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Catalyst selective and regiodivergent *O*- to *C*- or *N*-carboxyl transfer of pyrazolyl carbonates: synthetic and computational studies†

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The regiodivergent *O*- to *C*- or *N*-carboxyl transfer of pyrazolyl carbonates is described, with DMAP giving preferential *N*-carboxylation and triazolinylidenes promoting selective *C*-carboxylation (both with up to >99 : 1 regioselectivity). An enantioselective *O*- to *C*-carboxyl variant using NHC catalysis is demonstrated (up to 92% ee), while mechanistic and DFT studies outline the pathways operative in this system and provide insight into the reasons for the observed selectivity.

Introduction and background

The organocatalysed rearrangement of oxazolyl carbonates to the corresponding 4- or 2-carboxyazlactones was first described by Steglich and Höfle over forty years ago.[1] This reaction process has since attracted considerable attention thanks to its potential to generate synthetically useful α,α-disubstituted α-amino acid derivatives and is often regarded as a benchmark for the evaluation of Lewis base-catalysed reaction processes. Initially promoted by the achiral Lewis bases DMAP or PPY, the groups of Fu,[2] Vedejs,[3] Richards[4] and Gotor[5] have shown that chiral DMAP or PPY derivatives can induce high enantiocontrol in this reaction process.[6] Alternative chiral Lewis base catalysts that have been applied to this enantioselective rearrangement include chiral phosphines by Vedejs,[3] asymmetric imidazoles by Zhang,[7] and a variety of isothioureas by Gröger (acyl transfer),[8] ourselves[9] and Okamoto.[10] A dual-catalytic approach that utilises DMAP and a chiral thiourea has been demonstrated by Seidel,[11] while an ammonium betaine catalyst for this process has been utilised by Ooi.[12] Within this area we have previously shown that *N*-heterocyclic carbenes (NHCs) are versatile catalysts for the racemic Steglich rearrangement of oxazolyl carbonates.[13] Achiral triazolinylidenes promote this rearrangement process with low catalyst loadings and offer access to sterically hindered products, although chiral NHCs resulted in only modest enantiocontrol.[14]

The potential of this strategy to access stereodefined products with a quaternary stereogenic centre has seen this process extended to incorporate the asymmetric rearrangement of furanyl, indolyl and benzofuranyl carbonates,[15] alongside applications in total synthesis.[16] Notably, Vedejs *et al.* have investigated the regio- and enantioselective *O*- to *C*-carboxyl transfer of 5-arylfuranyl carbonates using TADMAP **1**,[17] with the regioselectivity dependent upon the electronic nature of the 5-aryl substituent (Fig. 1). Electron-donating aryl substituents favour α-functionalisation (α : γ up to 92 : 8), while an electron-withdrawing substituent favours γ-functionalisation (α : γ up to 20 : 80). Building upon these precedents, we considered alternative molecular scaffolds upon which to investigate *catalyst selective* regio- and enantioselective *O*-to *C*-carboxyl transfer processes.[18] While originally exploited in the dyeing and photographic industries, pyrazolinones and their derivatives have displayed a wide range of medicinal and pharmacological activities such as analgesic[19] and antipyretic properties,[20] anti-inflammatory,[21] anti-tumor,[22] anti-microbial,[23] anti-retroviral[24] as well as anti-ischemic effects[25] and neuroprotective properties.[26] These diverse applications have encouraged recent interest in novel synthetic methods to access enantioenriched pyrazolinones[27,28] and served as inspiration for our studies concerning the regio- and enantioselective *O*- to *C*-carboxyl transfer of pyrazolyl carbonates. Notably, triazolinylidene NHCs promote the rearrangement to generate *C*(4)-α,α-disubstituted pyrazolinones with high regioselectivity (up to >99 : 1 C : N) and in up to 92% ee, while catalytic DMAP gives *N*(1)-carboxyl pyrazolinones with high regioselectivity (up to 1 : 99 C : N). A mechanistic rationale for this observed selectivity is provided by computational studies on a representative model system.

