

# A C<sub>2</sub>-symmetric nickel diamine complex as an asymmetric catalyst for enecarbamate additions to butane-2,3-dione†

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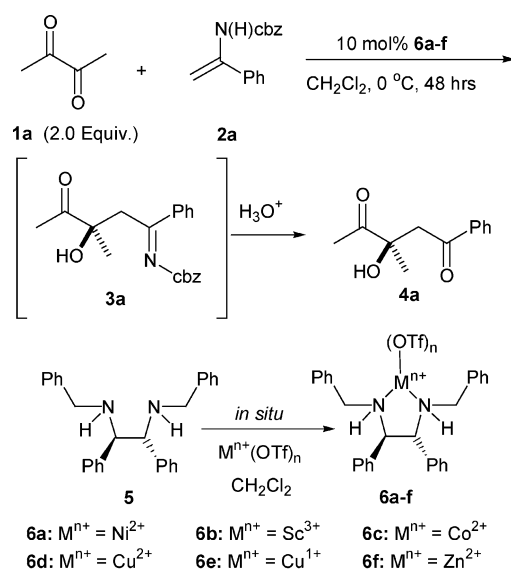
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Butane-2,3-dione was activated towards nucleophilic addition of enecarbamates by a series of metal triflate complexes of a C<sub>2</sub>-symmetric diamine to give stereogenic, aldol-like, *t*-alcohols, a novel nickel(II) triflate complex was identified as a good catalyst for this asymmetric transformation, and an *aquo* nickel(II) complex was identified by XRD techniques.

Our group has previously demonstrated the utility of enecarbamates as nucleophiles for C–C bond formation in asymmetric copper catalysed reactions of aldimines and aldehydes that afford stereogenic secondary 1,3-imino alcohols and amines.<sup>1</sup> Although enecarbamates provide a range of potential synthetic utilities, their use as nucleophiles in asymmetric catalysis has only recently been reported.<sup>1</sup>

Herein, we report that simple diketones **1a** and **1b** can be activated towards nucleophilic addition of enecarbamates **2a–c** with a reasonable degree of stereocontrol by a novel Lewis acidic cationic Ni(II) diamine complex, providing access to otherwise synthetically demanding stereogenic tertiary alcohols **4a–e**.<sup>2</sup> A crystal structure of a stable Ni(II) bis-aquo complex of ligand **5** revealed an octahedral geometry at the nickel.<sup>3</sup>

We initially chose to investigate cationic transition metal triflate complexes **6a–f** of a C<sub>2</sub>-symmetric diamine **5**, prepared *in situ* in CH<sub>2</sub>Cl<sub>2</sub>,<sup>4</sup> as catalysts for the addition of **2a** to **1a**, see Scheme 1. Enecarbamate **2a** was previously shown as a useful enecarbamate in work concerned with aldimine or aldehyde substrates.<sup>1</sup>



**Scheme 1** Aldol-like reaction of enecarbamate **2a** with diketone **1a**, and catalyst preparation.

The substrates were added to the catalyst solution, corresponding to *ca.* 0.07 M with respect to **2a**, *i.e.*, concentration

with respect to **6** is 0.007 M.<sup>5</sup> The crude reaction mixtures were treated with 3 N HCl<sub>aq</sub> to give the easier to handle and analyse diketone product **4a**.<sup>6</sup>

Catalyst **6a** resulted in the formation of product **4a** in a promising yield of 67%, the ee of this tertiary alcohol was 76%. Scandium(III) triflate in combination with **5** failed to catalyse the reaction under the conditions employed (Table 1, entry 2), and cobalt(II) triflate gave only a very small amount of the desired product (5% yield) with 45% ee (Table 1, entry 3). Whilst copper(II) triflate gave a slightly better yield than nickel(II) triflate the ee was slightly lower (Table 1, entry 4 *versus* entry 1), and comparison between catalysts derived from copper(II) and copper(I) triflates revealed the 2+ oxidation state to be superior (Table 1, entry 4 *versus* entry 5). That zinc(II) triflate catalyses the reaction (Table 1, entry 6) with similar selectivity to nickel(II) and copper(II) triflates (Table 1, entries 1 & 4 respectively), suggests similar modes of operation.

