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Synthesis of γ-substituted carbonyl compounds from DMSO-mediated oxidation of enynamides: mechanistic insights and carbon- and hetero-functionalizations†

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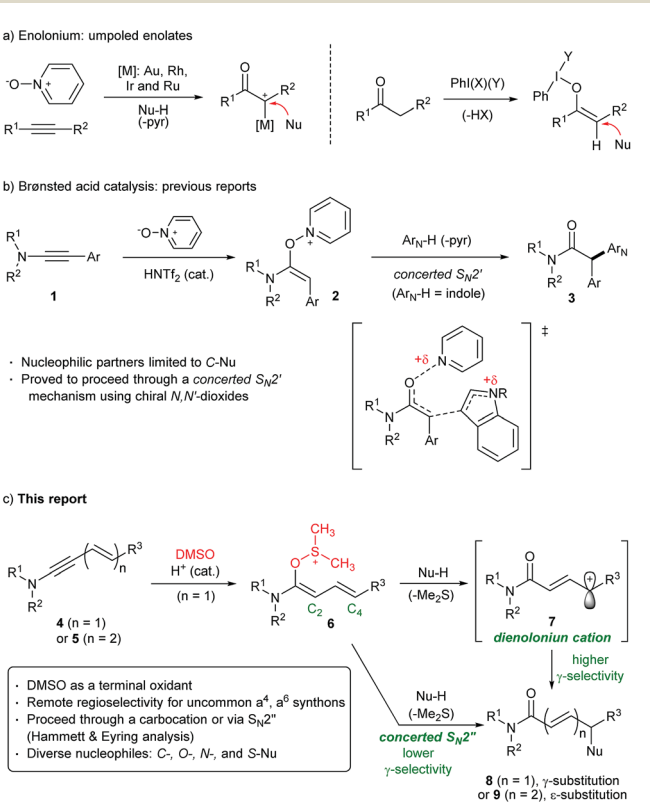
Oxidative coupling of 1,3-enynamides using DMSO as a terminal oxidant has been developed. Carbon as well as unmodified heteroatom nucleophiles, including aliphatic alcohols, thiols, and hydrazides, could be efficiently alkylated at the γ-position in a highly regioselective fashion. The kinetic analysis suggested a nucleophile-dependent mechanism ranging from a concerted S_N2'' to a carbocationic mechanism. Thus, the remote site-selectivity was ascribed to the partial positive charge developing at the terminal carbocationic center.

Introduction

Inverting natural polarity (Umpolung) allows for an outstanding opportunity to streamline redox efficient processes and enables novel disconnections with complementary selectivity to the traditional methods.[1] For example, under conditions of normal polarity, α-hetero-functionalization of carbonyl compounds often requires strongly basic conditions and/or elaborate, pre-oxidized heteroatom-electrophiles.[2] In contrast, Umpolung protocols allow for the use of unmodified heteroatom donors, which greatly facilitates the synthesis.

Towards umpoled enolate (a^2) synthons, oxidation of alkynes through transition metal catalysis (Au, Rh, Ir, Ru, and Zn)[3] and the hypervalent iodine chemistry of carbonyl compounds[4] have led the way (Scheme 1a). More recently, we[5] and others[6,7] have reported a non-metal protocol involving Brønsted acid that can catalyze the oxidation of ynamides **1** and induce subsequent addition of carbon nucleophiles, furnishing α-heteroaryl imides **3** (Scheme 1b). In this process, it was unambiguously proved that the key intermediate, adduct **2**, underwent a concerted S_N2' alkylation by the observation of chirality transfer from optically active *N*-oxides.[5a]

Compared to enolonium equivalents, direct access to umpoled a^4 synthons is rare. Although synthesis of γ-substituted-α,β-carbonyl compounds has been demonstrated using PhNO, DEAD, or oxygen gas,[8] generally applicable methods for the introduction of *O*-, *S*-, *N*- as well as carbon nucleophiles either at the γ- or ε-position are highly desirable as they are found in the scaffolds of numerous biologically active



Scheme 1 Vinylogous enolonium chemistry: γ-(or ε-) functionalizations.

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agents.[9] To this end, we envisioned that oxidation of 1,3-enynamides **4** would generate *dienolonium*, such as **6** that corresponds to an umpoled version of silyl dienol ethers in Mukaiyama reactions. It would be interesting to explore the unknown regioselectivity in the alkylation,[10,11] and to elucidate the underlying mechanism. Herein, we have developed an oxidative alkylation of enynamides **4** and dienynamides **5** that occurs with remarkable selectivity for the remote substitution furnishing γ-substituted **8** or ε-substituted **9**, respectively, and disclosed that the reaction proceeded through a mechanism ranging from concerted S_N2'' or through a dienolonium carbocation intermediate **7**, depending on the types of nucleophiles.

