Organic & Biomolecular Chemistry

PAPER

View Article Online
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Cite this: *Org. Biomol. Chem.*, 2016, **14**, 5673

Direct conjugate alkylation of α,β-unsaturated carbonyls by Ti^{III}-catalysed reductive umpolung of simple activated alkenes†

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Received 22nd December 2015,
Accepted 15th January 2016

DOI: 10.1039/c5ob02631h

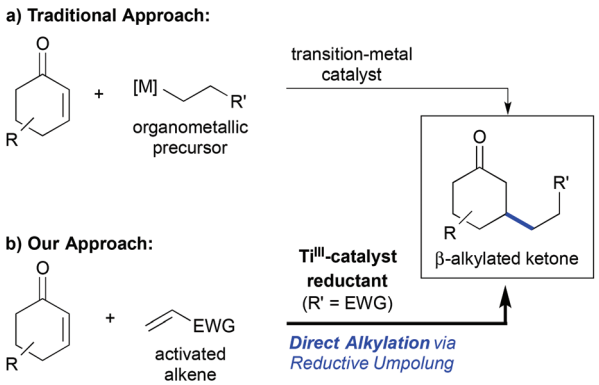
www.rsc.org/obc

The titanium(III)-catalysed cross-selective reductive umpolung of Michael-acceptors represents a unique direct conjugate β-alkylation reaction. It allows the cross-selective preparation of 1,6- and 1,4-difunctionalised building blocks without the requirement of stoichiometric organometallic reagents. In this full paper, the development and scope of the titanium(III)-catalysed cross-selective reductive umpolung of Michael-acceptors is described. Based on the observed selectivities and additional mechanistic experiments a refined mechanistic proposal is presented.

Introduction

The metal-catalysed conjugate addition reaction to enones and related Michael-acceptors has been a thriving research field over the past two decades. Nowadays, it is possible to perform this transformation in high yield and enantioselectivity using copper-, rhodium-, or palladium-catalysis for example,[1] and even the asymmetric construction of quaternary carbon centres can be achieved with high selectivity.[2] Still, one drawback of the classic protocols has been the requirement of organometallic coupling precursors that need to be prepared in advance (Scheme 1a). Only a few exceptions, most being Pd- or Ni-catalysed reductive Heck reactions, have been reported.[3]

Radical addition reactions to Michael-acceptors are complementary to traditional conjugate additions. They can be used to overcome this drawback and to address in particular conjugate β-alkylation reactions,[4] which have remained challenging using conventional catalytic conjugate addition approaches.[5] Hence, it has been shown that free radical additions using stoichiometric and catalytic conditions,[6] as well as radical additions after titanium-catalysed reductive epoxide opening,[7] can lead to the desired β-alkylated products in a very efficient manner. The advantage of the titanium-catalysed process was the superior catalyst control of the reaction selectivity, leading to high regio-, stereo- and even enantioselectivity.[4]



Scheme 1 (a) Traditional β-alkylation of enones using premetallated reagents. (b) Direct titanium(III)-catalysed reductive umpolung enables the use of simple alkene precursors.

In 2011, we communicated a direct reductive β-alkylation of enones that enabled the use of readily available activated alkenes such as acrylonitrile as cross-coupling partners (Scheme 1b).[8] Thus, the requirement of pre-metallated reagents or free radical conditions was overcome, which should be kept in mind with regard to more recent contributions in the field of reductive conjugate cross-couplings.[5a–c,9] The reaction was a titanium(III)-catalysed overall umpolung reaction that led to 1,6-ketonitriles and related products. Related reductive homocoupling reactions were known before and had been applied even on industrial scale,[10] but cross-selective tail-to-tail coupling of two Michael-acceptors had no precedence at that time. It should be noted that a redox-neutral NHC-catalysed cross-selective Michael umpolung was published shortly afterwards,[11,12] which led to α,β-unsaturated 1,6-difunctionalized motifs.

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†Electronic supplementary information (ESI) available: Additional screening tables, experimental and computational details, characterisation data and NMR spectra of new compounds. CCDC 1440298 and 1440299. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c5ob02631h

In this full account, we wish to disclose the initial development of the titanium-catalysed cross-coupling of Michael-acceptors and the further advancement towards substrate classes such as quinolones, chromones and coumarins.[13] The results lead to valuable implications for the future development of related transformations and the application of such direct β-alkylation reactions.

