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Kinetic Resolution of Racemic Secondary Alcohols Mediated by *N*-Methylimidazole in the Presence of Optically Active Acyl Chlorides

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N-Methylimidazole was used to promote the acylation of secondary racemic alcohols and to carry out their kinetic resolution through intermediate chiral acyl imidazolium chlorides. The kinetic resolution could be turned into a catalytic process in the presence of a catalytic amount of *N*-methylimidazole.

Introduction

Achiral acyl transfer reactions have been promoted by a number of highly active nucleophiles such as 4-(dimethylamino)pyridine (DMAP),[1,2] *N*-methylimidazole[3] and phosphanes.[4] Afterwards, successful chiral acylations[5] have been reported in the presence of stoichiometric amounts of chiral acylating agents such as DMAP[6] and imides.[7] Then, catalysed enantioselective acylations, accompanied by kinetic resolution of secondary alcohols, have been performed in the presence of chiral catalysts.[8,9] Finally, chiral nucleophiles[8] such as DMAP,[10–20] pyridines,[21] amidines,[22] phosphanes,[23] *N*-heterocyclic carbenes,[24] tetramizole derivatives[25] and alcohol derivatives,[26] as well as small peptides,[27] have also been applied in such reactions.

Prior studies from this laboratory were devoted to the synthesis and use of imidazolium derivatives as ionic liquid media for organometallic catalysis.[28] As a result of observations made during the synthesis of new chiral imidazolium salts, we observed a peculiar behaviour of *N*-methylimidazole. Thus, we wondered if the latter could be able to promote kinetic resolution of secondary aryl alcohols in the presence of chiral acylating agents.[29] Here, we report on our investigations of the potential of *N*-methylimidazole to mediate the transfer of chiral acyl residues with concomitant resolution of the reacting racemic secondary alcohols.

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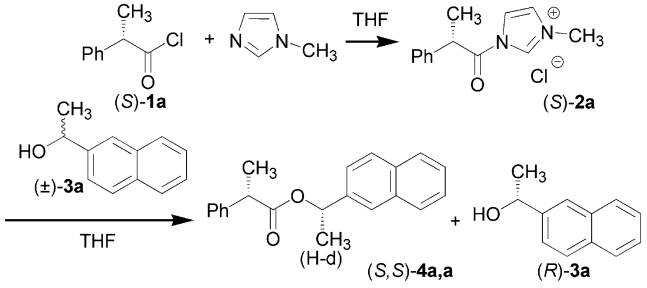
Results and Discussion

The reaction of *N*-methylimidazole with optically pure acyl chloride (*S*)-**1a** produced quantitatively the stable (*S*)-*N*-acyl *N*-methylimidazolium chloride (*S*)-**2a** (>99% isolated yield; Scheme 1). Compound (*S*)-**2a** is reactive towards water[30] and alcohols. For example, the reaction of (*S*)-**2a** with one equivalent of racemic secondary alcohol (±)-**3a**, in THF, produces chiral ester **4a**,**a** (20 °C, 2 h, 20% conversion determined by ^{1}H NMR spectroscopy). Ester **4a**,**a** is composed of two diastereomers (*S*,*S*/*S*,*R*) in a 98:2 ratio (96%*de*; Table 1, Entry 1; Scheme 1). The optical purity of recovered alcohol **3a** was 26%*ee* (*R*). As no special care had been taken to avoid trace amounts of water for the initial experiments and because of the sensitivity of the acyl imidazolium species towards water,[30] we carried out the same reaction under rigorously anhydrous conditions. The conversion reached 47% and the selectivity increased as well (**4a**,**a**: *S*,*S*/*S*,*R* 99:1; recovered **3a**: 91%*ee*; Table 1, Entry 2).



Scheme 1.

A control experiment carried out with optically pure acyl chloride (*S*)-**1a** and racemic (±)-**3a** in THF provided ester **4a**,**a** as a mixture of diastereomers (*S*,*S*/*S*,*R*, 1:1) with 9% conversion within 2 h at 20 °C (Table 1, Entry 3). A reaction was carried out also in the presence of pyridine (1 equiv., THF, 0 °C, 2 h). Ester **4a**,**a** was obtained quanti-

Table 1. Selectivities in the kinetic resolution of racemic secondary alcohols.