Meanwhile, one inherent disadvantage of the alkyne oxidation protocols is the necessity to use pyridine-*N*-oxide which liberates pyridine, complicating the acid catalysis. In this context, dimethyl sulfoxide (DMSO) is advantageous in that the byproduct (Me_2S) is easily removable (bp = 37 °C) and not so basic ($pK_a = -5.4$ in water).[12–14] Initially, we were concerned that the nucleophiles may attack the *O*-dienoxysulfenium intermediate **6** (Scheme 1c) at the *S*-atom (S_N2) rather than at C4 (S_N2'') as in interrupted Pummerer reactions.[15] Notwithstanding, a selective oxygenative coupling at the remote position was obtained and the usefulness of this oxidation is further demonstrated by the introduction of exceptionally diverse nucleophiles, ranging from carbon (indoles, furans, and silyl enol ethers) to heteroatom donors (aliphatic alcohols, thiols, and hydrazides) with good to excellent remote regioselectivity.

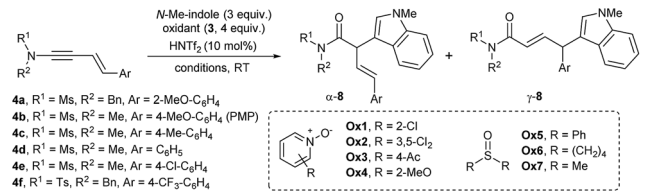
Results and discussion

Survey of reaction conditions and Umpolung alkylation with carbon nucleophiles

For the examination of site selectivity in the enynamide oxidation, we initially chose 1,3-enynamide **4a** bearing sterically encumbering *o*-MeO-C_6H_4 at C4 as a substrate that presents a regioselectivity challenge (Table 1). For initial screening, 3 equiv. of *N*-Me-indole along with 4 equiv. of *N*-oxides (**Ox1-4**) was employed. 2-Cl-Pyridine-*N*-oxide, **Ox1** mediated the formation of **8a** with a remarkable efficiency in only 5 min at rt, although the regioselectivity remained mediocre (α : γ = 1 : 4.5, entry 1).[16] Interestingly, diphenyl sulfoxide **Ox5** was also found to be a suitable oxidant for enynamides, while previous studies on the ynamide oxidation documented that [3,3]-sigmatropic rearrangement occurred dominantly.[14b] To our delight, DMSO (**Ox7**) displayed an excellent reactivity with α : γ = 1 : 5.6 (entry 7).[17] Change of solvents (entries 8–10) to 1,4-dioxane slightly improved the ratio to α : γ = 1 : 8.7, albeit at the expense of the reactivity (entry 10).

At this point, we turned to other derivatives of enynamides **4b–f** having different aryl groups at C4 (entries 11–15). It was revealed that both the α : γ selectivity and the reactivity in the γ-arylation with indoles critically depended on the electron-density of the Ar group at C4. For example, the reaction of 4-MeO-derivatives **4b** delivered **8ba** with a good ratio (α : γ = 1 : 10) in an excellent yield (entry 11). However, *p*-tolyl (**4c**), Ph (**4d**), 4-Cl-C_6H_4 (**4e**) and 4-CF_3-C_6H_4 (**4f**) derivatives showed decreasing reactivity and regioselectivity in the order, suggesting that a carbocation stabilizing group is needed at the C4 position. Remarkably, under the optimized conditions (entry 16), the oxidative coupling of **4b** occurred with only 1.2 equiv. of *N*-Me-indole and 1.2 equiv. of DMSO at 2.5 mol% of $HNTf_2$, without adversely affecting the yield (entry 16). Under these conditions, a gram-scale reaction (3.8 mmol of **4b**) proceeded smoothly as well (entry 17).