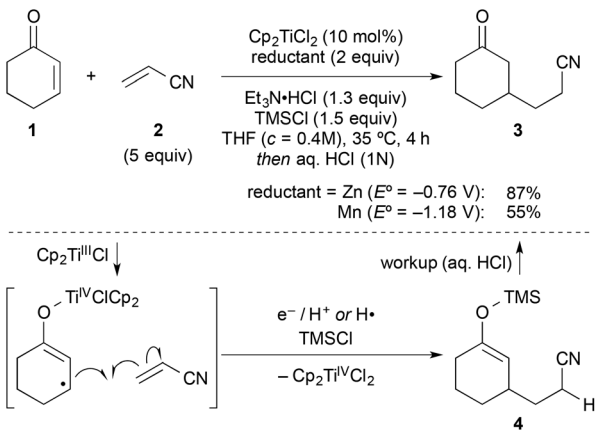
Results and discussion

Initial reaction optimisation

In a typical experiment, cyclohexenone (**1**) and 5 equiv. of inexpensive acrylonitrile (**2**) as coupling partner were reacted in the presence of titanocene dichloride [Cp_2TiCl_2] (10 mol%), zinc dust (2 equiv.), triethylamine hydrochloride (1.3 equiv.), and chlorotrimethylsilane (1.5 equiv.) in THF at 35 °C, to give alkylated ketone **3** in 87% yield after workup with aqueous HCl (Scheme 2). Manganese, a stronger reductant that has been frequently applied in catalytic reductive coupling reactions with titanocene catalysts and other metals,[7,14] gave significantly reduced yields. The reaction outcome was explained by a preliminary mechanistic proposal started with a single-electron-transfer from the *in situ* generated titanium(III)-catalyst to the enone, generating a nucleophilic allylic radical. This radical would then add to the component with the lowest LUMO (acrylonitrile), forming the new carbon–carbon bond. The resulting electron-poor carbon radical next to the nitrile was then quickly reduced and protonated under the reaction conditions. Alternatively, a hydrogen radical abstraction (for example from THF) could take place, which still remained to be investigated. The addition of chlorotrimethylsilane was then vital for achieving turnover through silylation of the titanium(IV)-enolate that is generated in the process. This resulted in **4** as crude product. It was found that 1–2 turnovers could be achieved as well by addition of small amounts of water. The amount of $Et_3N{\cdot}HCl$ was carefully balanced, since higher amounts led to the competing conjugate reduction of the enone, which was reported earlier by others.[15] A five-fold excess of acrylonitrile further suppressed this conjugate reduction as well as the homo-dimerisation of the enone or its premature silylation.

The reaction conditions were the result of a careful optimisation process. For example, tetrahydrofuran, which was often employed in catalyses involving single-electron-transfer reactions, was the most suitable solvent. Interestingly, a number of other solvents with a largely different dielectricity constant or Gutmann-donor number such as hexane, 1,4-dioxane, diethyl ether or dichloromethane gave reasonable yields as well. Other very similar solvents (toluene, chloroform, 1,2-dimethoxyethane) gave essentially no conversion to the product (Table 1). This illustrates that titanium(III)-chemistry is sensitive to a number of effects and reaction outcomes cannot be estimated easily. In fact, THF, which is only a moderate donor, was displaced from the Ti^{III}-centre by acrylonitrile forming a deep-purple complex. Chelating solvents (1,2-DME) and strong donors such as acetonitrile or DMF, on the other hand, inhibited the catalyst through irreversible coordination.[19] Thus we concluded, the major role of THF was to ensure a balanced solvation of the reaction partners ($Et_3N{\cdot}HCl$, is only moderately soluble, for example) and to promote an efficient reduction of Ti^{IV} to Ti^{III} by the metallic reductant.

The choice of triethylamine hydrochloride as additive emerged from a screening of various ammonium salts. Without such an ammonium salt additive only poor conversion to the desired product was observed (Table 2, entry 1). Hydrochlorides within a pK_a range of p$K_a^{H_2O}$ = 10–11 gave the most satisfying results. Quinuclidinium and diisopropylethylammonium salts that were within the pK_a range of triethylamine gave slightly lower yields (78% and 64%, respectively). The more acidic hydrochlorides of 2,4,6-collidine and pyridine as well as hydrochlorides of secondary amines had a negative impact on the reaction (entries 3, 4, 8, and 9). Interestingly, the addition of unprotonated triethylamine was beneficial too, but also lead to the formation of larger



Scheme 2 Typical coupling under the previously optimised reactions conditions und key steps of the originally proposed mechanism. Manganese gave inferior results.

Table 1 Results of the solvent screening

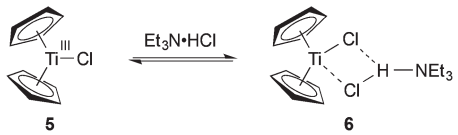
Entry	Solvent	ε_ρ [a]	DN[b]	Yield[c] (%)
1	*n*-Hexane	1.89 (20 °C)	0	60
2	1,4-Dioxane	2.22 (20 °C)	14.8	66
3	CCl_4	2.24 (20 °C)	0	2
4	Toluene	2.39 (20 °C)	0.1	3
5	Et_2O	4.27 (20 °C)	19.2	79
6	$CHCl_3$	4.81 (25 °C)	4	1
7	1,2-DME	7.3 (23.5 °C)	20.0	0
8	**THF**	**7.52 (22 °C)**	**20.0**	**90**
9	CH_2Cl_2	9.14 (20 °C)	1	61
10	1,2-DCE	10.42 (20 °C)	0	61
11	*t*-BuOH	12.5 (20 °C)	—	0
12	MeCN	36.64 (20 °C)	14.1	16
13	DMF	38.25 (20 °C)	26.6	5

[a] Relative permittivity, see ref. 16. [b] Gutmann donor number, see ref. 17. [c] Determined by GC-analysis with 1,3-dimethoxybenzene as internal standard.

Table 2 Screening of ammonium salts and TFA as additives

Entry	Additive	pK_a (H_2O)[a]	Yield[b] (%)
1	None	—	10
2	TFA	0.23	0
3	Pyridine·HCl	5.25	28
4	Collidine·HCl	7.48	55
5	**Et_3N·HCl**	**10.75**	**90**
6	Quinuclidine·HCl	11.0	78
7	iPr_2NEt·TFA	ca. 11	64
8	iPr_2NH·TFA	11.05	0
9	Piperidine·HCl	11.22	26
10	Et_3N	>20	48[c]

[a] Literature values, see ref. 18. [b] Determined by GC-analysis with 1,3-dimethoxybenzene as internal standard. [c] Significant amounts of the trimethylsilyl enol ether of cyclohexenone were observed.