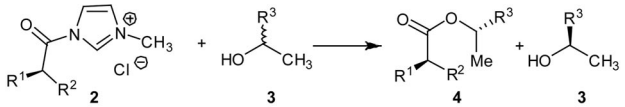
Entry	Acyl donor	Alcohol (±)-**3**	**4**	Conversion [%][a]	% *de* of **4**[a] (config.)	% *ee* of recovered **3** (config.)[b]	*S*[c]
1	**2a**	**3a**	**4a**,**a**	20	96 (*S*,*S*)	26 (*R*)	63
2	**2a**	**3a**	**4a**,**a**	47	98 (*S*,*S*)	91 (*R*)	316
3[d]	**1a**	**3a**	**4a**,**a**	9	–	–	–
4[e]	**1a**	**3a**	**4a**,**a**	100	–	–	–
5[f]	**1a**	**3a**	**4a**,**a**	100	–	–	–
6	**2a**	**3b**	**4a**,**b**	48	96 (*S*,*S*)	90 (*R*)	151
7	**2b**	**3b**	**4b**,**b**	48	4 (*R*,*R*)	5 (*S*)	1
8	**2c**	**3a**	**4c**,**a**	47	93 (*S*,*S*)	94 (*R*)	98
9	**2d**	**3a**	**4d**,**a**	48	2 (*S*,*S*)	2 (*R*)	1
10	**2a**	**3c**	**4a**,**c**	33	21 (*S*,*S*)	11 (*R*)	1.3
11	**2a**	**3d**	**4a**,**d**	15	0	0	–
12	**1a**[g]	**3a**	**4a**,**a**	48	98 (*S*,*S*)	92 (*R*)	327
13	**1a**[g]	**3b**	**4a**,**b**	48	95 (*S*,*S*)	91 (*R*)	124
14	**1c**[g]	**3a**	**4c**,**a**	47	94 (*S*,*S*)	95 (*R*)	120

[a] Determined by ^{1}H NMR spectroscopy. [b] Determined by chiral HPLC by employing a Chiralcel OJ® column. [c] Values were calculated according to the method of Kagan. See ref.[31] [d] Compounds **1a** and **3w** were reacted in THF. [e] Prior to the addition of racemic alcohol, **1a** was treated with a stoichiometric amount of pyridine. [f] Prior to the addition of the racemic alcohol, **1a** was treated with a stoichiometric amount of DMAP. [g] Reactions performed in the presence of 2 mol-% of *N*-methylimidazole.

tatively as a 1:1 mixture of diastereomers (Table 1, Entry 4). An identical result was obtained in the presence of DMAP (Table 1, Entry 5). Thus, as expected, the three nucleophilic nitrogen aromatic species promote the acylation of alcohol **3a** compared to the control experiment (Table 1, Entry 3). Nonetheless, a discriminating ability between the enantiomers of alcohol (±)-**3a** was observed exclusively in the presence of *N*-methylimidazole.

Next, three other optically pure acyl chlorides were prepared, namely, (*S*)-**1b**, (*S*)-**1c** and (*S*)-**1d**, and they were converted similarly into the corresponding acyl imidazolium chlorides **2b**–**d** (97 – >99% isolated yields; Figure 1). Acyl derivatives **2a**–**d** were treated with a series of racemic secondary alcohols (±)-**3a**–**e** (Figure 1) to afford esters **4** and alcohols **3** were recovered in an optically enriched form (Table 1, Entries 6–11). Very high selectivities were reached only for three combinations of acyl imidazolium chlorides and alcohols, namely, (*S*)-**2a**/(±)-**3a** (Table 1, Entry 2), (*S*)-**2a**/(±)-**3b** (Table 1, Entry 6) and (*S*)-**2c**/(±)-**3a** (Table 1, Entry 8). The selectivities thus largely depend upon the substituents on the alcohol but also on those on the chiral acyl imidazolium precursor. Acyl imidazolium chlorides bearing an aromatic residue α to the C=O group combined with secondary alcohols bearing a naphthyl residue induce the highest selectivities during acyl transfer. From the alcohol standpoint, the following order of selectivity has been found: **3a** (2-naphthyl) ≈ **3b** (1-naphthyl) > **3c** (phenyl) > **3d** (ethyl). For the latter, no selectivity was observed at all (Table 1, Entry 11).