Table 1 A survey of reaction conditions and substrates[a]

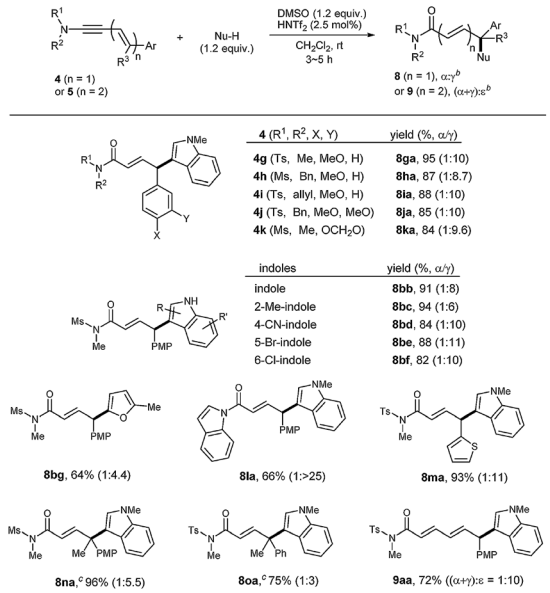


Entry	Substrate	Oxidant	Conditions	**2**[b] (%)	α : γ[c]
1	**4a**	**Ox1**	DCE, 5 min	**8aa**, 90	1 : 4.5
2	**4a**	**Ox2**	DCE, 15 min	**8aa**, 71	1 : 6.7
3	**4a**	**Ox3**	DCE, 6 h	**8aa**, 35	1 : 5.2
4	**4a**	**Ox4**	DCE, 10 h, 60 °C	**8aa**, 41	1 : 4.5
5	**4a**	**Ox5**	DCE, 5 min	**8aa**, 70	1 : 5.8
6	**4a**	**Ox6**	DCE, 5 min	**8aa**, 77	1 : 5.1
7	**4a**	**Ox7**	DCE, 5 min	**8aa**, 95	1 : 5.6
8	**4a**	**Ox7**	CH_3CN, 15 min	**8aa**, 62	1 : 6.8
9	**4a**	**Ox7**	MTBE, 0.5 h	**8aa**, 42[d]	1 : 7.8
10	**4a**	**Ox7**	1,4-Dioxane, 0.5 h	**8aa**, 66	1 : 8.7
11	**4b**	**Ox7**	DCE, 5 min	**8ba**, 96	1 : 10
12	**4c**	**Ox7**	DCE, 10 min	**8ca**, 83	1 : 2.7
13	**4d**	**Ox7**	DCE, 3 h	**8da**, 62	1 : 1
14	**4e**	**Ox7**	DCE, 7 h	**8ea**, 63	1 : 1
15	**4f**	**Ox7**	DCE, 3 h	—[e]	—
16[f]	**4b**	**Ox7**	DCM, 3 h	**8ba**, 97	1 : 10
17[f,g]	**4b**	**Ox7**	DCM, 3 h	**8ba**, 93	1 : 10

[a] **4** (0.1 mmol), oxidant **3** (4 equiv.), *N*-Me-indole (3 equiv.) and $HNTf_2$ (10 mol%) in solvents (0.1 M). [b] Isolated yields of **8** after chromatographic separation. [c] Determined from the crude ^1H NMR spectra. [d] Hydration byproduct was observed. [e] Hydration byproduct (74% yield). [f] *N*-Me-indole (1.2 equiv.) and DMSO (1.2 equiv.) were used in the presence of 2.5 mol% of $HNTf_2$. [g] With 3.77 mmol of **4b**.

With this initial reaction profile and the optimized conditions, we then inspected the reaction scope with various carbon nucleophiles (Table 2). The variation of *N*-alkyl and *N*-sulfonyl groups as well as electron-rich Ar groups (**8ga–8ka**) was all well accommodated with good reactivity and regioselectivity. Various indoles could also be incorporated without any event as in **8bb–8bf**. Notably, heterocyclic motifs such as 2-furyl (**8bg**), *N*-acyl indole (**8la**), or 2-thiophene (**8ma**) could be easily incorporated into the products. Notably, the formation of a quaternary center as in **8na** and **8oa** was very efficient with a useful level of γ-selectivity: even phenyl derivative **8oa** was obtained with higher selectivity compared to **8da** (entry 13, Table 1).[18] Subsequently, we went on extending the conjugation by preparing dienynamide **5a** ($n = 2$; R^1 = Ts, R^2 = Me; R^3 = H; Ar = 4-MeO-C_6H_4). To our delight, its reaction went smoothly to furnish the corresponding α,β,γ,δ-unsaturated imide **9aa** with high ε-selectivity.