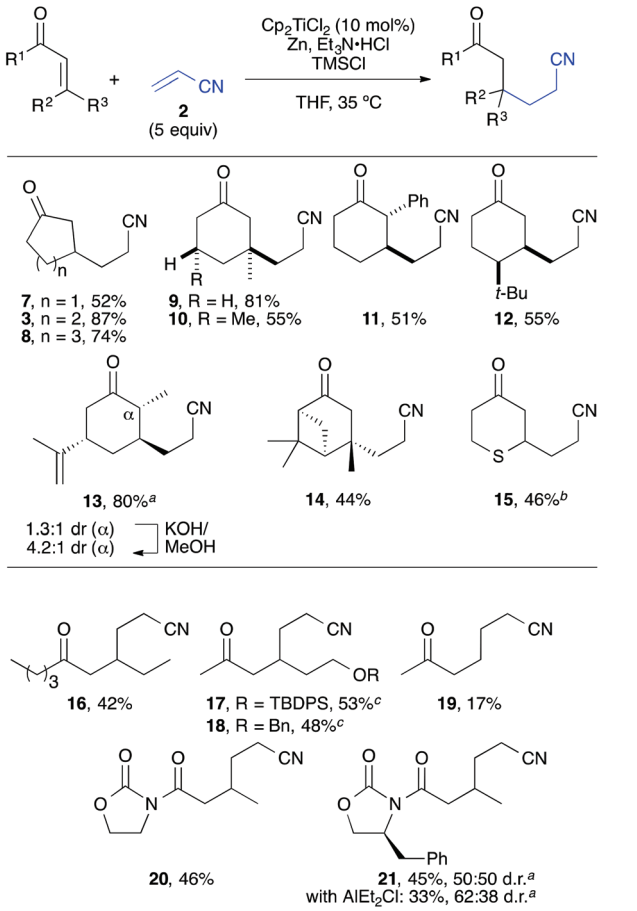
5 6

Scheme 3 Stabilising effect of added Et_3N·HCl on [$Cp_2Ti^{III}Cl$].

Table 3 Optimisation of the catalyst loading

Entry	Cp_2TiCl_2 [mol%]	t [h]	Yield[a] [%]
1	**10**	**2**	**90 (87%)**[b]
2	5	14	70
3	3	14	55
4	—	14	0

[a] Determined by GC-analysis with 1,3-dimethoxybenzene as internal standard. [b] Isolated yield in brackets.



Scheme 4 Reductive Coupling of Cyclic Enones with Acrylonitriles. Yield of isolated material. [a] Combined yield. [b] Syringe pump addition of the dihydrothiopyranone precursor. [c] Reaction at 0 °C.

amounts of the trimethylsilylenol ether of cyclohexenone (entry 10). The superiority of triethylamine hydrochloride, however, cannot be explained by its acidity alone and might stem from the tendency of Et_3N·HCl to form a Ti^{III}-Et_3N·HCl adduct **6** (Scheme 3) with the active titanium(III) monomer **5**, which was proposed to stabilize the catalyst.[20]

Lowering the catalyst amount to 5 mol% or 3 mol% still gave 70% and 55% yield, respectively (Table 3). However, the above mentioned competing reactions (silyl enol ether formation of **1** and homo-coupling of **1**) became more prominent. Without the titanocene catalyst, no product was formed.

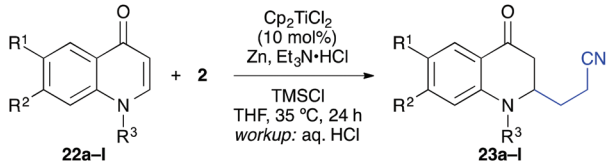
Scope of the enone

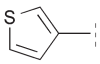
Using the optimised conditions, a series of substrates was coupled with acrylonitrile in a similar manner to give the corresponding 1,6-ketonitriles in moderate to high yields after workup with aqueous HCl (Scheme 4). Different enone ring sizes (**7–9**) and substitution patterns were tolerated that enabled the construction of quaternaty carbon centres at the β-position (**9, 10**). The coupling proceeded in excellent diastereoselectivity regarding the newly formed C–C bond, which allowed the selective conjugate alkylation of moderately complex substrates such as (*S*)-carvone and (*S*)-verbenone (**13, 14**). In addition, a dihydrothiopyranone (4-thiacyclohexenone) could be employed as well giving ketonitrile **15** in a moderate 46% yield. Here, a slow addition of the dihydrothiopyranone *via* a syringe-pump was required to prevent the undesired reductive dimerization of the substrate.

The scope could be further extended towards linear enone substrates that were transformed into the corresponding 1,6-ketonitriles **16–18** in reasonable yields (42–53%). Methyl vinyl ketone, however, led to uncontrolled polymerisation under the reaction conditions and, thus, only 17% of compound **19** were isolated. In addition, α,β-unsaturated amides containing achiral and chiral oxazolidinone units could be employed as well with moderate success. However, no diastereoselectivity was observed, even if precoordination of the substrate by $AlEt_2Cl$ was attempted.

The titanium-catalysed reductive umpolung/β-alkylation could be applied to a number of quinones, chromones, and coumarines as described in the following.[13] A series of substituted quinolones was treated under the same conditions with acrylonitrile as coupling partner and good yields were obtained

Table 4 Reductive coupling of 4-quinolones with acrylonitrile



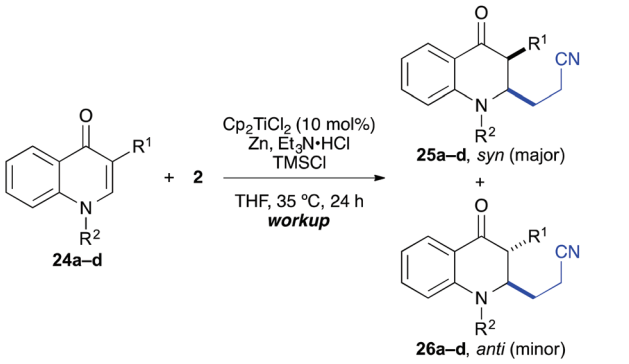
Entry	R^1	R^2	R^3	Product	Yield[a] [%]
1	H	H	Me	**23a**	77
2	H	H	Bn	**23b**	78[b]
3	MeO	H	Me	**23c**	56
4	Me	H	Me	**23d**	47
5	Ph	H	Me	**23e**	46
6	Ph	H	Bn	**23f**	21
7		H	Bn	**23g**	41
8		H	Bn	**23h**	48
9	Me	Me	Me	**23i**	48
10	Br	H	Me	**23j**	31
11	Br	H	Bn	**23k**	32
12	Cl	H	Me	**23l**	29