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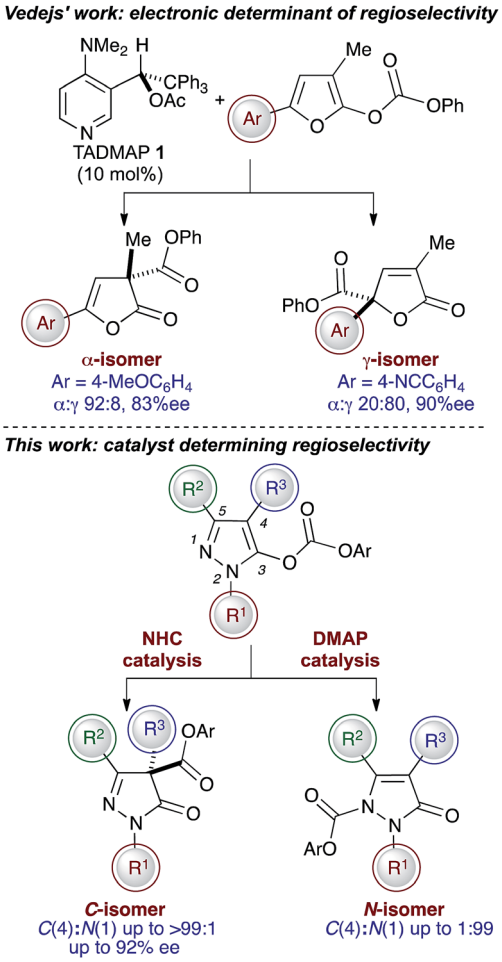
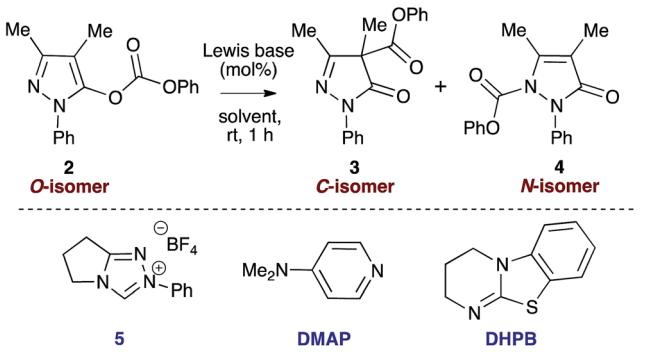


Fig. 1 Lewis base-promoted regiodivergent and enantioselective *O*- to *C*- or *N*-carboxyl transfer reactions of pyrazolyl carbonates.

Model studies: catalyst selective *O*- to *C*- or *N*-carboxyl transfer

Initial studies screened a range of Lewis base catalysts for their ability to promote the regioselective *O*- to *C*- or *N*-carboxyl transfer of a model *N*(2)-phenyl substituted pyrazolyl carbonate **2** that was readily prepared from commercially available materials (Table 1). In all cases, generation of the parent pyrazolinone as a side-product amounted to typically ~5% of the crude reaction product mixture, so only a ratio of *C*- to *N*-regioisomeric products is given unless stated.[29] Treatment of **2** with an NHC catalyst (generated *in situ* by deprotonation of the triazolium salt **5** with KHMDS) in THF gave the *C*-regioisomer **3** with high selectivity (>99 : 1 C : N), isolated in 44% yield (entry 1). Further optimisation showed that this NHC-promoted transformation could be performed using lower catalyst loadings in toluene (entries 2–4) while still giving **3** with excellent regioselectivity (>99 : 1 C : N). Remarkably, the use of DMAP in CH_2Cl_2 favoured *N*-carboxylation with high regioselectivity (7 : 93 C : N), giving **4** in 56% yield (entry 5). The regiochemistry of this carboxyl transfer was confirmed by X-ray crystal structure analysis of *N*-carboxylate **4**.[30,31] Rearrangement with isothiourea DHPB also favoured the *N*-carboxyl regioisomer but with lower reactivity compared to DMAP (entry 6). Further investigation of the DMAP-promoted reaction showed that THF and toluene proved poor solvents for this process, giving only ~25% conversion to product with modest C : N ratios (entries 7 and 8). These results indicate that catalyst promoted regiodivergent selectivity is observed in this process under either NHC or DMAP catalysis.

Table 1 Model studies for Lewis base catalyst selective carboxyl transfer



Entry	Lewis base (mol%)	Solvent	Conv.[a]	C : N ratio[a]	Yield (%)
1[b]	Precat **5** (20)[b]	THF	>95	>99 : 1[c]	44 (**3**)
2	Precat **5** (10)	Toluene	>95	99 : 1	49 (**3**)
3	Precat **5** (5)	Toluene	>95	>99 : 1	—
4	Precat **5** (2)	Toluene	>95	99 : 1	—
5	DMAP (20)	CH_2Cl_2	73	7 : 93	56 (**4**)
6	DHPB (20)	CH_2Cl_2	66	9 : 91	—
7	DMAP (20)	Toluene	25	18 : 82	—
8	DMAP (20)	THF	25	23 : 77	—

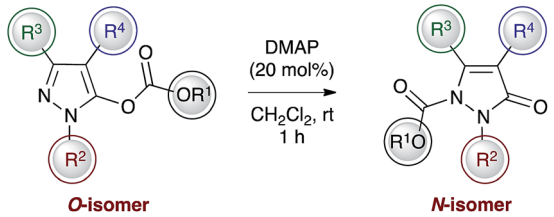
[a] Reaction conversion and C : N product ratio established by ^{1}H NMR spectroscopic analysis of crude reaction mixture. [b] NHC generated by deprotonation with KHMDS. [c] 17% parent pyrazolinone generated.