Since the best ee was obtained with nickel and, as it is relatively under-studied as a Lewis acid with respect to its first row neighbours, we selected nickel for further elaboration, even though a slightly better yield was obtained with Cu(OTf)<sub>2</sub>.<sup>7</sup> Previously, our group has reported the use of copper complexes as asymmetric catalysts,<sup>1</sup> we were keen to expand the scope of our study to other Lewis acidic, metal containing, species which also led us to focus our efforts on the understanding and application of a previously unreported nickel(II) triflate diamine complex.

For nickel(II) triflate variation of catalyst loading and reaction temperature did not give any significant improvement in either yield or ee (see Table 2 *versus* Table 1, entry 1), whilst good improvements were observed for extended reaction times, CH<sub>2</sub>Cl<sub>2</sub> was also shown to be the best solvent of those tried.

Surprisingly an increase in catalyst loading from 10 to 15 mol% resulted in a reduction in yield (67 *versus* 33%, Table 1, entry 1 and Table 2, entry 1, respectively), although ee was unaffected.

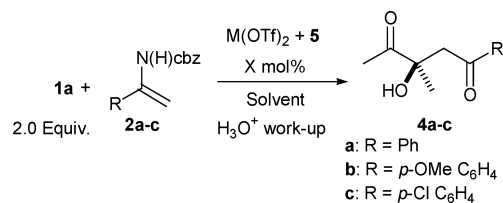
Similarly a reduction in catalyst loading led to a further reduction in yield but a slight improvement in ee (Table 2, entry 5 *versus* Table 1, entry 1 and Table 2, entry 1). The reaction did not proceed at –30 °C even after 72 h (Table 2, entry 3). Although the reaction did proceed a little at –20 °C, albeit in equimolar conversion to catalyst loading (Table 2, entry 7). Toluene proved to be slightly inferior to CH<sub>2</sub>Cl<sub>2</sub> (Table 2, entry 8). A reduction of catalyst loading to 6 mol% and concentration to 0.006 M gave a reduced ee (41%) along with a dramatically reduced yield (11%)

**Table 1** Transition metal-triflate catalysed reaction of **1a** with **2a**

Entry	Catalyst	Yield (%)	EE (%)
1	<b>6a</b>	67	76
2	<b>6b</b>	—	—
3	<b>6c</b>	5	45
4	<b>6d</b>	72	71
5	<b>6e</b> <sup>a</sup>	14	57
6	<b>6f</b>	31	75

<sup>a</sup> Cu(I)(OTf)<sub>2</sub>·0.5 PhH was used. Yield refers to isolated yield of hydrolysed ketone product.

† Electronic supplementary information (ESI) available: experimental details and analytical data. See <http://dx.doi.org/10.1039/b505404d>

**Table 2** Ni(OTf)<sub>2</sub> + **5** catalysed reactions of **1a** with **2a–c**; Y = yield of diketone; Tol = toluene; M = Ni(II) unless otherwise stated.

Entry	Product <sup>a</sup>	Temperature/°C	X	Catalyst/mM	Solvent	Y (%)	Ee (%)
1	<b>4a</b>	0	15	7	CH <sub>2</sub> Cl <sub>2</sub>	33	76
2	<b>4a</b> <sup>b</sup>	39	10	7	CH <sub>2</sub> Cl <sub>2</sub>	27	49
3	<b>4a</b> <sup>c</sup>	-30	10	7	CH <sub>2</sub> Cl <sub>2</sub>	—	—
4	<b>4a</b>	0	6	12	CH <sub>2</sub> Cl <sub>2</sub>	20	69
5	<b>4a</b>	0	5	7	CH <sub>2</sub> Cl <sub>2</sub>	15	79
6	<b>4a</b>	0	6	3	CH <sub>2</sub> Cl <sub>2</sub>	17	77
7	<b>4a</b>	-20	6	6	CH <sub>2</sub> Cl <sub>2</sub>	6	74
8	<b>4a</b>	0	10	8	Tol	47	75
9	<b>4a</b>	0	6	6	Tol	11	41
10	<b>4a</b>	0	10	8	4 : 1 Tol : CH <sub>2</sub> Cl <sub>2</sub>	46	80
11	<b>4a</b>	0	10	7	1 : 1 Tol : CH <sub>2</sub> Cl <sub>2</sub>	32	80
12	<b>4a</b>	0	10	9	1 : 4 Tol : CH <sub>2</sub> Cl <sub>2</sub>	15	79
13	<b>4a</b>	0	10	8	Et <sub>2</sub> O	26	70
14	<b>4a</b>	0	6	6	THF	—	—
15	<b>4a</b>	0	6	6	CH <sub>3</sub> CN	8	<2
16	<b>4a</b> <sup>d</sup>	0	10	7	CH <sub>2</sub> Cl <sub>2</sub>	94	84
17	<b>4b</b>	0	10	7	CH <sub>2</sub> Cl <sub>2</sub>	47	45
18	<b>4b</b> <sup>d</sup>	0	10	7	CH <sub>2</sub> Cl <sub>2</sub>	59	65
19	<b>4c</b>	0	10	7	CH <sub>2</sub> Cl <sub>2</sub>	20	75
20	<b>4c</b> <sup>d</sup>	0	10	7	CH <sub>2</sub> Cl <sub>2</sub>	90	82
21 <sup>e</sup>	<b>4a</b>	0	10	8	4 : 1 Tol : CH <sub>2</sub> Cl <sub>2</sub>	53	48
22 <sup>e</sup>	<b>4b</b>	0	10	7	CH <sub>2</sub> Cl <sub>2</sub>	84	35
23 <sup>e</sup>	<b>4c</b>	0	10	7	CH <sub>2</sub> Cl <sub>2</sub>	44	38