[a] Yield of isolated product. [b] 48 h reaction time.

for *N*-methylated and *N*-benzylated substrates having no further substitution (Table 4). The reaction worked also with substitution at position 7 and 8, although the yields were slightly diminished. For example, 7-methoxy, -methyl, -phenyl, -thiophen-3-yl, and -phenylethynyl groups worked well (entries 3–8). In some cases (*e.g.* R^1 = Ph), however, significant differences in yield were observed for the *N*-methylated and *N*-benzylated precursors (entries 5 and 6). Double substitution was tolerated as well (entry 9) and importantly, halogenation of the aromatic backbone was tolerated to some extend (entries 10–12).[21] This underlined the mildness of the title reaction.

The coupling worked significantly better with 3-substituted quinolones. Here, yields between 69% and 91% were obtained for 3-methyl and 3-phenyl derivatives (Table 5). Importantly, aqueous workup under protic conditions gave exclusively the *syn*-diastereomer, which was a result of a pseudo-axial orientation of the cyanoethyl chain due to steric repulsion with the *N*-alkyl group. Quenching the silyl enol ether under controlled conditions instead produced significant amounts of the *anti*-diastereomer (in a 2.4 : 1 *syn*/*anti* ratio), which could be separated and structurally confirmed by X-ray analysis (Fig. 1).[22,23] The workup had to be carried out with care and removal of the excess in acrylonitrile under reduced pressure was required. Otherwise, overalkylation in form of a subsequent Michael-addition of the enolate to acrylonitrile took place (Scheme 5). For example, if a reaction of **24a** (R = Me) or **24b** (R = Bn) with acrylonitrile was quenched by addition with TBAF at 0 °C, the desired products **25a** and **25b** were received in 30% and 42% yield, respectively, together with the corresponding double addition products **27a** and **27b** (42% and 39%, respectively).

Table 5 Diastereoselective reductive coupling of 3-substituted 4-quinolones



Entry	R^1	R^2	Products	Workup[a]	*syn*/*anti*	Yield[b] [%]
1a	Me	Me	**25a, 26a**	HCl	>95 : 5	86
1b				TBAF	>95 : 5	74
2a	Me	Bn	**25b, 26b**	HCl	>95 : 5	91
2b				TBAF	71 : 29	69
3a	Ph	Me	**25c, 26c**	HCl	>95 : 5	72
3b				TBAF	71 : 29	89
4a	Ph	Bn	**25d, 26d**	HCl	>95 : 5	85
4b				TBAF	70 : 30	69

[a] HCl workup: aq. 1 N HCl, 0 °C, 3 h. TBAF workup: TBAF (1 M in THF), −78 °C, 3 h. [b] Yield of isolated product.

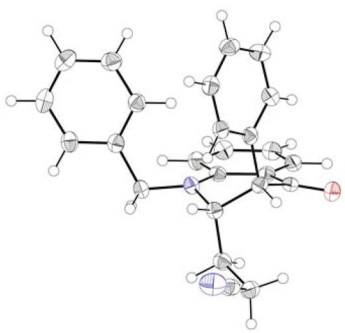
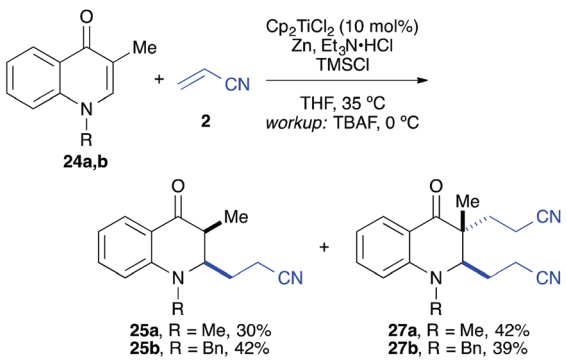
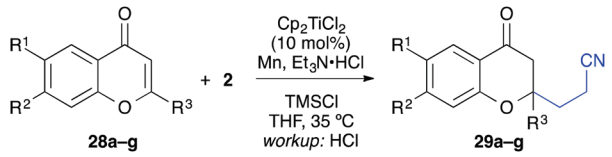


Fig. 1 X-ray structure of **26d**. Thermal ellipsoids drawn at 50% probability level.



Scheme 5 Workup with TBAF at 0 °C in presence of an excess of acrylonitrile led in part to double cyanoalkylation products.

Table 6 Reductive coupling of chromones with acrylonitrile



Entry	R^1	R^2	R^3	Product	Yield[a] [%]
1	H	H	H	**29a**	50 (36)[b]
2	Me	H	H	**29b**	42 (32)[b]
3	MeO	H	H	**29c**	37
4	Br	H	H	**29d**	0[c]
5	H	MeO	H	**29e**	32
6	H	H	Me	**29f**	17[b]
7	H	H	Ph	**29g**	31[b]

[a] Yield of isolated product. [b] Zinc dust was used as reductant. [c] Complex product mixture.