Scope and limitations

DMAP-catalysed selective *O*- to *N*-carboxyl transfer

The scope and limitations of these catalyst selective carboxyl transfer processes was next investigated through variation within the carbonate functionality and pyrazolyl scaffold at *N*(2)-, *C*(4)- and *C*(5)- (Table 2). Under DMAP catalysis in CH_2Cl_2, variation of the carbonate group gave the *N*-carboxyl products preferentially (≤16 : 84 C : N) that were isolated in good to moderate yield.[31] Although benzyl carbonate **6** showed poor conversion even after extended reaction times, trichloroethyl and aryl *N*-carboxylate products containing both electron-withdrawing and electron-donating substituents were produced with good conversions. The effect of structural perturbation within the pyrazolyl skeleton was next investigated. With an *N*(2)-methyl substituent, *C*(5)-aryl substitution resulted in modest conversion but still preferential *N*-carboxylation to **10**, while C(5)-methyl substitution gave preferential *N*-carboxyl product **11** with high selectivity and yield. Variation of the C(4)

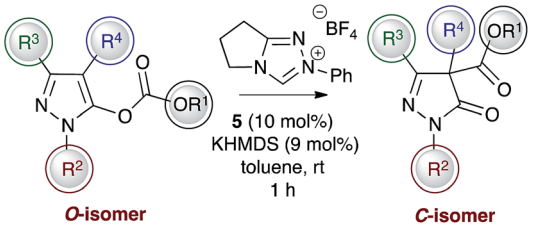
Table 2 DMAP-promoted *O*- to *N*-carboxyl transfer



Entry	R^1	R^2	R^3	R^4	C : N ratio[a]	*N*-Isomer	Yield (%)
1[b]	Bn	Ph	Me	Me	>1 : 99	**6**	10
2	CH_2CCl_3	Ph	Me	Me	16 : 84	**7**	64
3	Ph	Ph	Me	Me	7 : 93	**4**	56
4	4-FC_6H_4	Ph	Me	Me	6 : 94	**8**	66
5	4-$OMeC_6H_4$	Ph	Me	Me	7 : 93	**9**	32
6	Ph	Me	Ph	Me	6 : 94	**10**	14
7	4-FC_6H_4	Me	Me	Me	>1 : 99	**11**	60
8	4-FC_6H_4	Ph	Me	Et	3 : 97	**12**	74
9	4-FC_6H_4	Ph	Me	Bn	3 : 97	**13**	80
10	4-FC_6H_4	Me	Me	Et	>1 : 99	**14**	61
11	4-FC_6H_4	Me	Me	Bn	1 : 99	**15**	50
12	4-FC_6H_4	Me	Me	i-Bu	3 : 97	**16**	77

[a] C : N product ratios established by ^{1}H NMR spectroscopic analysis of crude reaction mixture. [b] Overnight reaction.

Table 3 NHC-promoted *O*- to *C*-carboxyl transfer



Entry	R^1	R^2	R^3	R^4	C : N ratio[a]	*C*-isomer	Yield (%)
1[b]	Bn	Ph	Me	Me	>99 : 1	**17**	12
2	CH_2CCl_3	Ph	Me	Me	>99 : 1	**18**	67
3	Ph	Ph	Me	Me	>99 : 1	**3**	49
4	4-FC_6H_4	Ph	Me	Me	>99 : 1	**19**	49
5	4-$OMeC_6H_4$	Ph	Me	Me	93 : 7	**20**	63
6[c]	Ph	Me	Ph	Me	>99 : 1	**21**	55
7	4-FC_6H_4	Me	Me	Me	97 : 3	**22**	71
8	4-FC_6H_4	Ph	Me	Et	>99 : 1	**23**	84
9	4-FC_6H_4	Ph	Me	Bn	99 : 1	**24**	73
10	4-FC_6H_4	Me	Me	Et	97 : 3	**25**	68
11	4-FC_6H_4	Me	Me	Bn	86 : 14	**26**	31
12	4-FC_6H_4	Me	Me	i-Bu	76 : 24	**27**	45

[a] C : N product ratios established by ^{1}H NMR spectroscopic analysis of crude reaction mixture.[29] [b] Overnight reaction. [c] 20 mol% catalyst, 18 mol% KHMDS.

substituent also led to preferential *N*-carboxylation (products **12–16**), irrespective of *N*(2)-Ph or -Me substitution.[32]