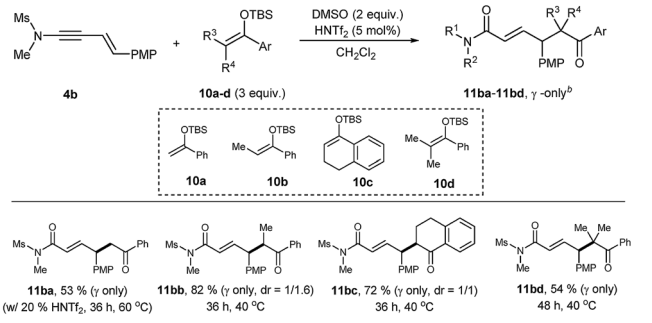
Table 2 Reactions with carbon nucleophiles[a]



[a] **4** (0.2 mmol), DMSO (1.2 equiv.), Nu-H (1.2 equiv.) and $HNTf_2$ (2.5 mol%) in CH_2Cl_2 (0.1 M) unless otherwise noted; isolated yields of **8** (or **9**) after chromatographic purification. [b] Determined from the crude ^1H NMR spectra. [c] 5 mol% of $HNTf_2$ was used; reaction time: 9 h.

On the other hand, the reaction of silyl enol ethers was much slower (Table 3). For example, the reaction of **4b** with di-substituted silyl enol ether **10a** in the presence of 20 mol% of $HNTf_2$ at 60 °C was incomplete even after 36 h, from which **11ba** was obtained in 53% yield. Tri-substituted silyl enol ethers **10b**, **10c** were more reactive, giving higher yields of **11bb** and **11bc**, respectively, in the presence of 5 mol% of $HNTf_2$. However, tetra-substituted silyl enol ether **10d**, reacted sluggishly. These indicated that a balance between the electron-density and the steric hindrance is necessary for an efficient coupling.

Table 3 Reactions with silyl enol ethers[a]



[a] **4** (0.2 mmol), DMSO (2 equiv.), silyl enol ethers (3 equiv.) and $HNTf_2$ (5–20 mol%) in CH_2Cl_2 (0.1 M); isolated yields of **11** after chromatographic purification. [b] The α/γ and diastereomeric ratio were determined from the crude ^1H NMR spectra.

Remarkably, all the reactions of silyl enol ethers were completely regioselective (α : γ = 1 : >25).

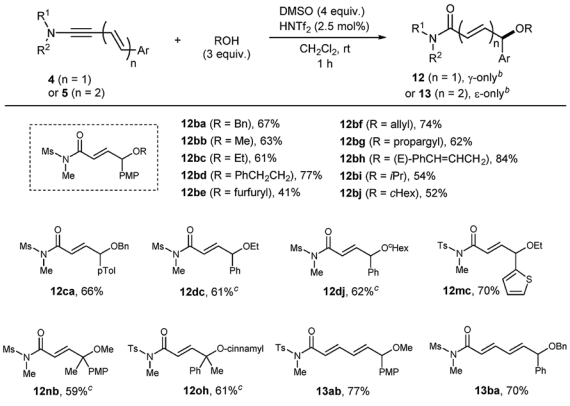
Umpolung alkylation with heteroatom nucleophiles

Heteroatom-functionalization at the a^4 or a^6 site may perhaps be the most important application of this Umpolung chemistry.[2,4b] Intermolecular Umpolung reaction leading to α-heterofunctionalization has been studied with various nucleophiles, including (thio)phenols,[19a] oxyacids,[19b,c] halogen,[19d] thiocyanate,[19d] azides,[19d,e] amines,[4f,19f,g] and TEMPO.[19h–j] Although unmodified phenols/thiols[19a] and amines[19f,g] could be used as nucleophiles, use of oxidizable aliphatic (primary and secondary) alcohols/thiols is surprisingly rare.[19]

When benzyl alcohol (3 equiv.) was tested as a nucleophile in the presence of DMSO (4 equiv.) and $HNTf_2$ (2.5 mol%), we were delighted to observe the formation of 67% of **12ba** with a complete γ-selectivity in less than 5 min at room temperature (Table 4). Previous hypervalent iodine chemistry allowed for the use of MeOH, EtOH and iPrOH, but required these alcohols as solvents.[20] In contrast, the current protocol can operate with only 3 equivalents of nucleophiles and is thus suitable for the more elaborate alcohol donors. Gratifyingly, the transformation was general not only for simple primary alcohols (**12ba–12bd**), but also for furfuryl, allyl, propargyl, and cinnamyl alcohols, furnishing **12be**, **12bf**, **12bg**, and **12bh**, respectively. Products with secondary alcohols **12bi**, **12bj** were also obtained in reasonable yields, but *tert*-butanol gave only a trace amount of the adduct (not shown). Notably, all the reactions of **4b** to form **12ba–12bj** were complete in less than 1 h and an exclusive γ-regioselectivity was obtained, in contrast to the carbon nucleophiles in Table 2.