Conformational features play a key role in the kinetic resolution of secondary alcohols during acylation. The alcohols can approach the acyl imidazolium intermediate along different orientations. In order to observe significant selectivity, one orientation has to be productive within the transition state. A reasonable rationale for the selectivity achieved with chiral acyl imidazolium salts would be the participation of strong noncovalent cation–π interactions between the imidazolium cation and an aryl group of the

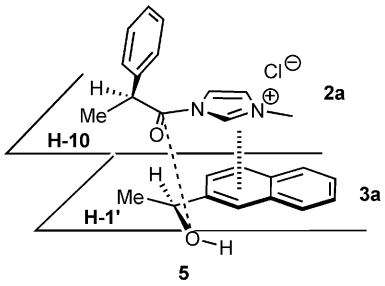


R^1	R^2	**2**	R^3	**3**	**4**
Ph	Me	(*S*)-**2a**	2-naphthyl	**3a**	**4a**,**a**
Ph	Me	(*S*)-**2a**	1-naphthyl	**3b**	**4a**,**b**
Ph	Me	(*S*)-**2a**	Ph	**3c**	**4a**,**c**
Ph	Me	(*S*)-**2a**	Et	**3d**	**4a**,**d**
H	(*R*)-CH(Me)Ph	(*R*)-**2b**	1-naphthyl	**3b**	**4b**,**b**
OMe	Ph	(*S*)-**2c**	2-naphthyl	**3a**	**4c**,**a**
OMe	Me	(*S*)-**2d**	2-naphthyl	**3a**	**4d**,**a**

Figure 1. Acyl transfer reaction: substrates and products.

incoming alcohol.[32,33] Cation–π interactions cannot be totally ruled out in pyridine-assisted acylation.[34] However, no selectivity was observed. The specific conformation of an intermediate cation–π complex (parallel stacking) enables the selective "intramolecular" attack of one alcohol enantiomer onto the acyl imidazolium chloride, as is suggested in complex **5** (Scheme 2). More selective acylations are found with intermediates exhibiting the highest noncovalent binding strengths. Such noncovalent interactions can account for the classification of the alcohol given above with respect to the selectivity of their resolution. Consequently, alcohol **3d** is acylated with no selectivity (Table 1, Entry 11). The selectivity achieved with alcohol (±)-**3c** bearing a phenyl group is significantly lower than that obtained with alcohols (±)-**3a** and (±)-**3b** bearing a naphthyl residue (11%*ee* vs. 90–91%*ee*; Table 1, Entry 10 vs. Entries 2 and 6). On the other side, even in the presence of favourable alcohol (±)-**3a** bearing a naphthyl residue, the small steric differentiation exhibited by acyl intermediate (*S*)-**2d** (Me and OMe substituents on the stereogenic centre) does not lead to any selectivity during acyl transfer (Table 1, Entry 9).

Next, to obtain more insight into the structure of the acyl imidazolium chloride/alcohol [**2a**/(±)-**3w**] intermediate that is expected to form during acylation, we carried out a



Scheme 2.

2D NMR spectroscopy experiment and acquired T-ROESY data. The existence of intense cross-peaks, particularly between the protons of the methyl residue on the imidazolium cation (H-10) and protons of the methyl group of the alcohol (H-1′) proves the close proximity between the acylating agent and the nucleophile as shown for compound **5** (Scheme 2 and Figure 2). Thus, the stability of that intermediate within the NMR timescale has to be quite noteworthy. Another intense cross-peak is attributed to the interaction between the methyl residue (H-10) of the imidazolium cation and the methyl group H-d of ester **4a**,**a** (Scheme 1), which results from the occurrence of the acylation process during NMR spectroscopic data acquisition. Cation–π interactions between the imidazolium cation and the naphthyl residue of the alcohol as well as those between the imidazolium cation and the naphthyl group of the ester product account thus for the observed 2D NMR cross-peaks.