NHC-catalysed selective *O*- to *C*-carboxyl transfer

Having demonstrated the generality of the DMAP-promoted *O*- to *N*-carboxyl transfer process, the NHC-catalysed *O*- to *C*-carboxyl transfer process was explored with toluene chosen as the reaction solvent (Table 3). Using achiral NHC precursor **5**, variation of the carbonate group (entries 1–5), as well as *N*(2)-, *C*(4)- and *C*(5)-substituents (entries 6–12) gave preferentially the *C*-carboxyl isomer with high selectivity (up to >99 : 1 C : N, up to 84% yield). The regioselectivity of the NHC-catalysed reaction appears essentially independent of the nature of the carbonate group and *C*(5)-substituent, however it is particularly sensitive to the steric constraint at *C*(4), with a *C*(4)-iso-butyl group giving reduced C : N selectivity (76 : 24 C : N, **27**, entry 12) relative to less hindered methyl substitution (97 : 3 C : N, **22**, entry 7). A more modest reduction in regioselectivity was observed on changing the *N*(2)-substituent from phenyl to methyl (for example, compare products **24** (99 : 1 C : N, entry 9) and **26** (86 : 14 C : N, entry 11)).

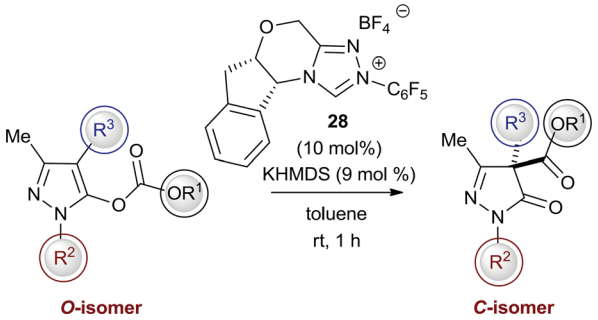
Enantioselective NHC-catalysed selective *O*- to *C*-carboxyl transfer

With the achiral NHC derived from salt **5** established as a regioselective catalyst for the formation of *C*-carboxyl pyrazolinones, the expansion of this methodology to the synthesis of enantioenriched products using chiral NHCs was probed.[14] A screen of chiral triazolium NHC catalysts for the asymmetric rearrangement of model substrate **2** into *C*-carboxyl **3** identified *N*-pentafluorophenyl precatalyst **28** as the optimal catalyst with regards to regio- and enantioselectivity (toluene was again preferred as solvent over THF as it gave superior product yields and enantioselectivity).[33] The full scope and generality of this asymmetric process was then investigated using NHC pre-catalyst **28** (Table 4). Aryl carbonates containing both electron-withdrawing and electron-donating substituents were tolerated with moderate levels of enantioselectivity (up to 68% ee, entries 1–3). By contrast, trichloroethyl carbonate showed good reactivity but poor enantioselectivity (entry 4). With a common *N*-(2)-phenyl substituent, other *C*-(4)-alkyl substituents were tolerated with promising enantioselectivity (up to 69% ee, entries 5 and 6). With an *N*-(2)-methyl substituent, a mixture of *N*- and *C*-carboxyl products favouring the *C*-carboxyl products was observed, with good to excellent levels of enantioselectivity for the *C*-carboxyl product achieved with methyl, ethyl and iso-butyl *C*-(4)-substitution (88–92% ee, entries 7–10). The absolute configuration within *C*-regioisomer **29** (entry 8) was assigned by X-ray diffraction with all other configurations assigned by analogy.[30]

Mechanistic investigations

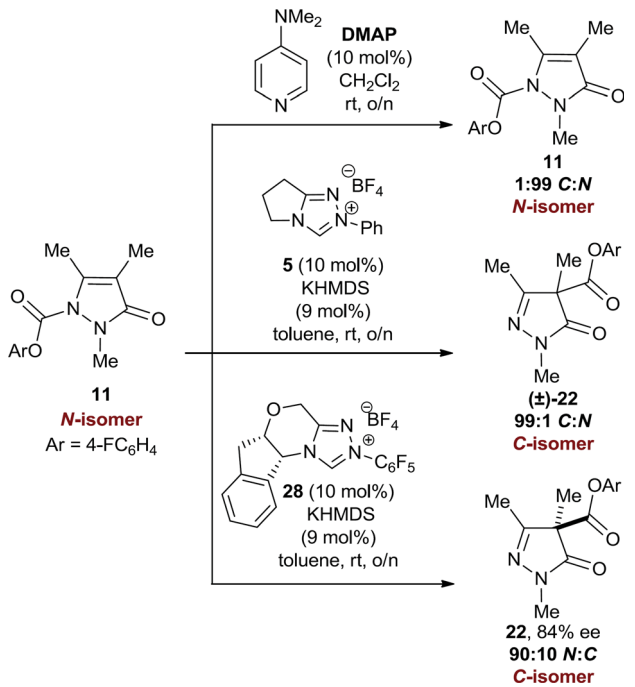
With this rearrangement reaction producing two regioisomeric products, the possibility of product interconversion due to the reversibility of the C–C and C–N bond-forming processes was investigated on model *N*(2)-Me substrates **11** and **22**. First, *N*-carboxylate **11** (1 : 99 C : N) was resubmitted to both DMAP