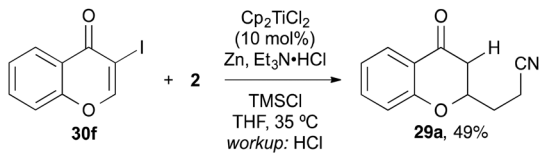
In analogy to the quinolone substrates, C3-unsubstituted chromones were moderately successful substrates for the titanium-catalysed reductive umpolung (Table 6). Manganese powder as reductant gave slightly better reaction yields than zinc dust. Electron-donating substituents were tolerated (37–50%), but no product could be isolated with 6-bromochromone (**28d**). A 2-methyl substituted chromone gave only 17% product and flavone itself was transformed into the desired chromanone in 31% yield, which corresponded to two catalyst turnovers. As observed before, the yields were significantly improved when C3-substituents were present (Table 7). Interestingly, not only alkyl and aryl groups could be installed at this position, but also halides such as chloride and bromide (entries 4 and 5).

The relative configuration was opposite to the quinolin-4-one products and the *anti*-diastereomer was isolated as major component after workup with aqueous HCl.

The workup procedure drastically influenced the product distribution. The diastereoselectivity could be even switched from the favoured *anti*-products to the *syn*-products in moderate to good diastereoselectivity when workup was carried out under kinetically controlled conditions (TBAF, −78 °C).

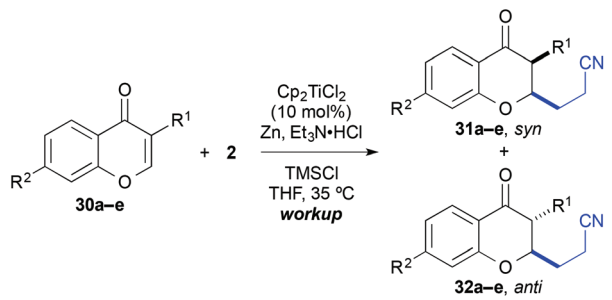
3-Iodochromone **30f**, however, was too reactive and suffered from dehalogenation under the reaction conditions and cross-coupling product **29a** was isolated (Scheme 6).

Finally, the cross-coupling with acrylonitrile was applied to the reductive β-cyanoalkylation of coumarins. Using precursors with a diverse substitution pattern, moderate yields were achieved for the cross-coupling reaction (Table 8). Attempts to further optimize the reaction outcome were unsuccessful.[24] The best yield (65%) was obtained with 6-methylcoumarin (entry 3). A quaternary stereocentre could be installed in 36% yield (entry 8) and α,β-disubstituted 2-chromanones were



Scheme 6 The reaction with 3-iodochromone afforded deiodinated chromanone **29a**.

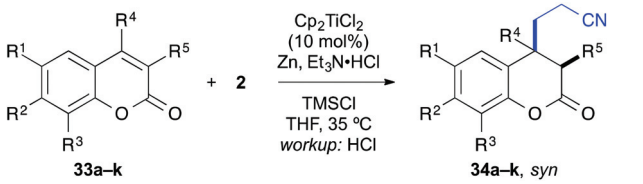
Table 7 Reductive coupling of 3-substituted chromones workup dependant switchable diastereoselectivity



Entry	R^1	R^2	Products	Workup	*syn*/*anti*	Yield[a] [%]
1a	Me	H	**31a, 32a**	HCl	**21 : 79**	69
1b				TBAF	**78 : 22**	78
2a	Ph	H	**31b, 32b**	HCl	**21 : 79**	73
2b				TBAF	**75 : 25**	62
3a	Ph	i-PrO	**31c, 32c**	HCl	**37 : 63**	82
3b				TBAF	**75 : 25**	81
4a	Cl	H	**31d, 32d**	HCl	**38 : 62**	49[b]
4b				TBAF	**64 : 36**	54[b]
5a	Br	H	**31e, 32e**	HCl	**22 : 78**	42[b]
5b				TBAF	**83 : 17**	42[b]

[a] Yield of isolated product. [b] Isolated as diastereomeric mixture.

Table 8 Reductive coupling of coumarins with acrylonitrile



Entry	R^1	R^2	R^3	R^4	R^5	Product	Yield[a] [%]
1	H	H	H	H	H	**34a**	42
2	Br	H	H	H	H	**34b**	36
3	Me	H	H	H	H	**34c**	65
4	H	Me	H	H	H	**34d**	46
5	H	MeO	H	H	H	**34e**	45
6	H	Me_2N	H	H	H	**34f**	26[b]
7	H	H	Me	H	H	**34g**	33
8	H	H	H	Me	H	**34h**	36
9	H	H	H	H	Me	**34i**	44[c]
10	H	Me_2N	H	H	Me	**34j**	38[b,d]
11	H	Me_2N	H	H	Ph	**34k**	24[b,d]

[a] Yield of isolated product. [b] Calculated yield from an inseparable mixture with the substrate (~1 : 1 ratio). [c] Only the *syn*-isomer was formed. [d] A single isomer was formed, which was assigned in analogy to **34i**.

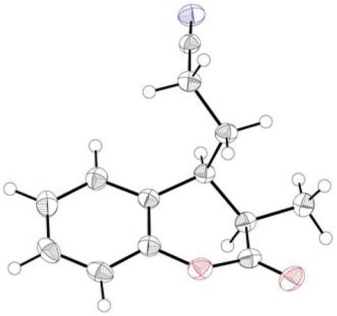


Fig. 2 X-ray structure of **34i**. Thermal ellipsoids drawn at 50% probability level.