<sup>a</sup> Reaction time was 48 h unless stated otherwise. <sup>b</sup> Black precipitate after 17 h, quenched at 24 h. <sup>c</sup> Reaction time was 72 h, no conversion was observed during the course of the reaction. <sup>d</sup> Reaction time was 336 h. <sup>e</sup> M = Cu(II).

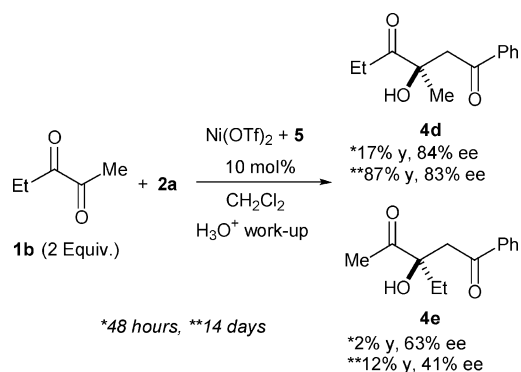
(Table 2, entry 9). Mixtures of toluene and CH<sub>2</sub>Cl<sub>2</sub> (Table 2, entries 10, 11 & 12) gave higher enantiomeric excesses than use of either solvent alone, but yields were reduced. For comparison **6d** was also used as a catalyst under the same conditions as entry 10 (Table 2, entry 21), as in Table 1 the yield using a copper(II) triflate derived catalyst is slightly higher than that using nickel (53 *versus* 46%) and the ee is somewhat lower (48 *versus* 80%). That concentration (of nickel complex), solvent and temperature can have such a significant influence on yield and ee might be due the formation of dimeric or oligomeric catalyst structures in solution. Dramatic concentration, solvent and temperature effects have been previously reported in other (Lewis acid) nickel catalysed reactions.<sup>8</sup> Trimeric nickel complexes were structurally confirmed for related nickel tmeda complexes in the solid state by Handley *et al.* who note the solution equilibrium between monomeric and trimeric diamine chelated complexes of nickel halides.<sup>9</sup>

The reaction to form **3a** was repeated as per Table 1, entry 1 and monitored with time by <sup>1</sup>H NMR spectroscopy. We observed that over the first 48 h the reaction seemed to be, approximately, *pseudo* first order with respect to the enecarbamate concentration. The observed initial rate constant ( $k_{\text{obsd}}$ ) was calculated from the data obtained over the first 40 h to be  $3 \times 10^{-6} \text{ s}^{-1}$  which implies a reaction half-life of 64.2 h.<sup>10</sup> This reaction was continued for five half lives with aliquots taken at various times (see the electronic supplementary information). At 74% conversion (by <sup>1</sup>H NMR) the remaining reaction mixture was purified, which gave **4a** in 83% ee. Repetition of this 14 d reaction gave **4a** in 94% yield and 84% ee (Table 2, entry 16). Enecarbamates **2b** and **2c** were also subjected to the same reaction conditions (Table 2, entries 17–20), a marked improvement in yield and ee was observed by extending the reaction time from 48 to over 300 h. The results obtained after 48 h for the