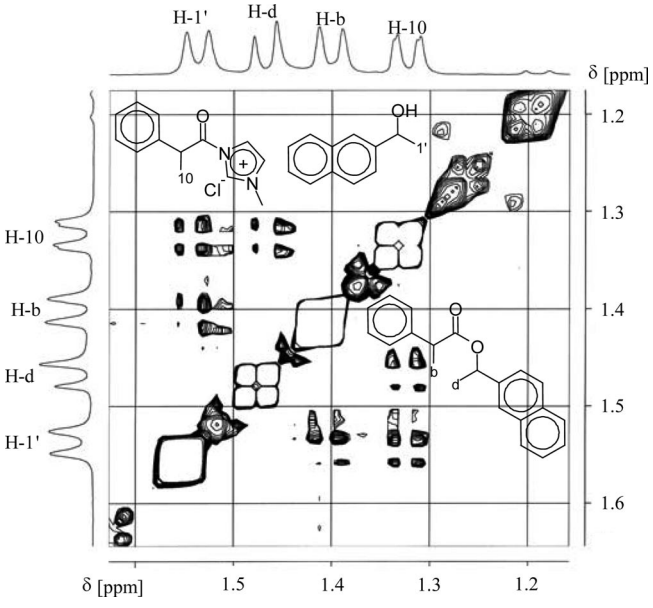
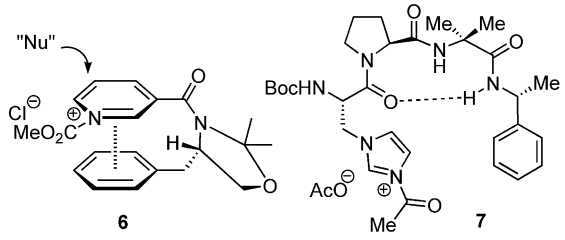


Figure 2. Partial contour plot of the T-ROESY spectrum of a mixture containing **2a** and (±)-**3w** 20% (m/m) diluted in $CDCl_3$, 300 K. Mixing time = 300 ms.

Such interactions have been pursued in an "induced-fit" acylation mechanism involving pyridinium acylating agents.[11–13,33] Upon acylation, a conformational change in the pyridinium residue produces a rigidified structure and shielding of one face of the acyl pyridinium cation. This allows the diastereoselective attack of a nucleophile on the opposite, less-hindered side as is schematised for **6** (Scheme 3). In this study, we have a quite different situation, as π–π stacking interactions orient the approach of the "incoming" nucleophile, as in **5**. In the latter, a combination of steric and electronic factors thus dictates the conformation of the stable and active chiral acyl imidazolium intermediate. In the case of the Miller short peptides[27a] bearing an imidazole residue, the formation of intramolecular π–π stacking within the folded peptide is rather detrimental to the selectivity of the acyl transfer process. In the case of Miller, other interactions such as hydrogen bonding through an amide group contribute to the selectivity of the reaction, as can be seen for **7** (Scheme 3). Thus, *trans*-2-(*N*-acetylamino)-cyclohexan-1-ol was found to be the best alcohol substrate for attaining high resolution. It is also noteworthy that no selectivity was achieved with alkyl aryl carbinols.



Scheme 3.

Next, we attempted to run a catalytic experiment while reacting acyl chloride (*S*)-**1a** with racemic alcohol (±)-**3a** in the presence of a catalytic amount of *N*-methylimidazole (2 mol-%; Table 1, Entry 12) and DBU as the auxiliary base. The latter was introduced in small amounts to neutralise the HCl produced. The progress of the reaction was followed by ^{1}H NMR spectroscopy. Relative to the noncatalysed background reaction of **1a** with racemic (±)-**3a**, an initial rate enhancement by a factor of 2350 was obtained in the presence of the catalytic amount of *N*-methylimidazole. After 2 h, the conversion reached 48%, and **4a**,**a** was obtained with a selectivity of 98%*de*. The optical purity of recovered alcohol **3a** was 92% (Table 1, Entry 12), which is thus close to the results obtained with preformed acyl imidazolium chloride (Table 1, Entry 2). This suggests that, in the catalysed reaction, the mechanism is also going quite fast through the acyl imidazolium intermediate rather than through an uncatalysed process, which is a slow process anyhow (see above). The same trend was obtained for the reaction of other key acyl chlorides with racemic alcohols under the catalytic conditions (Table 1, Entries 13 and 14). We discovered thus a peculiar behaviour of imidazole in assisting the acylation of secondary alcohols. The ability of high medium organisation of imidazolium salts, which is a key property of imidazolium-based ionic liquids, can account for the results obtained in this study.

