective in this regard, and enantioselective variants have been reported during the last decade, nucleophiles have been mostly limited to ketones.[3] Catalytic generation in situ of metal enolates derived from carboxylic acid derivatives is still a formidable task owing to the high pK_a value of the α protons. The development of a suitably activated carboxylic acid derivative and/or a new catalyst capable of promoting catalytic ester enolate formation in situ would thus be of considerable significance. Recently, Evans et al. reported highly diastereo-

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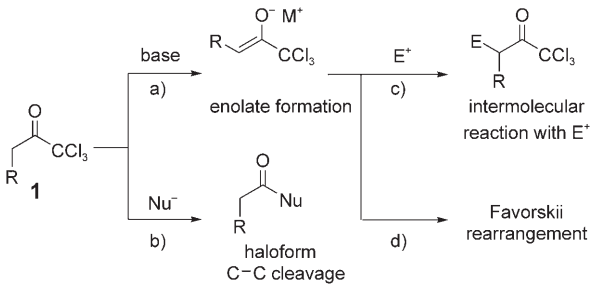
and enantioselective catalytic aldol reactions by using *N*-acyloxazolidinones and *N*-acylthiazolidinethiones as donors.[4] Shair and co-workers have also developed remarkable diastereo- and enantioselective aldol reactions with malonic acid half-thioesters.[5] We have in turn contributed an aldol reaction with nitriles.[6] On the other hand, methods applicable to the direct Mannich-type reaction[1b] of ester-equivalent donors are rare. We previously reported the use of an *N*-acylpyrrole as an ester-equivalent donor in Mannich-type reactions;[7] however, the reaction was limited to an α-hydroxy-substituted nucleophile. A direct catalytic Mannich-type reaction with an alkyl-substituted ester-equivalent donor has not been reported.[8] Herein we investigate the utility of trichloromethyl ketones **1** (Scheme 1) as Mannich donors. A catalytic amount of *p*-MeO-C_6H_4OLi promotes the direct Mannich-type reaction of **1** with high diastereoselectivity (*syn*/*anti* = 6:1–> 20:1) and in good yield (up to 96%). Trichloromethyl ketones not only serve as ester and amide synthetic equivalents, but also enable unique transformations. Conversions of Mannich adducts, including the stereoselective synthesis of trisubstituted azetidine-2-carboxylates, are demonstrated herein.

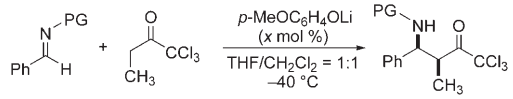
Trichloromethyl carbinols[9] and trichloromethyl ketones[10] are versatile building blocks in synthesis. The trichloromethyl group is a good leaving group;[11] thus, trichloromethyl ketones can be readily converted into carboxylic acids,[10a] esters,[10b] and amides.[10c] Furthermore, the strong inductive effect of the trichloromethyl group lowers the pK_a value of the α protons of trichloromethyl ketones sufficiently to allow catalytic deprotonation. These properties make **1** a promising ester-equivalent donor. Nonetheless, to our knowledge, there are no reports of **1** being used for stereoselective intermolecular carbon–carbon bond-forming reactions, probably owing to stability problems under basic conditions.[12] The requisite selectivities for utilizing enolates of **1** are summarized in Scheme 1. Careful selection of base and reaction conditions is important to promote the desired catalytic enolate formation a) while preventing undesired haloform C–C bond cleavage[10] b). It is well-known that Favorskii rearrangements of trichloromethyl ketones readily proceed under basic conditions.[13] Therefore, the desired intermolecular reaction with electrophiles c) must proceed faster than intramolecular Favorskii rearrangement d). We hypothesized that, in the presence of a suitably activated electrophile, the intermolecular path c) could be favored because the Favorskii rearrangement generates a strained cyclopropanone intermediate.



Scheme 1. Possible reaction pathways of trichloromethyl ketones under basic conditions.