Table 4 Substrate scope of enantioselective rearrangement[29,32]



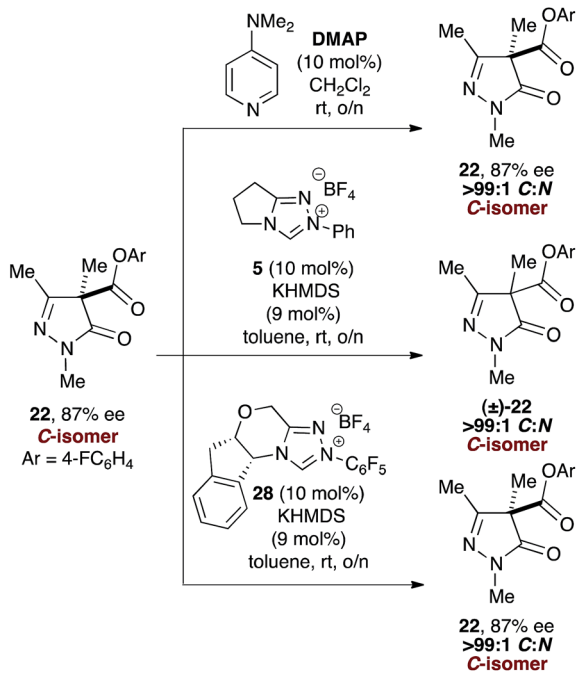
Entry	R^1	R^2	R^3	C : N ratio[a]	*C*-isomer	Yield (%)	% ee[b]
1	Ph	Ph	Me	99 : 1	**3**	77	62
2[c]	4-FC_6H_4	Ph	Me	>99 : 1	**19**	54	60
3[d]	4-$OMeC_6H_4$	Ph	Me	>99 : 1	**20**	57	68
4[c]	CH_2CCl_3	Ph	Me	99 : 1	**18**	75	10
5	4-FC_6H_4	Ph	Et	>99 : 1	**23**	74	69
6	4-FC_6H_4	Ph	Bn	99 : 1	**24**	67	60
7	4-FC_6H_4	Me	Me	77 : 23	**22**	65	87
8[d]	Ph	Me	Me	85 : 15	**29**	61	86
9[c]	4-FC_6H_4	Me	Et	83 : 17	**25**	54	90
10[d]	4-FC_6H_4	Me	i-Bu	55 : 45	**27**	23	92

[a] C : N product ratios established by ^{1}H NMR spectroscopic analysis of crude reaction mixture. [b] Established by HPLC analysis on a chiral stationary phase. [c] 3 h reaction. [d] Overnight reaction.



Scheme 1 Re-treatment of *N*-carboxyl **11** with DMAP and NHCs derived from **5** and **28**.

and NHC catalysis (Scheme 1). With DMAP, exclusively starting material was returned after overnight reaction, while treatment with an achiral NHC derived from **5** gave the *C*-regioisomer **22** (99 : 1 C : N). Furthermore, treatment of *N*-carboxylate **11** with the chiral NHC derived from precatalyst **28** gave 10% conversion to *C*-carboxylate **22** in 84% ee.



Scheme 2 Re-treatment of *C*-carboxyl **22** with DMAP and NHCs derived from **5** and **28**.

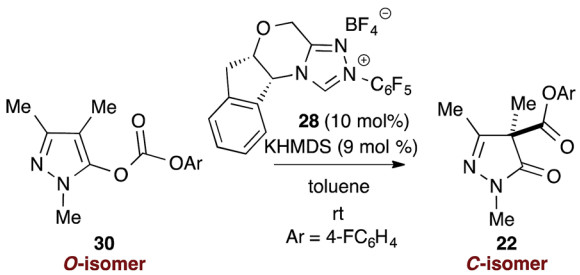
However, while treatment of enantioenriched *C*-carboxylate **22** (87% ee) with either DMAP or chiral NHC **28** returned **22** exclusively (87% ee), treatment with the achiral NHC derived from **5** gave *C*-carboxyl **22** in racemic form.[34] Treatment of (±)-*C*-carboxylate **22** with chiral NHC **28** also returned (±)-**22** (Scheme 2).