Conclusions

In summary, we have shown, for the first time, that *N*-methylimidazole can mediate the kinetic resolution of racemic secondary alcohols during transfer of a chiral acyl moiety via intermediate chiral acyl imidazolium chlorides. Such a property is not exhibited at all by pyridine- and DMAP-mediated acylations. The process, which is quite selective for some acyl chloride/secondary alcohol combinations and which has been turned into an organocatalytic process, is expected to be applicable to a variety of aryl acyl chlorides in combination with a diversity of naphthyl-based secondary alcohols. Research is under way to design a catalytic system able to perform dynamic kinetic resolution while combining an imidazole-based catalytic acyl transfer system with an alcohol racemisation promoter.

Experimental Section

General Experimental Procedures: All reactions were performed under anhydrous conditions and under an inert atmosphere of nitrogen. Reagents were used as obtained from commercial sources without further purification. THF and diethyl ether were distilled prior to use from sodium/benzophenone ketyl under an atmosphere of nitrogen. Toluene was distilled from Na/Hg. Dichloromethane was distilled from calcium hydride and stored under an atmosphere of nitrogen. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ and chemical shifts are expressed in ppm relative to internal Me_4Si (δ =0.00 ppm) and were recorded with a 300 MHz spectrometer. Chiral separations were performed by HPLC with a Chiralcel OJ® (Daicel) column. The esters prepared are known compounds.

(*S*)-1-Methyl-3-(2-phenylpropanoyl)-1*H*-imidazol-3-ium Chloride [(*S*)-2a]:[35] A round-bottomed flask equipped with a condenser and a dropping funnel was charged with (*S*)-2-phenyl propionic acid (**1a**; 250 mg, 1.7 mmol) and toluene (25 mL) and cooled to 0 °C. Then, thionyl chloride (2.5 mmol) was added dropwise. After addition, the reaction mixture was heated at reflux for 2 h. After cooling, the solvent was evaporated in vacuo. The crude residue was dissolved in THF (10 mL), and the solution was cooled to 0 °C. *N*-Methylimidazole (1.8 mmol) was added dropwise under vigorous stirring. A white precipitate formed in the reaction medium. At the end of the addition, the medium was stirred for 2 h at room temperature. Acyl imidazolium chloride (*S*)-**2a** was isolated through filtration. The solid was washed with anhydrous diethyl ether and dried under vacuum (white solid, 425 mg, >99%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.47 (s, 1 H, NC*H*N), 7.31–7.16 (m, 7 H, H_{arom} and H_{imid}), 3.99 (s, 1.5 H, N-CH_3), 3.97 (s, 1.5 H, N-CH_3), 3.60 (d, J = 7 Hz, 0.5 H, C*H*), 1.36 (d, J = 7 Hz, 1.5 H, CH_3), 1.34 (d, J = 7 Hz, 1.5 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.1 (*C*=O), 142.4 (N*C*N), 138.1 (C_{arom}-CH), 129.6 (C_{ortho}), 127.7 (C_{meta}), 127.6 (C_{para}), 122.3 and 119.7 (C_{imid}), 46.3 (*C*H-CH$_3$), 36.2 (N-*C*H$_3$), 17.7 (*C*H$_3$-CH) ppm. $C_{13}H_{15}ClN_2O$ (250.73): calcd. C 62.28, H 6.03, N 11.73; found C 61.96, H 5.91, N 11.32.