The faster rates with alcohol nucleophiles allowed us to use a less electron-rich aryl group at C4. For example, the reaction with **4c** (Ar = *p*-tol) with benzyl alcohol proceeded uneventfully. However, the reaction with **4d** (Ar = Ph) was very slow and

Table 4 Reactions of (di)enynamides with *O*-nucleophiles[a]



[a] **4** (0.2 mmol), DMSO (4 equiv.), ROH (3 equiv.) and $HNTf_2$ (2.5 mol%) in CH_2Cl_2 (0.1 M) unless otherwise noted; isolated yields of **12** (or **13**) after chromatographic purification. [b] Determined from the crude ^1H NMR spectra. [c] 5 mol% of $HNTf_2$; reaction time: 6 h.

required 5 mol% of $HNTf_2$ and a longer time (6 h) for completion, giving reasonable yields of **12dc** and **12dj** with an exclusive γ-selectivity. Alkoxylation products with a tetra-substituted center, **12nb** and **12oh** were also obtained in reasonable yields, employing 5 mol% $HNTf_2$. Finally, the reaction could be extended to dienynamides **5a**, **5b**, affording completely ε-selective alkoxylation products **13ab** and **13ba** in good yields.

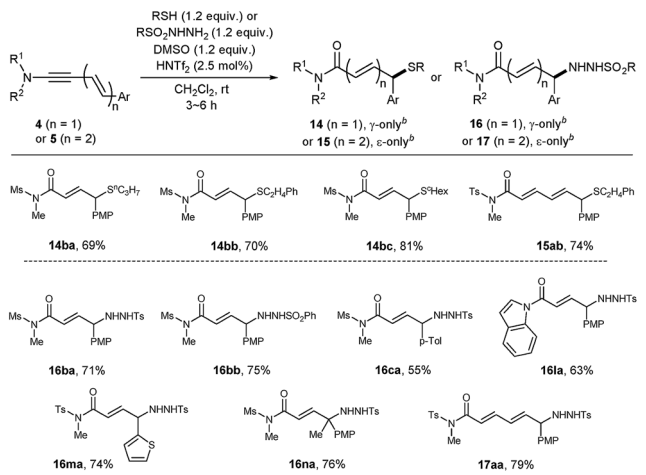
Encouraged by the success of alcohol nucleophiles, the reaction scope was extended to *S*- and *N*-nucleophiles as well (Table 5). Gratifyingly, with these nucleophiles, only a slight excess of donors (1.2 equiv.) and DMSO (1.2 equiv.) in the presence of $HNTf_2$ (2.5 mol%) were sufficient. Aliphatic thiols were suitable nucleophiles, furnishing **14ba**, **14bb** and **14bc** with exclusive γ-selectivity, and the dienimide **15ab** with exclusive ε-selectivity. However, in contrast to $Zn(OTf)_2$-catalyzed oxidative coupling,[19a,d] aromatic thiol derivatives (PhSH) failed to deliver the corresponding product **14** (not shown).

Towards *N*-functionalization, various *N*-nucleophile donors were tested, including amines, amides, and hydroxylamines. Among them, sulfonyl hydrazides were found to be effective nucleophiles. With *p*-toluenesulfonyl- or benzenesulfonyl hydrazide, the corresponding products **16** or **17** were obtained in a completely regioselective manner. The connectivity of a hydrazide adduct **16ma** was unambiguously confirmed by single crystal X-ray crystallography.[21]