nickel catalysed formation of **4b** and **4c** (Table 2 entries 17 and 19 respectively) can be compared with those using copper(II) (Table 2, entries 22 and 23) under the same conditions. For the comparisons given here copper(II) triflate derived catalyst **6d** was found to consistently give lower enantiomeric excesses than the corresponding nickel(II) triflate catalyst, yet under the same conditions higher yields are obtained with the copper catalyst, the largest difference in yield (37%) was observed for the formation of **4b**. Obviously 14 d reactions are not practical in an everyday sense but these results show two principle important points: (i) **6a** is indeed a useful Lewis acid catalyst for activation of diketones to reaction with enecarbamates, and (ii) reactions are only limited by turnover frequency and not catalyst inhibition or decomposition.<sup>11</sup> A related study by Evans *et al.* concerning copper catalysed enolsilane addition to pyruvate esters revealed that addition of TMSOTf greatly enhanced reaction rate (catalyst turnover), by assisting the intermolecular silylation of the respective product.<sup>12</sup> In our case the addition of TMSOTf to the reaction of **1a** with **2a** might affect an intermolecular silylation giving the corresponding TMS-ether of **3a**. Under the same conditions as those for Table 1, entry 1 in the presence of 1 equivalent of TMSOTf the reaction did not proceed at all, after the usual work-up only acetophenone and benzylcarbamate (*i.e.*, hydrolysis of **2a**) were observed. It is also worth noting that the TMS-enolate of acetophenone was subjected to the same reaction conditions as those given in Table 1, entry 1 (*i.e.*, enecarbamate {NH-cbz} was substituted for TMS-enolate {OSiMe<sub>3</sub>}), following acidic work-up diketone **4a** was isolated in 13% yield and 73% ee, that is ee is only a little lower for the TMS-enolate but the yield of the same product under the same conditions is greatly reduced.

Having established for, nickel(II) triflate mediated catalysis of enecarbamate additions to a symmetrical dimethyl ketone **1a**,

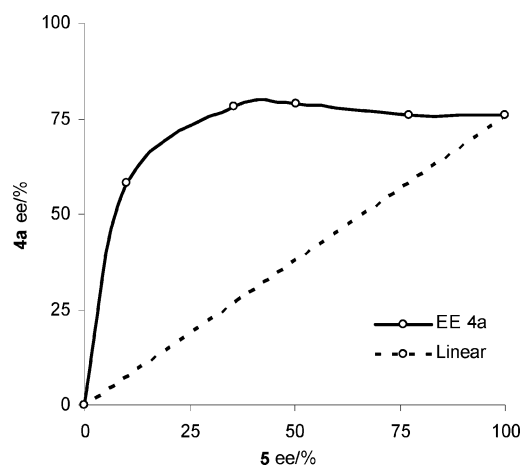
that longer reaction times can provide significant improvements in yield and slight improvements in ee, and that enecarbamate **2a** is a better acetophenone-enolate analogue than the corresponding TMS-enolate, we next examined the unsymmetrical diketone, pentane-2,3-dione **1b**, under the same reaction conditions as Table 1 entry 1 and Table 2 entry 16 (see Scheme 2).



**Scheme 2** Aldol-like reaction of enecarbamate **2a** with diketone **1b**; effect of long reaction time.

For the same reaction conditions as for the formation of **4a** a much more dramatic increase in overall yield of the two products (**4d** & **4e**) was observed, *i.e.*, 19% overall yield for a 48 h reaction increases to >99% combined yield for the analogous 14 d reaction. However it should be noted that no corresponding increase in ee was observed, the minor product's ee was reduced by 20%, the major product's ee was only 1% lower. Also that selectivity between addition to the ethyl or methyl ketone is reduced a little for longer reaction times (8.5 : 1 *versus* 7.0 : 1 respectively).

The non-linear effect of ligand ee was examined with respect to catalyst **6a**, for the formation of **4a**. The *in situ* catalyst preparation was carried out with mixtures of racemic and single enantiomer (*R,R*)-**5**, reactions were performed under the same conditions as that given in Table 1, entry 1 accept stock solutions of ligand were added. Fig. 1 shows the relationship between ligand and product enantiomeric excesses, a strong positive non-linear effect was observed.