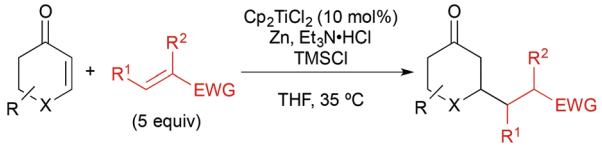
formed in similar quantities by the reductive cyanoethylation reaction. The diasteroselectivity was again very high and the *syn*-diastereomers were isolated as sole products. The relative *syn*-configuration was unambiguously confirmed by X-ray analysis of product **34i** (Fig. 2).[22]

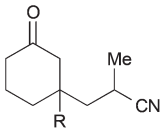
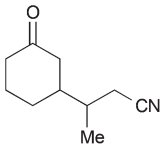
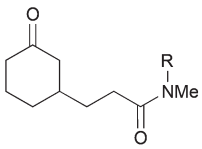
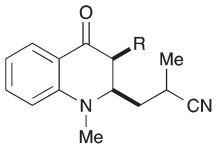
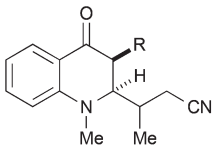
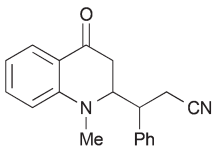
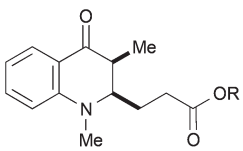
Scope of the coupling partner

Importantly, the reaction was not limited to acrylonitrile as coupling partner. Substituted acrylonitrile derivatives and a number of other activated alkenes including acrylamides and acrylates could be employed as coupling partners as well (Table 9). With cyclohexenone, we first observed that methacrylonitrile worked almost as well as acrylonitrile itself (entry 1) and even the quaternary carbon could be formed smoothly (entry 2). The reaction with crotononitrile was hampered (entry 3), probably due to increased sterics leading to a reduction in yield to 27%. In both cases, a 1 : 1 mixture of diastereomers was received. The coupling with N,N-dimethylacrylamide was unsuccessful, since this compound appeared to inhibit the catalyst (entry 4). This could be successfully addressed by the installation of a tosyl group at the amide nitrogen, which prevented the amide resonance and lowered the coordination tendency (entry 5). The coupling proceeded smoothly with 73% yield in the presence of added cinnamonitrile, which increased the yield by about 20%. Cinnamonitrile itself was an inferior coupling partner (<5%), but it was empirically found to be beneficial for this reaction. One possible rationale for this effect could be a coordination and stabilisation of the catalyst.

In a second series of experiments with *N*-methyl-4-quinolones **22a** and **24a**, good results were obtained for the couplings with methacrylonitrile as well. 3-Methylquinolone **24a** gave again exclusively the *syn*-product with respect to the ring substitution in excellent 90% yield. The product was obtained as an inseparable ~1 : 1-mixture of diastereomers with respect to the additional stereocentre at the nitrile α-carbon (entry 7). With crotononitrile, the yields were again reduced to *ca.* 30% (*cf.* entry 3) but a moderate diastereoselectivity of 1.6 : 1 dr was observed by NMR for the reaction with **24a** (entry 9). Cinnamonitrile, which was employed for entry 5 as a beneficial additive, could be coupled in 18% yield to product **44** (entry 10).

Table 9 Scope of the cross-coupling partner



Entry	Product		dr	Yield[a] [%]
1		**35**, R = H	—	71
2		**36**, R = Me	50 : 50	70[b]
3		**37**	50 : 50	27[b]
4		**38**, R = Me	—	0
5		**39**, R = Ts	—	73[c]
6		**40**, R = H	57 : 43	36[b]
7		**41**, R = Me	58 : 42	90[b]
8		**42**, R = H	55 : 45	28[b]
9		**43**, R = Me	62 : 38	29[b]
10		**44**	62 : 38	18
11		**45**, R = Me	—	35[d]
12		**46**, R = Et	—	47[d]
13		**47**, R = *t*-Bu	—	37[d]
14		**48**, R = Ph	—	52
15		**49**, R = Mes	—	81

[a] Yield of isolated product. [b] Combined yield. [c] Cinnamonitrile (20 mol%) was added to the reaction mixture. [d] Workup with TBAF instead of aq. HCl.

With the 3-methylated quinolone **24a** as substrate, acrylates could be employed efficiently in the reductive catalytic umpolung as well (entries 11–15). Here, reasonable results were obtained with methyl, ethyl, and *tert*-butyl acrylate. The yield was slightly improved with the less electron-rich phenyl acrylate and with the sterically hindered mesityl acrylate,[25] the coupling proceeded smoothly in 81% yield. In all cases, no cross-coupling was observed in absence of the titanocene catalyst.

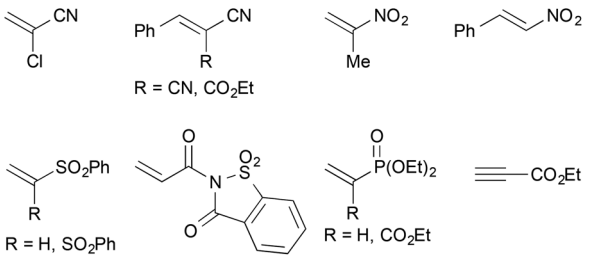


Fig. 3 Unsuitable cross-coupling partners.