These results, combined with a crossover experiment upon a mixture of *N*-carboxylate products,[35] indicate that *O*- to *C*- or *N*-carboxyl transfer reactions with DMAP are *irreversible* in this model system, with *N*-carboxylation kinetically preferred; *N*- to *C*-carboxyl transfer is disfavoured with DMAP. With the achiral NHC derived from precatalyst **5**, *O*- to *C*- or *N*-carboxyl transfer reactions are *reversible*, with the *C*-isomer thermodynamically preferred, while *N*- to *C*-carboxyl transfer is also favoured. However, with the chiral NHC, *O*- to *C*-carboxyl transfer is *irreversible* with high enantiocontrol, while *N*- to *C*-carboxyl transfer is also allowed with good enantiocontrol. To probe this latter hypothesis, the reaction conversion, C : N product ratio and ee of the *O*- to *C*-rearrangement of **30** to **22** using precatalyst **28** was monitored (Table 5). ^{1}H NMR spectroscopic analysis of the reaction mixture showed increasing ratios of C : N products over time, further evidence of catalysed *N*- to *C*-carboxyl transfer.[30] The ee of the *C*-carboxylate product **22** was however essentially independent of the reaction time and C : N ratio, consistent with our previous observations.

Computational insight

Computations were next performed on a simplified model substrate to elucidate the mechanism and origins of the observed regioselectivity. We employed M06-2X[36]/6-31+G**[37]/PCM[38]//M06-2X/6-31G*/PCM in toluene for NHC catalysis and dichloromethane for DMAP, as implemented in Gaussian09.[39] Manual, exhaustive conformational searches were performed to ensure all relevant intermediates and transition state structures

Table 5 Monitoring ee and product ratios with time



Entry	Time (min)	Conversion[a]	C : N ratio[a]	% ee[b]
1	10	85	65 : 35	86
2	30	>98	69 : 31	87
3	60	>98	70 : 30	87
4	360	>98	78 : 22	86

[a] Product conversion and C : N product ratios established by ^{1}H NMR spectroscopic analysis of crude reaction mixture. [b] Established by HPLC analysis on a chiral stationary phase.

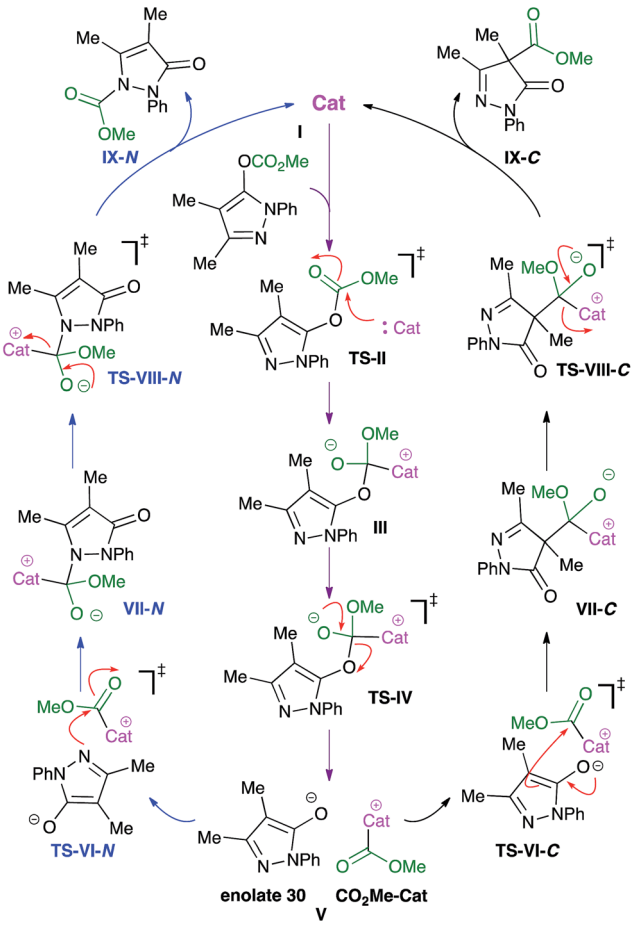


Fig. 2 Detailed proposed mechanism for *C*- and *N*-carboxylation.

(TSs) were located. Intrinsic reaction coordinate (IRC) computations were performed on all TSs to verify reaction pathways. *C*- and *N*-carboxylations share the same general mechanism shown in Fig. 2. Initial *O*-carboxylate attack by catalyst (**TS-II**) and subsequent tetrahedral intermediate collapse (**TS-IV**) leads to common intermediates, enolate **30** and carboxylated catalyst (**CO_2Me-Cat**). Regiodivergence occurs by recapture of carboxyl group by enolate **30** at either *C*(4)- or *N*(1)- (**TS-VI**). The dissociation of the catalyst from the resulting tetrahedral intermediate (**TS-VIII**) releases the final products.