We investigated Mannich-type reactions of trichloromethyl ketone **1a**[14] with imines **2a–d** bearing different protecting groups (Table 1, entries 1–4) at −40 °C in the presence of *p*-MeO-C_6H_4OLi (10 mol%) as a base.[15] With **2a** and **2b**, no Mannich adduct was observed (Table 1, entries 1 and 2). Imines **2c** and **2d**, which bear electron-withdrawing substituents, produced the desired Mannich adducts in good yield and with high *syn* selectivity (Table 1, entry 3: 12 h, 95% yield, *syn*/*anti* = 14:1; entry 4: 1 h, 88% yield, *syn*/*anti* > 20:1). Because the *N*-diphenylphosphinoyl (*N*-Dpp) imine **2d** had the best reactivity and *syn* selectivity,[16] it was used for further optimization. As shown in Table 1, entries 5 and 6, 3-Å molecular sieves were effective in allowing the molar excess of **1a** to be decreased while maintaining high reaction yield. The reaction of **1a** (2 equiv) proceeded smoothly in the presence of 3-Å molecular sieves, affording the Mannich adduct **3da** after 3 h in 96% yield with an excellent d.r. (> 20:1). The reaction proceeded equally well with only 5 mol% of base (Table 1, entry 7). The success of the Mannich reaction with 5–10 mol% catalyst loading implies that side reactions such as the Favorskii rearrangement, which quenches catalytic base by production of HCl, are negligible.

Table 1: Optimization of reaction conditions.

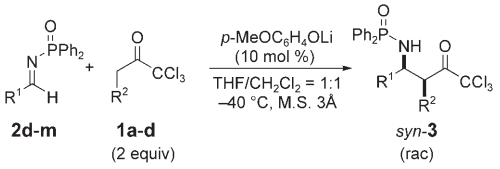


Entry	PG (imine)	Catalyst [mol%]	**1a** [equiv]	Additive	*t* [h]	Yield [%][a]	Product	*syn*/*anti*[b]
1	Bn (**2a**)	10	5	–	24	0	**3aa**	–
2	*p*-$MeOC_6H_4$ (**2b**)	10	5	–	24	0	**3ba**	–
3	*p*-Ts (**2c**)	10	5	–	12	95	**3ca**	14:1
4	$Ph_2P(O)$ (**2d**)	10	5	–	1	88	**3da**	> 20:1
5	$Ph_2P(O)$ (**2d**)	10	2	–	3	84	**3da**	> 20:1
6	$Ph_2P(O)$ (**2d**)	10	2	M.S. 3 A[c]	3	96	**3da**	> 20:1
7	$Ph_2P(O)$ (**2d**)	5	2	M.S. 3 A[c]	3	95	**3da**	> 20:1

[a] Yield of isolated product. [b] Determined by ^{1}H NMR spectroscopic analysis. [c] 200 mg mmol^{-1} of **2d** was used. M.S. 3 A = 3-Å molecular sieves, PG = protecting group.

As summarized in Table 2, Mannich-type reactions proceeded well using various aryl (Table 2, entries 1–4), heteroaryl (Table 2, entries 5–6), alkenyl (Table 2, entry 7), and alkyl[17] *N*-Dpp imines (Table 2, entries 8–10). In all examples, the reactions were complete within 1–6 h, and good to excellent diastereoselectivity (*syn*/*anti* = 6:1–> 20:1)[18] was obtained. Notably, the reaction proceeded in good yield when using readily isomerizable aliphatic *N*-Dpp imines. The low pK_a value of **1a**, ascribed to the inductive effects of the

Table 2: Catalytic direct *syn*-selective Mannich-type reactions of trichloromethyl ketones **1a–1d** with *N*-Dpp imines **2d–2m**.[a]