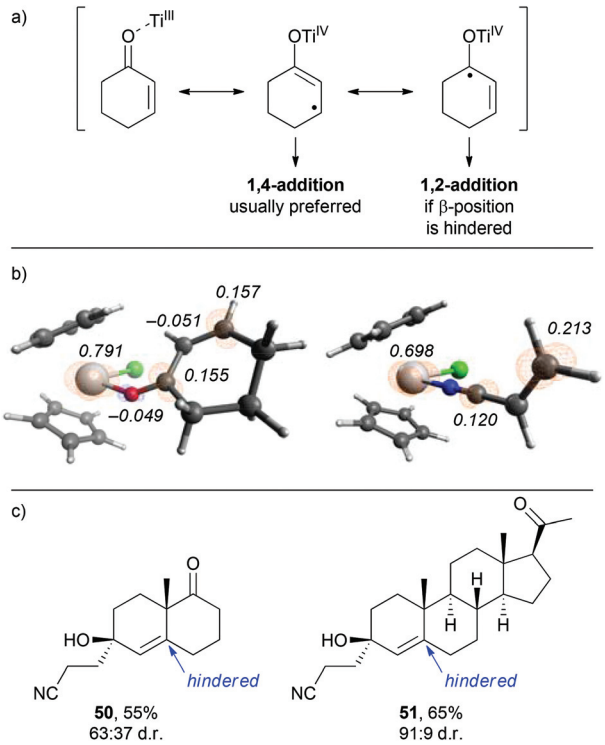
In addition, a number of other electron-deficient alkenes were tested as potential coupling partners with less success (Fig. 3). Other common nitrile-based Michael-acceptors such as 2-chloroacrylonitrile or Knoevenagel products of malononitrile or ethyl cyanoacetate did not undergo the desired reaction. This was also true for 2-nitropropene and β-nitrostyrene as well as vinyl sulfones. A saccharine-derived acrylamide, vinyl diethyl phosphonate or a propargylic ester were not suitable as well. In several cases, the reduction of the activated alkene was observed instead of the desired cross-coupling reaction. With *N*-acryloylsaccharine, for example, formation of the corresponding propionic amide took place.

Mechanistic discussion

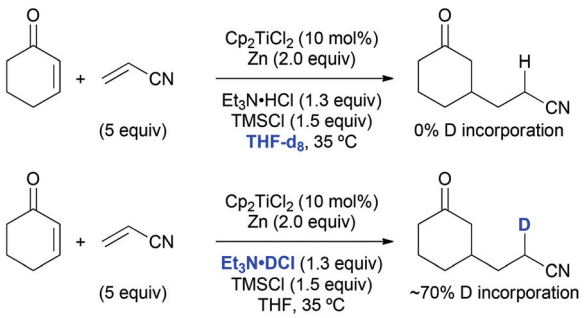
From the observations that were made during our studies, several conclusions could be drawn regarding the underlying reaction mechanism, which allowed us to refine the initially proposed mechanism.

As shown in Scheme 7, coordination of the *in situ* formed titanium(III)-catalyst to the enone substrate could also be interpreted as the formation of an allylic ketyl radical anion that remained coordinated to a titanium(IV)-centre. In fact, the unpaired electron was in part located at the titanium centre, at the β-carbon and at the carbonyl carbon as illustrated by the three resonance structures shown in Scheme 7. This was supported by the calculated spin density distribution at the $Cp_2Ti^{III}Cl$–cyclohexenone complex. It was majorly located at the titanium centre and in part located at the carbonyl and β-carbon.[24] A similar situation was found for an acrylonitrile–titanium(III) complex. This situation explained our experimental results: reductive coupling at the β-position leading to conjugate addition products (*e.g.* ketonitrile **3**) was the usually preferred pathway. However, substrates with increased sterical bulk at the β-carbon led to a change in the regiochemistry and the corresponding 1,2-addition products were formed.[26] For example, the reductive cross-coupling of the Wieland–Miescher ketone gave the corresponding cyanoethylated allylic alcohol **50** in 55% yield and moderate diastereoselectivity. A similar experiment with progesterone afforded the corresponding product **51** in excellent 91 : 9 dr and 65% yield.

The origin of the hydrogen atom that was transferred to the nitrile α-carbon in course of the standard coupling between cyclohexenone and acrylonitrile was probed as well. A reaction run in THF-d_8 did not lead to any deuterium incorporation

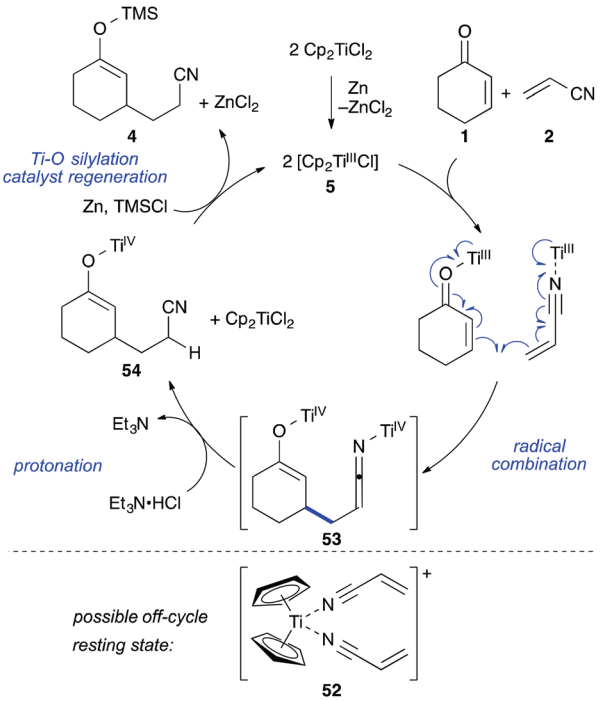


Scheme 7 Substrate-dependent divergent regioselectivity. (a) Mesomeric forms of a Ti^{III}–cyclohexenone complex. (b) Calculated spin density distribution for Ti^{III}–cyclohexen-one and Ti^{III}–acrylonitrile complexes (iso value = 0.01). (c) Observed 1,2-addition products from sterically hindered enone substrates.



