

# Long-Lived Polymer Supported Dimeric Cinchona Alkaloid Organocatalyst in the Asymmetric $\alpha$ -Amination of 2-Oxindoles

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**ABSTRACT:** Nearly quantitative yields and high enantiomeric purity (89-95% *ee*) were attained in the course of 100 reaction cycles of a polystyrene resin-supported *Cinchona* alkaloid organocatalyst in the enantioselective  $\alpha$ -amination of 2-oxindoles with diethyl azodicarboxylate. The catalytic material proved stable for >5300 h operation time over eight months.

**KEYWORDS:** *supported organocatalysis, enantioselective catalysis, 2-oxindoles, azodicarboxylates, extended recycling*

## Introduction

Inspired by the Merrifield's idea of solid phase synthesis, the development of supported enantioselective catalysts has been in the pipeline for the past fifty years.<sup>1</sup> The motivations behind these efforts may range from simplified product purification to the attainment of better catalytic properties. Above all, the possibility of recovering and re-using the catalyst more and more times stands, however, as the single most important stimulus to drive the research in the field. This latter aim has been repeatedly acknowledged in the literature, with Gun'ko, Connon and co-workers suggesting 20 reaction cycles as the minimum that would encourage the preparation of insoluble polymer bound (IPB) enantioselective catalysts "by the practitioner interested only in its use as a tool".<sup>2</sup> Moreover, Hübner, de Vries, and Farina recently stressed the importance of evaluating the productivity increase, if any, of an IPB system over the corresponding soluble catalyst, in order to assess its practical advantages in the industrial perspective.<sup>3</sup>

Nevertheless, just a few of the IPB systems reported to date appear to attain the recycling capability noted above (for selected examples, see refs.<sup>2,4</sup>) and much less so were demonstrated to substantially surpass it. Indeed, to the best of our knowledge only three examples have been disclosed, where effective recycling of a supported asymmetric catalyst for more than 50 times was achieved.

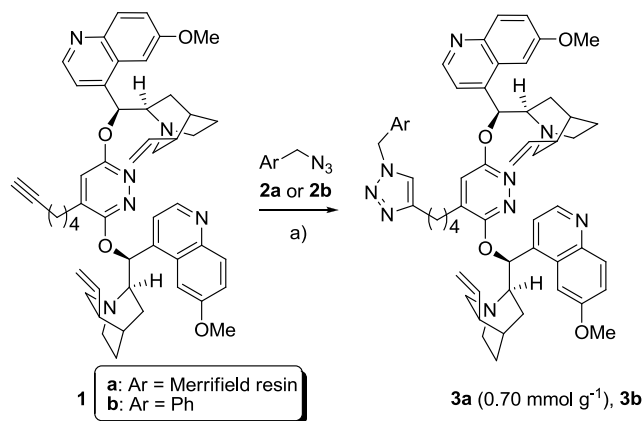
In an early contribution, Lectka and co-workers attained 60 reaction cycles of a 9-*O* quinine ester on Wang resin, in asymmetric [2+2] cycloaddition reactions carried out in sequentially linked columns.<sup>5</sup> However, because the alkaloid derivative "was employed at undisclosed loadings (yet considerably higher than 100 mol%)"<sup>2</sup> at least from the practical point of view one of the main advantages of asymmetric catalysis can be less than obvious in this example.

More recently, Hashimoto and co-workers,<sup>6</sup> and Opwis, List and co-workers<sup>7</sup> reported impressive durability for a chiral Rh(I) carboxylate on polystyrene support (100 reaction cycles) and, respectively, a bifunctional *Cinchona* alkaloid derivative on textile fibers (Nylon 6,6; up to 300 reaction cycles).

While setting new endurance standards in the field of IPB systems, these examples show nonetheless some limitations when the preparation of the supported catalyst is examined: In the case of former, the access to a [Rh<sub>2</sub>(S-PTTL)<sub>4</sub>] monomer suitable for immobilization appears less than optimal for scaling-up because of the statistical synthetic approach and the need of repeated chromatographic separation for obtaining chiral derivatives and other styryl intermediates.<sup>6</sup> Conversely, the radical grafting employed in the preparation of the textile organocatalyst is one of the easiest immobilization methods reported to date; however, in this case the approach appears somewhat limited in scope by the low catalyst loading on the support (max. 0.025 mmol g<sup>-1</sup>) and the risk of degradation of the chiral derivative under the 222 nm UV irradiation employed for the grafting.<sup>7</sup>

These observations prompted us to address the still pending question whether all the three main features required for practical usage, i.e. simple and scalable preparation, satisfactory catalytic performance, and possibility of extended re-use,<sup>8</sup> could be conjugated within a single, properly designed IPB chiral catalyst architecture.