DMAP catalysis

The DMAP-mediated carboxyl transfer preferentially results in *N*-carboxylation. Shown in Fig. 3, initial *O*-carboxylate attack (**TS-II**) by DMAP affords tetrahedral intermediate **III**, collapse of which (**TS-IV**, 20.4 kcal mol^{-1}) affords ion pair intermediates **V** (**CO_2Me-DMAP** and enolate **30**). The *C*- *vs.* *N*-regiocontrol is established when the substrate enolate **30** attacks the carboxylated DMAP either *via* *C*(4)- or *N*(1). Consistent with the experimental results, the *N*-carboxylation process is favoured computationally by ~5 kcal mol^{-1} (**DMAP-TS-VI-*N***, $\Delta G^{\ddagger}$ = 21.9 kcal mol^{-1} *vs.* **DMAP-TS-VI-*C***, $\Delta G^{\ddagger}$ = 26.6 kcal mol^{-1}). Interestingly, the *N*-carboxylation is stepwise addition of enolate and extrusion of catalyst, whereas the *C*-carboxylation process

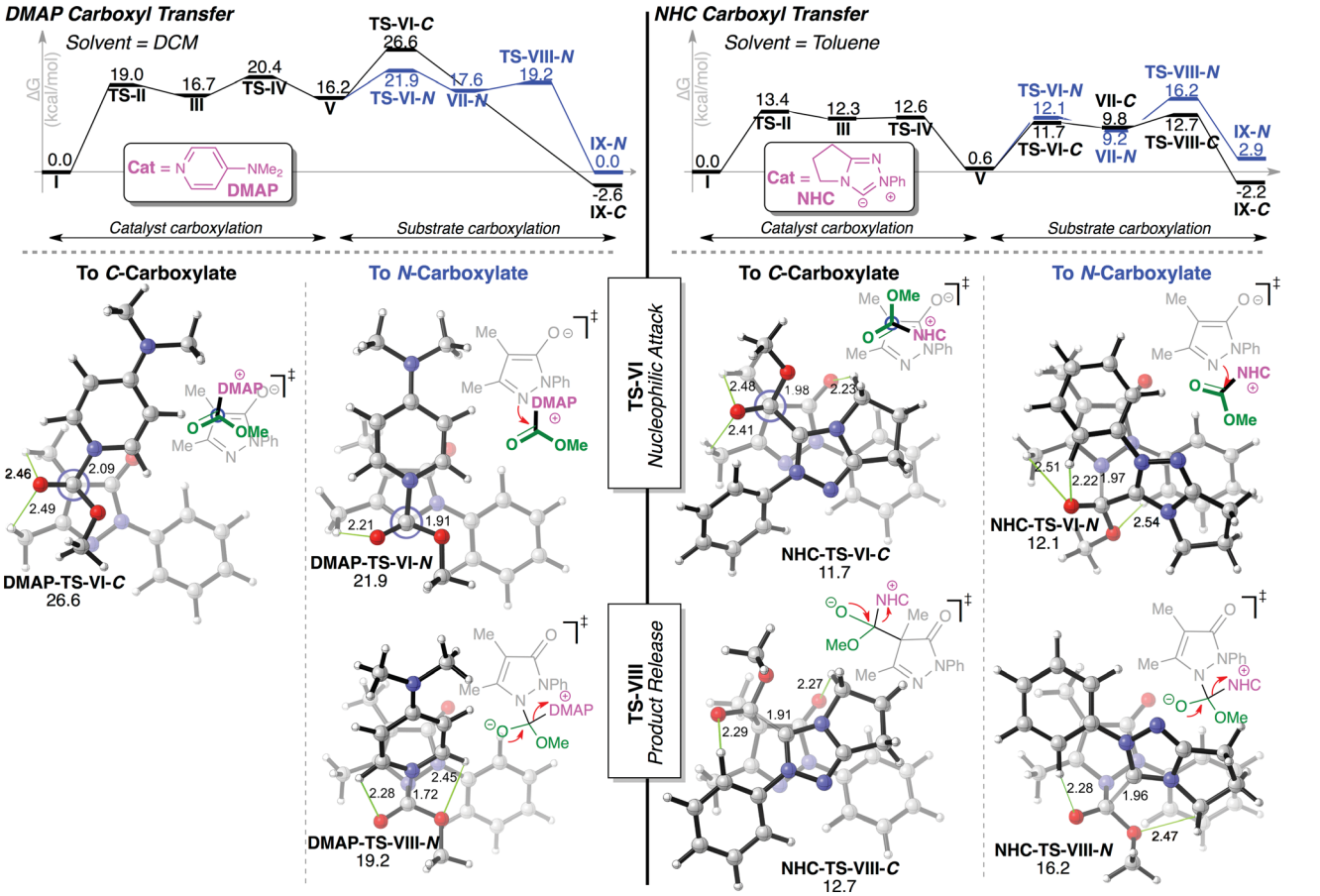


Fig. 3 Reaction coordinate diagrams (*top*) and regioisomeric *TSs* (*bottom*) for DMAP-catalysed (*left*) and NHC-promoted (*right*) carboxyl transfer for major *C*-carboxylate (black) and minor *N*-carboxylate (blue). Green lines indicate stabilizing C–H···O hydrogen bonds, grey lines & Newman projections forming/breaking bond.