(*S*)-1-Methyl-3-(3-phenylbutanoyl)-1*H*-imidazol-1-ium Chloride [(*S*)-2b]: Prepared by a method similar to that outlined for (*S*)-**2a**. Yield: >99%. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.46 (d, J = 7.1 Hz, 3 H, CH_3), 3.21 (m, 1 H, C*H*), 3.46 (m, 1 H, CH*H*), 3.53 (m, 1 H, C*H*H) 3.86 (s, 3 H, N-CH_3), 7.27 (m, 5 H, H_{arom}), 8.04 (s, 1 H, H_{imid}), 8.64 (s, 1 H, H_{imid}), 9.61 (s, 1 H, NC*H*N) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.9 (*C*H$_3$-CH), 35.3 (*C*H-CH$_3$), 35.5 (*C*H$_2$), 42.3 (N-*C*H$_3$), 122.2 and 126.2 (C_{imid}), 127.4 (C_{para}), 127.7 (C_{meta}), 128.7 (C_{ortho}), 142.4 (N*C*N), 146.9 (C_{arom}-CH), 163.8 (*C*=O) ppm. $C_{14}H_{17}ClN_2O$ (264.75): calcd. C 63.52, H 6.47, N 10.58; found C 63.12, H 6.27, N 10.70.

(*S*)-3-(2-Methoxy-2-phenylacetyl)-1-methyl-1*H*-imidazol-3-ium Chloride [(*S*)-2c]: Prepared by a method similar to that outlined for (*S*)-**2a**. Yield: >99%. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.68 (s, 3 H, OCH_3), 3.87 (s, 3 H, N-CH_3), 5.23 (s, 1 H, C*H*), 7.53 (m, 5 H, H_{arom}), 7.97 (s, 1 H, H_{imid}) 8.24 (s, 1 H, H_{imid}), 9.67 (s, 1 H, NC*H*N) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 35.4 (N-*C*H$_3$), 54.9 (*C*H$_3$O), 89.5 (*C*H-O), 121.2 and 125.3 (C_{imid}), 128.6 (C_{meta}), 129.5 and 130.3 (C_{ortho}), 139.1 (C_{arom}-CH), 140.6 (N*C*N), 164.7 (*C*=O) ppm. $C_{13}H_{15}ClN_2O_2$ (266.73): calcd. C 58.54, H 5.67, N 10.50; found C 58.17, H 5.55, N 10.67.

(*S*)-3-(2-Methoxypropanyl)-1-methyl-1*H*-imidazol-3-ium Chloride [(*S*)-2d]: Prepared by a method similar to that outlined for (*S*)-**2a**. Yield: >99%. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.53 (d, ^3J = 7.3 Hz, 3 H, CH_3), 3.56 (s, 3 H, N-CH_3), 3.90 (s, 3 H, OCH_3), 4.02 (m, 1 H, C*H*), 7.96 (s, 1 H, H_{imid}), 8.02 (s, 1 H, H_{imid}), 9.61 (s, 1 H, NC*H*N) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 5.4 (*C*H$_3$-CH), 35.4 (N-*C*H$_3$), 55.5 (*C*H$_3$O), 85.3 (*C*H-O), 120.5 and 130.3 (C_{imid}), 140.1 (N*C*N), 164.3 (*C*=O) ppm. $C_8H_{13}ClN_2O_2$ (204.66): calcd. C 46.95, H 6.40, N 13.69; found C 46.67, H 6.23, N 13.42.

General Procedure for the Reaction of Acyl Imidazolium Chlorides with Alcohols: The imidazolium chloride salt (1.7 mmol) was dissolved in THF (5 mL) and treated with the selected racemic alcohol (1.7 mmol) at room temperature under vigorous stirring. The acid produced was neutralised by the addition of small amounts of DBU. Aliquots are taken from the reaction mixture and filtered through a small pad of 4-polyvinylpyridine. After evaporation of the solvent under reduced pressure and drying under vacuum, the crude mixture was analysed by ^{1}H NMR spectroscopy and chiral HPLC to determine the conversion and the selectivity.

General Procedure for the Catalysed Acyl Transfer Reaction in the Presence of *N*-Methylimidazole: The acyl chloride (1.7 mmol), the racemic alcohol (1.7 mmol) and *N*-methylimidazole (2 mol-%) were combined in THF (5 mL). The reaction mixture was stirred vigorously at room temperature for 2 h. The progress of the reaction was followed as described above for the stoichiometric reaction.

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