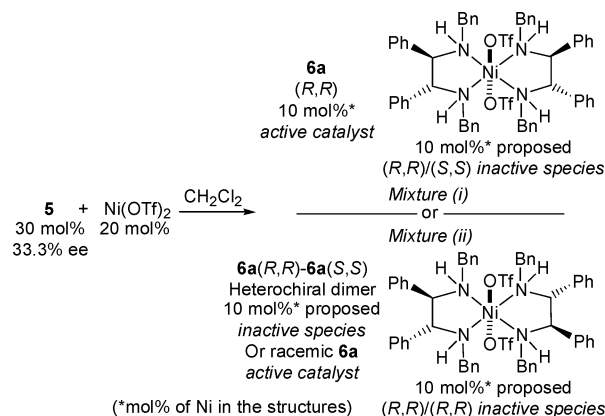


**Fig. 1** Non-linear effect of ligand **5** in reactions under the same conditions as Table 1, entry 1.

Enantiomeric excess of **5** and yield of product **4a** follows the approximate trend that lower ee gives lower yield (see supplementary information). That a strong positive non-linear effect was observed, is good evidence for the favourable formation of heterochiral bis-chelated Ni(OTf)<sub>2</sub> complexes or heterochiral dimers of complex **6a**, and that these structures are not active catalysts. Since use of excess ligand served to reduce the efficacy of a catalyst prepared from single enantiomer **6a** (ee and yield

were reduced) we surmised bis-chelated metal complexes were likely the origin of deactivation, although this would necessitate the presence of free Ni(OTf)<sub>2</sub> in the non-linear effect experiments and hence a non-chiral pathway might be observed.

In order to clarify this further an experiment was performed employing 30 mol% of 33.3% ee ligand in combination with 20 mol% nickel(II) triflate, two proposed outcomes are given in Scheme 3.

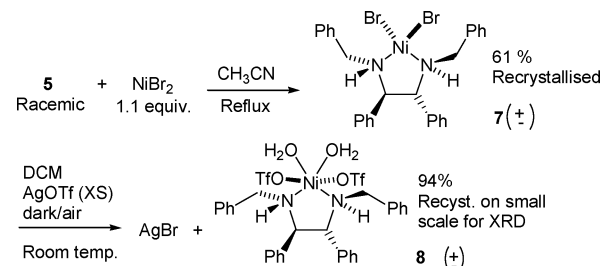


**Scheme 3** Proposed outcomes of mixing excess low ee ligand and Ni(OTf)<sub>2</sub>.

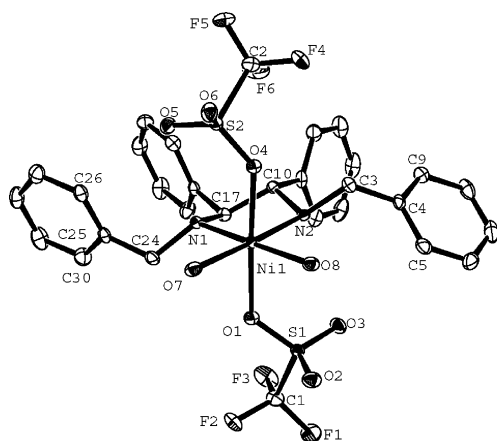
Use of this catalyst mixture resulted in isolation of **4a** in 72% ee and 47% yield, that is ee is approximately the same as Table 1, entry 1 but the yield is reduced, suggesting that the same active catalyst species is present but to a lesser extent than in the 10 mol% single enantiomer case.

Using the same conditions as Scheme 3 the reaction was repeated with slightly higher ee **5** (50% ee), in this case product **4a** was obtained in an improved 75% yield and the ee remained almost unchanged (74% ee). More active catalyst is present with 50% ee ligand yet no reduction in ee was observed which implies the lack of a competitive achiral pathway. These results lead us to tentatively suggest that the formation of 2 : 1 *R,R* : *S,S* trimeric structures, similar to the TMEDA complexes previously reported,<sup>3c</sup> also play a role in a complicated deactivation equilibrium in the large non-linear effect we observed. To elucidate this and/or related structures by XRD or other means is currently the focus of attention for this program of research, we hope to report more details regarding this at a later date.

To date, elucidation of the anhydrous catalyst structure **6a** by single crystal X-ray diffraction has not proved successful. However, a racemic model for the binding of **5** to Ni(II) (the corresponding Ni(II) bromide complex **7**) was easily synthesized. Compound **7** was converted, *via* a non-anhydrous silver triflate mediated halide abstraction, to the bis-aquo complex **8** (see Scheme 4). Compound **8** was successfully crystallised from CH<sub>2</sub>Cl<sub>2</sub>-hexane-Et<sub>2</sub>O after many trials (see Fig. 2).<sup>‡</sup> Other than identifying the almost complete absence of **5**, no useful NMR data could be obtained from **7** or **8**.