In view of the already demonstrated effectiveness of the synthetic route and their competency in a few organocatalyzed asymmetric transformations,<sup>4b,9</sup> recently introduced pyridazine *Cinchona* alkaloid derivatives on polystyrene resins were selected for this purpose.



a) CuI (5 mol%), DIPEA (1 equiv.), CH<sub>2</sub>Cl<sub>2</sub>, r.t., 3 days.

**Scheme 1.** Preparation of the IPB alkaloid organocatalyst **3a** and soluble model compound **3b**.

## Results and discussion

The supported quinidine ether **3a** was prepared (Scheme 1) by *click*-anchoring **1** onto azido-Merrifield resin in **2a**, as described.<sup>4b,10</sup> The approach, which takes advantage of Cu-catalyzed azide-alkyne cycloaddition reaction (CuAAC) for linking chiral units to insoluble polymer supports,<sup>11</sup> confirmed the possibility of obtaining the immobilized catalyst through steps that do not require chromatographic purifications at any stage. Interestingly, on the larger scale and with the extended reaction time adopted in the present investigation, **3a** was obtained with an alkaloid loading (0.70 mmol g<sup>-1</sup> or 53% by weight) that was significantly larger than achieved before.

Given that 3-amino-2-oxindoles with a quaternary stereocenter are known to be key building-block for biologically active compounds and clinical candidates, their synthesis using affordable catalytic procedures is actively sought.<sup>12</sup> With this goal in mind, the organocatalytic asymmetric  $\alpha$ -amination (AaA) of 2-oxindoles, developed independently by the groups of Barbas III,<sup>13</sup> Chen,<sup>14</sup> and Zhou,<sup>15</sup> was chosen as a convenient playground for evaluating the recyclability of the IPB *Cinchona* derivative.

Following an initial lead,<sup>9</sup> examination of the soluble model **3b** of the supported alkaloid units confirmed that the pyridazine central spacer could stand as an effective replacement of the phthalazine one in some of the literature catalysts.<sup>13,15</sup> In particular, optimization of the original conditions of Barbas III and co-workers<sup>13a</sup> revealed that **3b** performed best when the AaA of *N*-benzyl protected 2-oxindoles **4a-i** with diethyl azo-dicarboxylate (DEAD, **5**) was carried out in moderately concentrated (0.08-0.14 M) THF solutions (see SI, Table S1).

Thanks to the excellent swelling of polystyrene resins in THF, these results opened the way to the study of the corresponding heterogeneous reactions (Table 1). Therefore, **4a** in THF was exposed to **5** in the presence of 10 mol% of the supported catalyst **3a**. When the reaction was initially performed at [4a] = 0.08 M, the expected aminated product **6a** formed smoothly (Table 1, entry 1). However, the

isolated yield was still modest after an extended reaction time of 64 h and **6a** showed lower enantiopurity with respect to the corresponding homogeneous reaction. Therefore, a brief optimization study was undertaken, which included examination of the effect of catalyst loading and substrate concentration. Gratifyingly, doubling the catalyst amount led to some increase in the substrate conversion and product yield in 48 h (Table 1, entry 2), while a significant improvement of *ee*'s came by raising [4a] to 0.14-0.20 M (Table 1, entries 3 and 4). Even if the origin of such an intriguing concentration effect is not clear at present, the practical implication of these findings was the possibility of running AaA reactions with less solvent in comparison to analogous optimized procedures in the homogeneous phase (typically 0.1 M in substrate).<sup>13b,14-15</sup> Considering the marginally superior *ee* in the case of [4a] = 0.14 M, these conditions were adopted in further runs.