(black, Fig. 3) proceeds *via* a concerted, asynchronous carboxylation.[40] This difference in concerted/stepwise behaviour reflects the lack of electrostatic stabilizing effects in **DMAP-TS-VI-*C*** *vs.* **DMAP-TS-VI-*N***. In **DMAP-TS-VI-*N***, there is a substantial spatial overlap between the positively charged carboxylated DMAP and the attacking enolate **30**, as the enolate oxygen and π bond is in closer proximity to the carboxylated DMAP. This is in contrast to **DMAP-TS-VI-*C***, where there is a relatively poor spatial overlap, with only the enolate oxygen in proximity to the positively charged DMAP ring.

NHC catalysis

NHC catalysis leads preferentially to *C*-carboxypyrazolinone product. NHC attack of the *O*-carboxylate substrate (**TS-II**, 13.4 kcal mol^{-1}) and subsequent collapse (**TS-IV**, 12.6 kcal mol^{-1}) of the tetrahedral intermediate (**III**, 12.3 kcal mol^{-1}) leads to ion pair intermediates **V** (**CO_2Me–NHC** and enolate **30**). The NHC favours the *C*-carboxylation pathway by 3.5 kcal mol^{-1} (>99 : 1 C : N, **NHC-TS-VIII-*C*** and **NHC-TS-VIII-*N***), in agreement with experiments. This selectivity arises due to the large relative instability of **NHC-TS-VIII-*N***, where the close proximity of the enolate oxygen and the relatively negatively charged areas of the carboxylated NHC results in a destabilizing repulsive interaction. This is in contrast to **NHC-TS-VIII-*C***, where this repulsive interaction is replaced by stabilizing C–H···O hydrogen bonds[41] between the NHC and the enolate **30**. The computed reaction coordinates corroborate the experimentally observed reversibility of the NHC-catalysed process. NHC addition to the *N*-carboxylated product (**NHC-TS-VIII-*N***) is energetically accessible, with a reverse barrier of 13.3 kcal mol^{-1} (from **NHC-IX-*N***). The forward process leading to the *C*-carboxylation is favoured by 2.6 kcal mol^{-1} over the forward process for the *N*-carboxylation (Fig. 3), resulting in exclusive production of *C*-carboxylated product upon retreatment of *N*-carboxylated product with achiral NHC (as observed in Scheme 1).

Structural comparison of enolate π *vs.* σ reactivity

The remarkable switch in regioselectivity observed between DMAP and NHC catalysis in this system is a result of the markedly different reactivity patterns of the intermediate carboxylated DMAP or NHC and their interaction with the pyrazoline enolate as illustrated in Fig. 3. This is most striking in **DMAP-TS-VI-*N***, where favoured nucleophilic attack from the substrate does not originate from the *N*(1)-lone pair of the

substrate enolate in the σ-plane, but rather the π-system of the extended enolate. This is in contrast to the analogous (disfavoured) **NHC-TS-VI-*N***, where nucleophilic attack is predicted to occur from the *N*(1)-lone pair of the substrate enolate in the σ-plane. As yet, the exact origins of this π *vs.* σ reactivity are unknown. Our working hypothesis is that the relatively sterically unencumbered conjugated DMAP promotes π-π electrostatic interactions,[42] allowing the π-system of the extended enolate to be an energetically more competent nucleophile compared with the σ-*N*(1)-lone pair.

Conclusion

In conclusion, the regiodivergent *O*- to *C*- or *N*-carboxyl transfer of pyrazolyl carbonates has been investigated, with DMAP giving preferential *N*-carboxylation and triazolinylidenes promoting selective *C*-carboxylation (both with up to 99 : 1 regioselectivity). An enantioselective *O*- to *C*-carboxyl variant using NHC catalysis is demonstrated (up to 92% ee), while mechanistic and DFT studies outline the pathways operative in this system and delineate insight into the structural reasons for the observed selectivity. Current investigations from within our groups are focused upon the demonstration of further Lewis base-mediated organocatalytic transformations and developing further computational insight into these transformations.

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