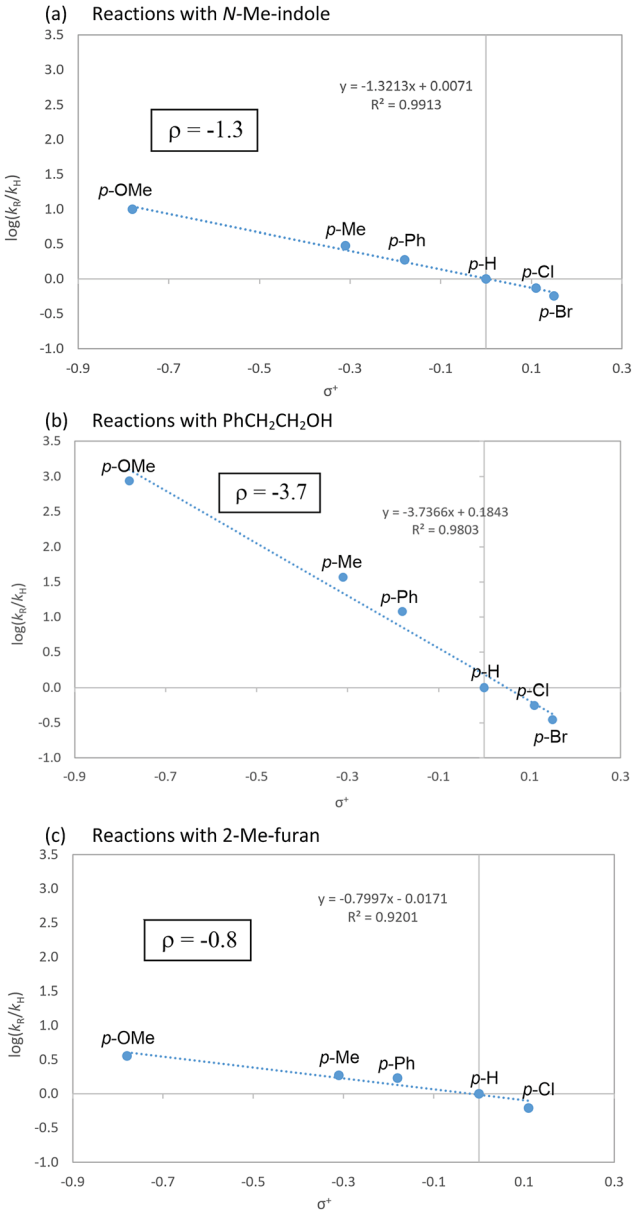
Kinetic study and mechanistic insights

To gain a mechanistic insight into the remote Umpolung functionalizations and to probe the nature of the intermediates involved, kinetic analysis was conducted. To the best of our knowledge, kinetic analysis on the Brønsted acid-catalyzed oxidative coupling of ynamides that can be used to check the validity of the DFT theoretical studies[13e,22] is unavailable. We set

Table 5 Reactions of (di)enynamides with *S*-, *N*-nucleophiles[a]

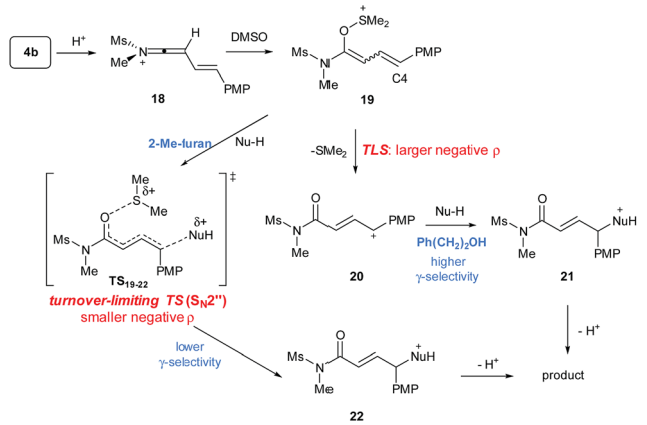


[a] **4** (0.2 mmol), DMSO (1.2 equiv.), Het-H (1.2 equiv.) and $HNTf_2$ (2.5 mol%) in CH_2Cl_2 (0.1 M); isolated yields after chromatographic purification. [b] Determined from the crude ^1H NMR spectra.



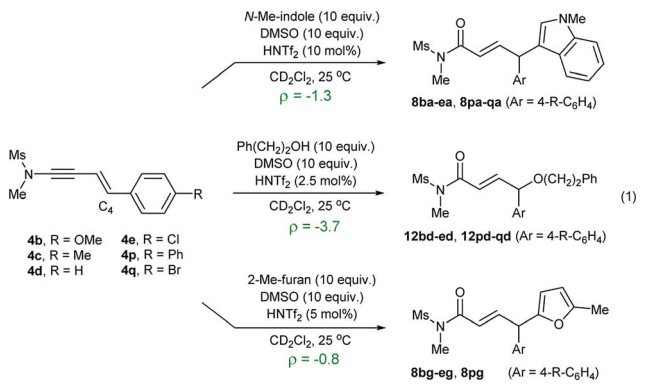
Scheme 2 Hammett correlation with *N*-Me-indole, $Ph(CH_2)_2OH$ and 2-Me-furan as nucleophiles according to eqn (1).