The IPB-catalyst **3a** was screened next in the AaA of different 1-benzyl-2-oxindoles (Table 1, entries 5-12). Irrespective of the C-3 substituent, the corresponding products were obtained in good yield and enantiomeric purity after a fixed reaction time of 48 h. In detail, substrates containing (substituted)benzyl (**4a,b** and **4d-f**) and other unsaturated groups at C<sub>3</sub> (**4g** and **4h**) afforded the aminated product with *ee* values around 90%. The only exception to this trend was the 3-methoxy derivative **4c** (Table 1, entry 6), whose reaction provided **6c** in around 10% lower enantiomeric purity. Some reduction of the *ee* was observed also in the reaction of the less hindered 3-methyl derivative **4i** (Table 1, entry 12). Nonetheless, this latter substrate turned to undergo AaA in a more enantioselective fashion than expected on the basis of literature precedents (i.e. 76% *ee* with 10 mol% of the phthalazine ether **7** in Et<sub>2</sub>O).<sup>13a</sup> In the event, the *ee* value attained with the IPB-catalyst **3a** matched within  $\pm 4\%$  that provided with the same substrate by the soluble model **3b**. With the exception of **4i**, noted above, the results proved also consistent with those afforded by the literature organocatalyst **7** under comparable conditions.<sup>13a</sup>

Because promising endurance already emerged from recycling of **3a** in the initial substrate screening (see Table 1), the central issue of its extended re-use could be addressed next. In order to facilitate the evaluation of trends in activity and stereoselectivity, **4a** was selected as a fixed 2-oxindole substrate and catalyst **3a**, recovered from previous runs (Table 1, entries 2-4 and Figure 1, cycles 1-3), was repeatedly employed under optimized conditions.

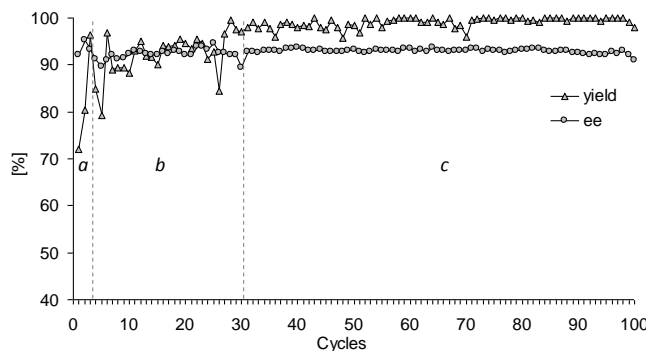
Quite surprisingly, additional cycles initially afforded **6a** in disappointingly variable yields (Figure 1, cycles 4-30). After examining the possible causes, the culprit was identified in the fluctuation of the room temperature at night. For this reason, further catalysis experiments were carried out by thermostating the reaction vessel at 29°C. Much to our delight, under these conditions the apparently erratic behavior was not observed anymore and the aminated product **6a** was consistently obtained in nearly quantitative isolated yield and >90% *ee*, throughout the entire series of new reaction runs (Figure 1, cycles 31-100).

**Table 1. Results in the heterogeneous AaA of 1-benzyl-2-oxindoles.**

Entry	Catal. (mol%)	Substrate (R)	C (M) <sup>a</sup>	Prod.	Yield (%) <sup>b,c</sup>	ee (%) <sup>c,d</sup>
1 <sup>e</sup>	10	<b>4a</b> (Bn)	0.08	<b>6a</b>	51 (90)	92 (96)
2	20	<b>4a</b> (Bn)	0.08	<b>6a</b>	72	92
3	20 <sup>f</sup>	<b>4a</b> (Bn)	0.14	<b>6a</b>	81 (90)	95 (96)
4	20 <sup>f</sup>	<b>4a</b> (Bn)	0.20	<b>6a</b>	>95	93
5	20	<b>4b</b> (4-Me-Benzyl)	0.14	<b>6b</b>	84 (>95)	91 (91)
6	20 <sup>f</sup>	<b>4c</b> (3-MeO-Benzyl)	0.14	<b>6c</b>	>95 (>95)	81 (85)
7	20 <sup>f</sup>	<b>4d</b> (4-MeO-Benzyl)	0.14	<b>6d</b>	93 (>95)	91 (89)
8	20 <sup>f</sup>	<b>4e</b> (4-Cl-Benzyl)	0.14	<b>6e</b>	>95 (>95)	89 (89)
9	20 <sup>f</sup>	<b>4f</b> (4-F-Benzyl)	0.14	<b>6f</b>	>95 (>95)	91 (92)
10	20 <sup>f</sup>	<b>4g</b> (Allyl)	0.14	<b>6g</b>	92 (>95)	91 (91)
11	20 <sup>f</sup>	<b>4h</b> ( <i>E</i> -Cinnamyl)	0.14	<b>6h</b>	91 (>95)	89 (87)
12	20 <sup>f</sup>	<b>4i</b> (Me)	0.14	<b>6i</b>	>95 (>95)	85 (86)