**Scheme 4** Synthesis of a nickel(II) bromide complex of a racemic diamine ligand and subsequent halide abstraction.



**Fig. 2** Representation of the crystal structure of **8**, protons omitted for clarity. Selected bond distances (Å), angles (°) and torsions (°): Ni(1)–O(1) = 2.107(1), Ni(1)–O(4) = 2.105(1), Ni(1)–O(7) = 2.044(1), Ni(1)–O(8) = 2.084(1), Ni(1)–N(1) = 2.075(1), Ni(1)–N(2) = 2.083(1), O(8)–Ni(1)–O(7) = 89.17(5), N(2)–Ni(1)–N(1) = 85.08(5), N(2)–C(10)–C(17)–N(1) = 53.7(2).

The crystal structure of **8** (Fig. 2) shows an octahedral nickel(II) complex where the two triflate moieties are bound directly to the metal, the ligand is bound equatorially, and two equatorial ancillary water ligands completed the octahedron. This is in contrast to a related nickel(II) bisoxazoline complex reported by Evans *et al.* where a square pyramidal structure was observed, one triflate was bonded with nickel(II) the other was more dissociated (in the solid state).<sup>7a</sup> It is likely that the flexibility of the benzyl arms of ligand **5** allow for satisfactory completion of the octahedron about nickel, maintaining a  $C_2$  environment at the metal. Efficient chiral relay through the amino nitrogens upon coordination was also confirmed for compound **8** (see supplementary information for more details).

Owing to the novelty of nickel(II) catalysed enecarbamate additions to carbonyls further studies into improved activity and selectivity of nickel(II) are underway in our laboratory. Altering the electronic properties of the metal by changing the ligand or counter ion might facilitate the higher turnover frequencies desirable for a broadly applicable catalytic system.

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## Notes and references

‡ CCDC reference numbers 269067. See <http://dx.doi.org/10.1039/b505404d> for crystallographic data in CIF or other electronic format.

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- Overnight pre-mixing of ligand and metal triflate at rt was performed.
- Conditions were selected based on previous work, see reference 1a.
- That structure **3a** was formed initially was confirmed by <sup>1</sup>H NMR spectroscopy in *d*<sub>6</sub>-benzene of the crude reaction product and accurate mass spectroscopy (Found: [M + H]<sup>+</sup>, *m/z*, (ESI) 340.1606. C<sub>20</sub>H<sub>22</sub>NO<sub>4</sub> requires 340.1549).
- For representative examples of nickel(II) complexes as chiral Lewis acids in catalysis see: (a) D. A. Evans, W. Downey and J. L. Hubbs, *J. Am. Chem. Soc.*, 2003, **125**, 8706; (b) S. Kanemasa, Y. Oderaotoshi and E. Wada, *J. Am. Chem. Soc.*, 1999, **121**, 8675; (c) S. Kanemasa, Y. Oderaotoshi, J. Tanaka and E. Wada, *J. Am. Chem. Soc.*, 1998, **120**, 12355; (d) H. Suga, A. Kakehi and M. Mitsuda, *Chem. Lett.*, 2002, 900; (e) W. Zhuang, R. G. Hazell and K. A. Jørgensen, *Chem. Commun.*, 2001, 1240; (f) S. Iwasa, H. Maeda, K. Nishiyama, S. Tsushima, Y. Tsukamoto and H. Nishiyama, *Tetrahedron*, 2002, **58**, 8281; (g) H. Suga, T. Nakajima, K. Itoh and A. Kakehi, *Org. Lett.*, 2005, **7**, 1431.
- See references 7b–c.
- See reference 3c.
- Observed rate constant,  $k_{\text{obsd}}$ , determined by plotting  $-\ln([E]/[E]_0)$  versus time/s (E = enecarbamate **2a**, [E] determined by <sup>1</sup>H NMR spectroscopy, see supplementary information). Half-life (h),  $t_{1/2} = \ln 2 / (k_{\text{obsd}} \times 3600)$ .
- The requirement for diketone chelation was demonstrated by use of acetophenone or butanone as substrates, 10 mol% loading of **6a** at 0 °C for 48 h, none and <5% conversion was observed respectively (confirmed by <sup>1</sup>H NMR spectroscopy only).
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