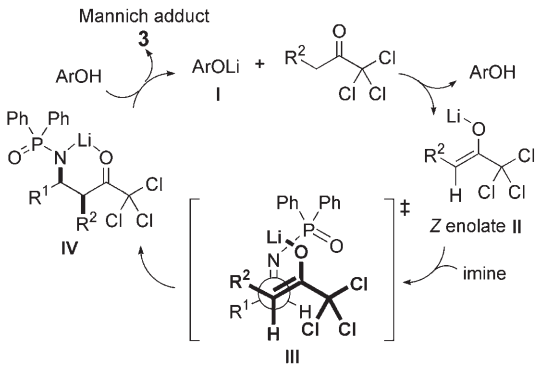
Entry	R^1 (Imine)	R^2 (**1**)	*t* [h]	Yield [%][b]	**3**	*syn*/*anti*[c]
1	Ph (**2d**)	CH_3 (**1a**)	3	96	**3da**	>20:1
2	*p*-Cl-C_6H_4 (**2e**)	CH_3 (**1a**)	4	93	**3ea**	>20:1
3	*p*-Me-C_6H_4 (**2f**)	CH_3 (**1a**)	6	89	**3fa**	>20:1[d]
4	*p*-$MeOC_6H_4$ (**2g**)	CH_3 (**1a**)	5	68	**3ga**	>20:1[d]
5	2-furyl (**2h**)	CH_3 (**1a**)	1	88	**3ha**	6:1
6	2-thienyl (**2i**)	CH_3 (**1a**)	2	89	**3ia**	8:1
7	(*E*)-PhCH=CH (**2j**)	CH_3 (**1a**)	1	81	**3ja**	7:1
8[e]	cyclohexyl (**2k**)	CH_3 (**1a**)	2	78	**3ka**	>20:1[d]
9[e]	$(CH_3)CHCH_2$ (**2l**)	CH_3 (**1a**)	3	71	**3la**	>20:1[d]
10[e]	*n*-Bu (**2m**)	CH_3 (**1a**)	3	73 (61)[f]	**3ma**	>20:1[d]
11[g]	Ph (**2d**)	CH_3CH_2 (**1b**)	2	87	**3db**	14:1
12[h]	Ph (**2d**)	$PhCH_2$ (**1c**)	6	90	**3dc**	>20:1
13	Ph (**2d**)	$BnO(CH_2)_2$ (**1d**)	1	89	**3dd**	11:1

[a] 2 equivalents of **1** was used unless otherwise noted. [b] Yield of isolated product after column chromatography unless otherwise noted. [c] Determined by ^{1}H NMR spectroscopic analysis of the crude mixture. [d] Minor isomer was not detected. [e] Reaction was performed in the absence of 3-Å molecular sieves using **1a** (5 equiv). [f] Product was isolated by crystallization ($CHCl_3$/hexane) without chromatography. [g] 3 equivalents of **1b** was used. [h] Reaction was performed at −60 °C.

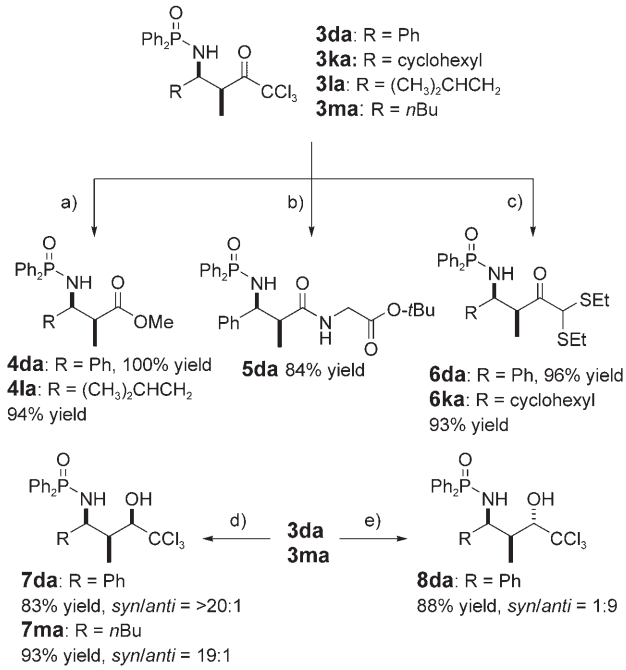
trichloromethyl group, allowed chemoselective nucleophilic activation. Furthermore, Mannich adducts are quite crystalline and can be isolated without chromatography after extractive workup. For example, diastereomerically pure **3ma** was isolated in 61% yield by crystallization of a crude mixture from $CHCl_3$/hexane (Table 2, entry 10). Besides **1a**, trichloromethyl ketones with longer side chains (**1b** and **1c**) and oxygen functionality (**1d**) were applied (Table 2, entries 11–13); they afforded Mannich adducts in 87–90% yield with good diastereoselectivity (11:1–>20:1). The Mannich-type reaction of **1c** was performed at −60 °C to prevent side reactions.