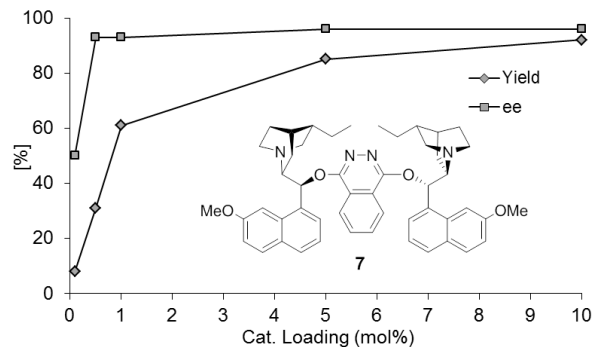
<sup>a</sup> Substrate concentration. <sup>b</sup> Isolated yield after *flash* chromatography. <sup>c</sup> In parentheses, data obtained under comparable conditions with the soluble model catalyst **3b**. <sup>d</sup> By chiral HPLC; the prevailing enantiomer had (S) configuration (see SI). <sup>e</sup> Reaction run for 64 h. <sup>f</sup> Recycled IPB organocatalyst from the previous run.

Because these results confirmed the possibility of using **3a** more and more times, it became interesting to contrast its overall performance with that of the soluble alkaloid derivative **7** from the literature. For the reasons discussed elsewhere,<sup>16</sup> this comparison involved the assessment of enantioselectivity and productivity *P* (= mol of product per mol of catalyst employed)<sup>17,18</sup> in the homogeneous reaction, as functions of catalyst loading. Hence, the AaA of **4a** with **5** was studied with progressively diminishing amounts of **7**, under conditions otherwise analogous to those employed in the heterogeneous experiments.



**Figure 1.** Recycling of **3a** in the heterogeneous AaA of **4a**. Conditions: For cycles 1-3 (a), see Table 1, entries 2-4; for the other runs, 20 mol% **3a**, 1.2 equiv. **5**, THF, [**4a**] = 0.14 M, 48 h (65 h during week-end), and *T*=19-27°C (b) or *T*=29°C (c).

The outcome of these runs (Figure 2) showed that the homogenous process can tolerate 20-fold reduction of catalyst loading below the reported literature value (10 mol%),<sup>13a</sup> before erosion of the enantiomeric purity of product **6a** becomes noticeable. At the same time, however, the reaction rate was largely impaired under these conditions. This was especially evident towards the low-end side (0.1-1 mol%), where dramatically reduced substrate conversion and product yield were recorded at 48 h, or even after an extended reaction time of 300 h. Therefore, even if the data in Figure 2 actually translate into progressively increasing *P* at lower loadings (e.g. *P*@*ee*=61@93% with 1 mol% of **7**, see Figure 3), such an approach to the intensification of the homogeneous process is clearly not viable below the 5 mol% threshold.



**Figure 2.** AaA of **4a** in the presence of variable amounts of the soluble organocatalyst **7** (for the conditions, see Figure 1c; data at 0.1-1 mol% catalyst loading were obtained with 300 h reaction time).