out to perform a Hammett study with a set of enynamides differing in *para*-substituents, **4b** (4-OMe), **4c** (4-Me), **4d** (4-H), **4e** (4-Cl), **4p** (4-Ph), and **4q** (4-Br) to probe the electronic effect of aryl groups at C4 according to eqn (1) (Scheme 2). In the substitution with *N*-Me-indole, the $\log(k_R/k_H)$ displayed a linear correlation with σ^+ parameters, with a negative ρ value (−1.3) (Scheme 2a). Upon changing the nucleophile to an alcohol, $Ph(CH_2)_2OH$, the rate became significantly more sensitive to σ^+ with $\rho = -3.7$ (Scheme 2b), while the reaction with 2-Me-furan nucleophile showed a decreased sensitivity ($\rho = -0.8$) (Scheme 2c). Interestingly, the observed regioselectivity in the reaction of enynamides **4b** (R = 4-MeO) with nucleophiles was in good accordance with the reaction constant ρ. For example, increasing α/γ ratio was observed in the order of 2-Me-indole (1/4.4 for **8bg**),



Scheme 3 A continuum mechanism between S_N2'' and *via* an enolonium cation.

N-Me-indole (1/10 for **8ba**), and $Ph(CH_2)_2OH$ (0/100 for **12bd**), where the corresponding ρ values were −0.8, −1.3, and −3.7, in the order. The observed reaction constant ρ reflects the build-up of a positive charge at C4 in the turnover-limiting step (TLS) and based on this, we formulated a tentative mechanism as in Scheme 3. At one extreme, $Ph(CH_2)_2OH$ ($\rho = -3.7$) would favor a route where S–O cleavage occurs first, forming an enolonium carbocation **20**, which is then trapped to yield **21**. At the other end of the continuum, 2-Me-furan ($\rho = -0.8$) will follow a route in which a more synchronous cleavage of the S–O bond and the formation of a new C–C bond (TS_{19-22}) occur and as a result, less charge builds up at C4.[23] Here, the γ-selectivity in the alkoxylation may be due to the formation of the more stable conjugated product and this tendency weakens with the S_N2'' pathway.



Next, the temperature dependence of the reaction rate (k_{obs}) for the reaction of **4b** with *N*-Me-indole was examined in the range of 298–328 K (Fig. 1).[15] From the Eyring equation, the activation parameters were determined to be $\Delta H^{\ddagger} = 83.5$ kJ mol^{-1} and $\Delta S^{\ddagger} = -37.6$ J K^{-1} mol^{-1}. The large negative entropy of activation is consistent with an associative transition state, such as TS_{19-22}.[24] Other associative steps, such as protonation of the enynamides (**4b** to **18**) or addition of DMSO (**18** to **19**) were excluded, because if these earlier steps were turnover-limiting, different sensitivity (ρ) depending on the nucleophiles (Scheme 2) should not have been observed.

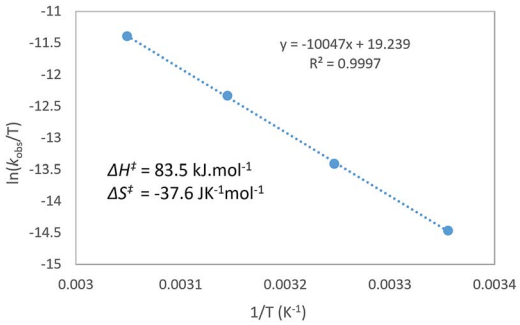
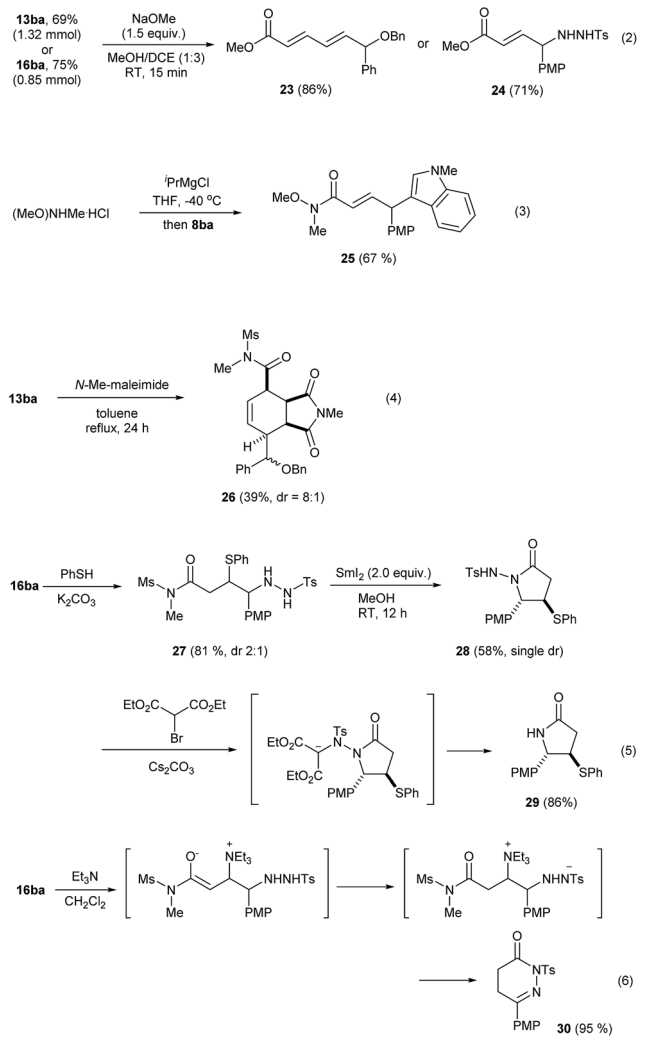