A postulated catalytic cycle and a transition-state model that explains the observed *syn* selectivity are illustrated in Scheme 2. *p*-MeO-C_6H_4OLi first deprotonates the α proton of **1**. Trichloromethyl ketones favor the formation of *Z* enolate **II** because of steric pressure from the bulky trichloromethyl group.[19] The observed high *syn* selectivity is accounted for by the *Z*-enolate transition state **III**. Protonation of **IV** by *p*-MeO-C_6H_4OH regenerates the catalyst and affords **3**.

The synthetic utility of the trichloromethyl ketone moiety was demonstrated by the transformations shown in Scheme 3. Mannich adducts **3da** and **3la** were readily converted into esters **4da** and **4la** in 100% and 94% yield, respectively, by treatment with NaOMe in MeOH for 15 min, during which no epimerization was observed. Treatment of **3da** with NaOH followed by coupling with Gly-O*t*Bu gave amide **5da** in 84%



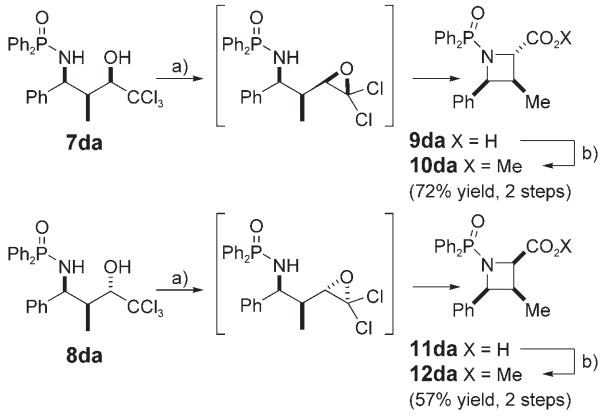
Scheme 2. Postulated catalytic cycle and transition-state model for *syn* selectivity.



Scheme 3. Transformations of the trichloromethyl ketone moiety. Reagents and conditions: a) NaOMe, MeOH, 0→25 °C, 15 min; b) 1. NaOH, THF/H_2O, 0 °C, 20 min; 2. Gly-O*t*Bu·HCl, HOAt, EDC·HCl, Et_3N, 0 °C→RT, 14 h; c) EtSLi, EtSH, THF, 0 °C, 15 min; d) $LiAl(OtBu)_3H$, THF/CH_2Cl_2, −40 °C, 5 h; e) $Zn(BH_4)_2$, THF/Et_2O, −78 to −40 °C, 16 h. EDC = 1-ethyl-3(3-dimethylaminopropyl)carbodiimide.

yield (two steps). The trichloromethyl ketone unit functions not only as a synthetic equivalent for esters and amides, but also as a unique template for further transformations. Treatment of **3da** and **3ka** with basic ethanethiol for 15 min afforded dithianes **6da** and **6ka** in 96% and 93% yield, respectively.[10d] In this case, the thiol acts as both a nucleophile and a reductant to give synthetically useful protected aldehydes. *syn*-Selective reduction of the Mannich adducts with $LiAl(O\text{-}tBu)_3H$ afforded the N-protected amino alcohols **7da** and **7ma**, whereas *anti*-selective reduction with $Zn(BH_4)_2$ afforded the N-protected amino alcohol **8da**.[20] The synthetic versatility of **7** and **8** can potentially be utilized in stereoselective transformations as reported by Corey and

Link.[9a,b] Furthermore, we also succeeded in the highly stereocontrolled synthesis of azetidines (Scheme 4). By treating **7da** with aqueous NaOH in 1,2-dimethoxyethane (DME), we obtained the azetidine-2-carboxylic acid **9da**. The