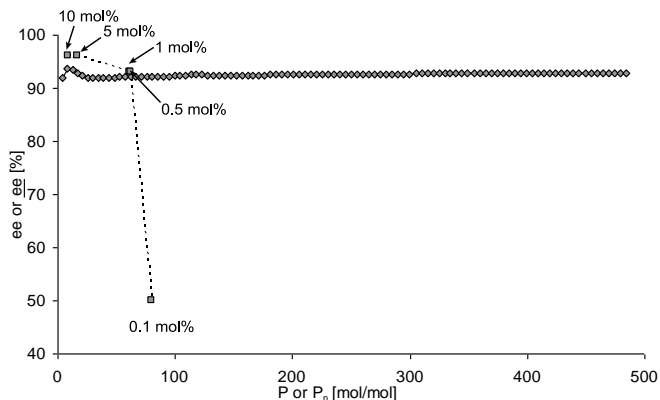
By contrast, the demonstrated endurance of **3a** led to smooth increase of cumulative productivity  $P_n$  (see Figure 3), which indeed reached  $P_{100}@ee=484@93\%$  (equivalent to approx. 0.2 mol% effective catalyst usage) at the end of the series. Because **7** provides no more than  $P=10-16$  under acceptable conditions (5 -10 mol% loading, see Figure 2), the results for **3a** correspond to a larger than 30-fold increase of product obtained with a given initial amount of the chiral derivative. Rather obviously, this achievement was made possible by the straightforward recovery of **3a** by filtration and by the fact that, according to Figure 1, an average catalyst loss significantly lower than 1% per cycle can be safely inferred. Therefore, even if the recovery of **7** by various techniques (e.g. solvent extraction or chromatography) is certainly possible, it appears unlikely that the accomplishment of such a task for the soluble catalyst (and the subsequent increase of productivity on re-use) would be as effective as for **3a**.

Another aspect that deserves a comment is the fact that the reaction cycles summarized in Figure 1 involved exposure of **3a** to reactants and solvents for >5300 h, over eight months. This choice was not dictated by poor performance of the IPB catalyst with respect to its soluble counterparts,<sup>19</sup> but was just a consequence of the relatively slow kinetics of the organocatalytic transformation under exam.<sup>13a</sup> In any case, the circumstance gave the opportunity to examine recycling of a polystyrene-supported catalyst for a time span longer than ever before, including the recalled investigation of Hashimoto and co-workers (approx. 33 h, according to published data).<sup>6</sup> Besides confirming the high chemical stability of the linkages embedded in **3a**, the most remarkable observation in this respect was that the polymeric material could stand prolonged stirring (albeit at low speed, 40-60 rpm), without troublesome filtration and incomplete recovery caused by breaking to fines. Contrarily to the common concern that Merrifield-type resins are very prone to mechanical wearing,<sup>20</sup> unless special techniques (e.g. “tea-bag”) are adopted,<sup>21</sup> it seems then that under favorable conditions – particularly the low stirring rate in the present investigation – their serviceability can extend much beyond what generally believed.

Finally, it has to be mentioned that a single recrystallization from MTBE of pooled samples of **6a** was sufficient for obtaining >99% ee product in the mother liquor (85% yield) and a small amount of crystals with lower ee (22%). Hence, even though the enantioselectivity degree of the heterogeneous reaction proved somewhat reduced in comparison with the use of **7** in the homogeneous phase (96-99% ee, see SI, Table S1 and ref.<sup>13a</sup>), the behavior of the enantiomers of **6a** upon crystallization eventually allowed the isolation of the product in high enantiomeric purity.<sup>22,23</sup>

### Concluding remarks

In summary, the present study adds a third entry to the very limited set of enantioselective IPB catalytic systems for which effective recycling in the three-digits range could be demonstrated.



**Figure 3.** Enantioselectivity vs. productivity for **7** at different loadings (broken curve) and in the recycles of **3a** (20 mol%; solid curve) in the AaA of **4a**. (for the conditions, see Figure 1; for the meaning of  $P$ ,  $P_n$ , and  $ee$ , see the text).

Rather obviously, the result would not have been possible if the chiral derivative itself underwent appreciable chemical degradation in the reaction mixture. In this respect, it can be speculated that the base-catalysis mechanism proposed for *Cinchona* alkaloids<sup>13a,14</sup> is well fit for avoiding potentially deactivating intermediates like, e.g., those involved in the related AaA of linear aldehydes with supported diphenylprolinol organocatalysts.<sup>24,25</sup>

Instrumental to the attainment of extended operational life was also the robustness of the linkage between chiral units and polystyrene resin and, more in general, of the catalytic material as a whole. In turn, this allowed to demonstrate that multi-thousand hour endurance is not limited to the photochemically grafted Nylon fibers by Opwis, List and co-workers,<sup>7</sup> but is a sizeable possibility also for IPB organocatalyst prepared by more conventional bench-top techniques.

In conclusion, we feel that the main achievement of the present study stands in the demonstration that scalable synthesis, satisfactory activity, excellent asymmetric induction, and extended recycling could be conjugated, for the first time, into a single IPB catalyst architecture. Given the excellent serviceability of **3a**, analogous supported *Cinchona* alkaloid derivatives are currently under exam for their use in continuous-flow reactors.