Fig. 1 Eyring plot at 298–328 K in the reaction of **4b** with *N*-Me-indole to form **8ba**.

Finally, the reaction order was examined with respect to various reactants. The rate (k_{obs}) of the formation of **8ba** was found to be inversely proportional to the concentration of *N*-Me-indole (Fig. S5†), which, at first, seemed contradictory to the turnover-limiting trapping of **19** to form **22**. However, this should be due to the depletion of $HNTf_2$ by the basicity of indoles and the indole moiety in the product **8ba**, as k_{obs} is linearly related to the concentration of $HNTf_2$ (Fig. S7†). In fact, for $PhCH_2CH_2OH$, k_{obs} was apparently independent of the concentration of the alcohol (Fig. S6†), likely because the increased concentration of the nucleophile counter-balanced the buffering of the superacid ($HNTf_2$). Meanwhile, the reaction rate (k_{obs}) was zeroth order in DMSO, which suggested that once the keteniminium **18** is formed, trapping with DMSO to yield **19** is very rapid and much faster than the dissociation to **20** or attack by *N*-Me-indole. This accounts for the chemoselectivity of this Umpolung alkylation process that occurs efficiently in a situation of multiple possible nucleophiles.[5b,d]

Synthetic applications

The current Umpolung alkylation provides unique structures that are difficult to obtain otherwise. Therefore, we examined their synthetic utility which is summarized in Scheme 4. Initially, **13ba** (from 1.91 mmol of **4b**, 69%) and **16ba** (1.13 mmol of **4b**, 75%) were prepared on a larger scale without any event. Esterification of these occurred chemoselectively to furnish the corresponding ε-alkoxydienoates **23** or γ-hydrazidoenoates **24**, respectively, in good yields (eqn (2)). The imide product **8ba** could be converted into a Weinreb amide **25** under basic conditions (eqn (3)).[25] The ε-alkoxy-α,β,γ,δ-unsaturated imide **13ba** underwent Diels–Alder cycloaddition with *N*-methyl maleimide to give **26** with an exclusive *endo*-selectivity and a good level of substrate-controlled diastereoselectivity (dr = 8 : 1, eqn (4)). Conjugate addition with thiolate gave **27** with dr = 2 : 1. Subsequently, attempts to cleave the N–N bond in this mixture with SmI_2 failed and instead **28** was obtained as a side product, presumably because of the Lewis acidity of Sm(III). Interestingly, **28** was obtained as a single diastereomer,[26] from the major diastereomer of **27**. The N–N bond cleavage could then be achieved through a non-reductive method comprising alkylation of **28** and the *in situ* E1cb-elimination to form the



Scheme 4 Synthetic applications of the products.

lactam **29** (86%) (eqn (5)).[27] Interestingly, the compound **16ba** was found to be quite sensitive to bases and, upon treatment with Et_3N, cyclic hydrazone **30** was obtained in an excellent yield. Presumably, this occurs through a series of events, comprising conjugate addition of Et_3N, proton transfer, ring closure, elimination of Et_3N and isomerization (eqn (6)).

Conclusions

Herein, we reported a generally applicable synthesis of γ-substituted-α,β-unsaturated carbonyl compounds. This DMSO-based oxidation protocol can accommodate diverse carbon- and heteronucleophiles, including oxidizable heteroatom donors, in a highly chemo- and regio-selective manner. The origin of the remote-selectivity was interrogated by kinetic analysis and this suggested that the reaction proceeds through an S_N2'' or *via* a dienolonium carbocation, depending on the nucleophiles. This may provide mechanistic insights which may be of use in devising strategies for the future enantioselective processes.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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