Scheme 4. Stereoselective synthesis of azetidines from trichloromethyl carbinols. Reagents and conditions: a) aq. NaOH, DME, 25 °C, 24 h; b) $TMSCHN_2$, MeOH/hexane, 25 °C. TMS = trimethylsilyl.

reaction is considered to proceed via a *gem*-dichlorooxirane intermediate.[9a] Intramolecular ring opening affords the azetidine ring. After conversion into the corresponding methyl esters, methyl azetidine-2-carboxylate **10da** was isolated in 72% yield (two steps).[21] From **8da**, *all-syn*-substituted methyl azetidine-2-carboxylate **12da** was obtained, albeit in moderate yield (57% in two steps). The relative configuration of **12da** was confirmed by single-crystal X-ray crystallographic analysis (Figure 1).[21,22] Because stereoselective syntheses of 3,4-*syn*-substituted azetidine-2-carboxylic acids, particularly sterically hindered *all-syn*-substituted azetidines, are rare, the present stereoselective method should prove useful to medicinal chemists studying nonnatural amino acid motifs.[23]

In summary, we successfully developed a chemoselective catalytic nucleophilic activation of trichloromethyl ketones and applied this method to intermolecular C–C bond-forming reactions. Direct Mannich-type additions of trichloromethyl ketones to various *N*-Dpp imines in the presence of catalytic amounts of a weak Brønsted base proceeded in good yield and high *syn* selectivity (62–96%, *syn*/*anti* = 6:1–>20:1). Transformations of the Mannich adducts formed were demonstrated, including a highly stereoselective synthesis of azetidines. Efforts toward the use of trichloromethyl ketones in conjunction with chiral catalysts in Mannich and other addition reactions are ongoing.

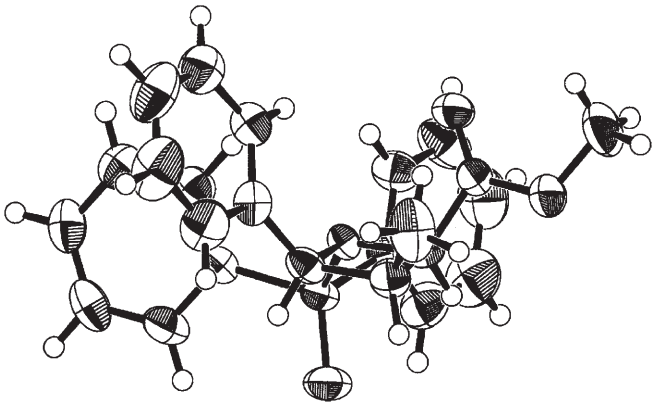


Figure 1. X-ray crystallographic structure of azetidine **12da**. Ellipsoids drawn at the 50% probability level.

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[20] The relative configuration of **8da** was determined by X-ray crystallographic analysis of the corresponding cyclic carbamate; see Supporting Information.

[21] For the determination of the relative configurations of **10da** and **12da**, see Supporting Information.

[22] CCDC 295183–295185 (**12da**, **3fa**, cyclic carbamate derived from **8da**, respectively) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[23] For the synthesis of azetidine-2-carboxylic acids (L-aze analogues) and their incorporation into peptides, see the review: a) F. Couty, G. Evano, D. Prim, *Mini-Rev. Org. Chem.* **2004**, *1*, 133, and references therein; for selected recent examples, see: b) D. Enders, J. Gries, *Synthesis* **2005**, 3508, and references therein; c) F. Couty, G. Evano, N. Rabasso, *Tetrahedron: Asymmetry* **2003**, *14*, 2407; d) S. Hanessian, N. Bernstein, R.-Y. Yang, R. Maguire, *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1437; e) A. P. Kozikowski, Y. Liao, W. Tückmantel, S. Wang, S. Pshenichkin, A. Surin, C. Thomsen, J. T. Wroblewski, *Bioorg. Med. Chem. Lett.* **1996**, *6*, 2559.