## ASSOCIATED CONTENT

Supporting Information (SI): Synthetic procedures and characterization details (PDF).

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## Notes

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- (17) In the absence of a specific IUPAC definition, other than for the biotechnological field (see ref. 18a), the term 'productivity' has been used in the literature in connection with both time-related (e.g. average turnover frequency at reaction end, TOF) and time-independent features of a catalyst (e.g. total turnover number, before de-activation or upon recycling, TTON). For examples in either sense, see refs. 18b-d. Because the focus of the present investigation was about catalyst durability, the latter meaning is adopted herein (for the use of the symbol *P* in similar context, see ref. 18e).

(18) (a) McNaught, A. D.; Wilkinson, A. *IUPAC Compendium of Chemical Terminology, 2nd ed. (the "Gold Book")*. XML on-line corrected version; Blackwell Scientific Publications: Oxford, 2006. (b) Behr, A.; Neubert, P. *Applied Homogeneous Catalysis*; Wiley-VCH, 2012. (c) Makwana, V. D.; Sivalingam, G.; Vakil, S. M. *Int. J. Chem. Eng. Appl.* **2014**, *5*, 6-12. (d) Sattler, A.; Aluthge, D. C.; Winkler, J. R.; Labinger, J. A.; Bercaw, J. E. *ACS Catalysis* **2016**, *6*, 19-22. (e) McNair, R. J. In *Catalysis of Organic Reactions*; Scaros, M. G., Prunier, M. L., Eds.; Dekker: New York, 1995, p 1-11.

(19) Concerning catalytic activity, **3a** (average TOF  $\approx 0.1 \text{ h}^{-1}$ ) proved less effective than the other two long-lived supported systems mentioned in the Introduction. This is especially true in comparison with the Rh(I) carboxylate by Hashimoto and co-workers (average TOF around  $135 \text{ h}^{-1}$ , see ref. 6). As shown by the soluble derivatives **3b** and **7**, these differences are not due to immobilization effects but are just a consequence of the low specific activity of the alkaloid derivatives in the AaA reaction under exam. While high turnover rate is clearly an ideal requisite of any catalytic system, we feel that the circumstances met in the present study are exactly where the availability of easily prepared and robust IPB systems can prove beneficial the most. In particular, the possibility to recover and reuse the valuable chiral inductor for hundred times -with a procedure as simple as a filtration- may help in lifting one of the main drawbacks of many enantioselective metal-free homogenous systems reported to date, i.e. the need of large loadings of the expensive chiral organocatalyst for balancing slow reaction kinetics.

(20) Kasaplar, P.; Riente, P.; Hartmann, C.; Pericàs, M. A. *Adv. Synth. Catal.* **2012**, *354*, 2905-2910.

(21) (a) Houghten, R. A. *Proc. Natl. Acad. Sci. U. S. A.* **1985**, *82*, 5131-5135. (b) Comina, P. J.; Beck, A. K.; Seebach, D. *Org. Process Res. Dev.* **1998**, *2*, 18-26.

(22) Unless a "true racemate" with eutectic compositions very close to 100% *ee* is supposed, the phenomenon does not fit typical phase diagrams for mixtures of enantiomers (see ref. 23). Nevertheless, a similar behaviour has been previously reported by Zhou and co-workers (ref.15). At variance with the literature study, where the very strong tendency of the racemate to crystalize was related to a network of hydrogen bonds involving also the unprotected 2-oxindole N-H fragment, the findings of the present study suggest that it might be a more general feature of this class of chiral compounds, including those with protected endocyclic nitrogen.

(23) J. Jaques, A. C., S. H. Wilen *Enantiomers, Racemates, and Resolutions*; J. Wiley & Sons: New York, 1981.

(24) Fan, X.; Sayalero, S.; Pericàs, M. A. *Adv. Synth. Catal.* **2012**, *354*, 2971-2976.

(25) For a stable supported bifunctional thiourea organocatalyst in the AaA of 1,3-dicarbonyls, see: Kasaplar, P.; Ozkal, E.; Rodriguez-Escrich, C.; Pericas, M. A. *Green Chem.* **2015**, *17*, 3122-3129.

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