Scheme 8 Deuterium experiments point towards a nitrile α-protonation event.

into the product (Scheme 8). If a carbon-centred radical was present at this position a deuterium radical abstraction from the solvent would have been likely to occur. On the contrary, a reaction with triethylamine deuterochloride resulted in about 70% deuteration of the product at this position, which was evidence for a protonation step under the usual reaction conditions. This protonation at the nitrile α-carbon was unselective due to the absence of stereoelements in its proximity, which explains the formation of 1 : 1 diastereomeric mixtures in the reactions with methacrylonitrile (see Table 9, entries 2, 6, and 7).



Scheme 9 Mechanistic proposal for the reductive umpolung of Michael-acceptors.

Together with the results from our previous study on the mechanism of the titanium(III)-catalysed cross-acyloin type coupling,[27] these observations led to a refined mechanistic proposal for the standard reaction (Scheme 9).

The reaction formally begins with the formation of two equivalents of **5** from [Cp_2TiCl_2] zinc followed by reaction with enone **1** and nitrile **2** to form coordination complexes. These complexes are in equilibrium through ligand-exchange processes. It is likely that a cationic resting state **52** is formed by solvation of the remaining chloride and coordination of a second acrylonitrile molecule (acrylonitrile was employed in a 50 fold excess with respect to the catalyst). This species could be the reason for the observed colour change to deep purple after addition of acrylonitrile and before addition of TMSCl during the reaction setup. A similar cationic resting state was previously established for the related ketone–nitrile coupling by X-ray analysis.[27] The C–C bond formation would then take place in form of a catalyst-controlled radical combination, avoiding the presence of free radicals and leading to bistitanated ketenimine-enolate **53**. The metallated ketenimine was quickly protonated by the hydrochloride (which was supported by the deuterium experiment) forming enolate **54**. The titanium enolate was then cleaved by chlorotrimethylsilane releasing the crude product in form of silyl enol ether **4** and enabling catalyst turnover. Zinc then regenerated the titanium(III) catalyst **5**. If desired, the silyl enol ether **4** could be isolated as one regioisomer in 87% yield (workup with water and filtration over florisil)[8] or quenched with HCl or TBAF to afford the corresponding ketonitrile as done for the tables in this work.

Conclusions

In conclusion, we have established the titanium(III)-catalysed reductive umpolung of Michael-acceptors as an efficient cross-coupling tool for the synthesis of building blocks with functional groups in 1,6-distances. This was demonstrated on 70 examples in total including couplings with acylonitriles, acrylamides and acrylates. Precursors with increased sterical hindrance could be employed for the selective synthesis of 1,4-difunctionalised products. A refined mechanistic picture was proposed based on the observed product distributions, the regio- and stereoselectivity, as well as the deuterium experiments. In the future, the development of related reductive cross-couplings will be accelerated due to the selectivity trends and mechanistic insight gained in this study. The method itself will be useful for the preparation of synthetic building blocks with functionalities in unnatural bond distances. Currently, efforts are undertaken to develop an enantioselective variant of this direct reductive β-alkylation reaction.

Experimental section

Standard procedure for the Ti^{III}-catalysed reductive umpolung

A flame-dried 50 mL-Schlenk tube containing a magnetic stirbar was charged under argon atmosphere with Cp_2TiCl_2 (12.4 mg, 0.05 mmol, 10 mol%), Zn (65.0 mg, 1.00 mmol, 2.0 equiv.) und $Et_3N{\cdot}HCl$ (89.5 mg, 0.650 mmol, 1.3 equiv.). Stirring was started. The vessel was evacuated and backfilled with argon after a few minutes. Absolute THF (1.25 ml) was added and after 1 min the mixture had turned from red to lime-green. The substrate (*e.g.* **1**, 0.5 mmol, 1.0 equiv.) was added followed by the cross-coupling partner (*e.g.* **2**, 2.5 mmol, 5 equiv.) and TMSCl (95.2 µl, 1.5 equiv.). The reaction vessel was sealed with a greased glass-stopper and the reaction stirred for the given time at 35 °C in an oil bath or at the given temperature after which the reaction was brought back to room temperature. Unless noted otherwise, workup was carried out by addition of 1 N aqueous HCl (4 ml) and CH_2Cl_2 and stirring was continued for 30 minutes at room temperature (23 °C). The mixture was transferred into a separation funnel containing H_2O (20 ml) and CH_2Cl_2 (20 ml). The biphasic mixture was shaken, the organic layer separated and the aqueous layer extracted with additional CH_2Cl_2 (3 × 10 ml). The combined organic extracts were dried (Na_2SO_4), concentrated and purified by flash chromatography as described.

Workup with TBAF under kinetically controlled conditions (see Tables 6 and 7)

The reaction was setup as described in the standard procedure. After the given reaction time, all volatile components were removed under reduced pressure and heating was discontinued. The residue was treated with CH_2Cl_2 (5 ml) and cooled to −78 °C. At that temperature, TBAF (1 M in THF, 2.50 ml, 2.5 equiv.) was added dropwise. The mixture was stirred for another 3 h at −78 °C and then allowed to warm to room temp-

erature (23 °C). The mixture was transferred into a separation funnel containing H_2O (20 ml) and CH_2Cl_2 (20 ml). The biphasic mixture was shaken, the organic layer separated and the aqueous layer extracted with additional CH_2Cl_2 (3 × 10 ml). The combined organic extracts were dried (Na_2SO_4), concentrated and purified by flash chromatography as described.

For a full list of materials and methods, detailed experimental data, compound characterizations and computational details, see the ESI.†

Acknowledgements

The Fonds der Chemischen Industrie (Liebig-Fellowship and Dozentenpreis to J. S.) and the Deutsche Forschungsgemeinschaft DFG (STR 1150/3-1, STR 1150/7-1, and Heisenberg-fellowship to J. S.) are gratefully acknowledged for their support. We thank Sven Tauscher for initial contributions.

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