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# One-pot synthesis of ketones and symmetrical anhydrides from carboxylic acids

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A one-pot synthesis of ketones from carboxylic acids is presented, employing 2-nitrobenzenesulfonyl chloride as an activating reagent in the presence of organomagnesium or organolithium nucleophiles. Additionally, activation of the carboxylic acids with 2-nitrobenzenesulfonyl chloride enabled the formation of symmetrical anhydrides. Subsequent conversion of these anhydrides into the desired ketones also proceeded with good yields.

Introduction

Ketones are widely found in natural products, pharmaceuticals, and dyes, playing a significant role in organic chemistry.[1,2] Converting carboxylic acid to a ketone is a highly demanding organic transformation.[3,4] Numerous commonly employed reactions, such as the Mannich reaction, Baeyer–Villiger oxidation, and Grignard reaction, illustrate a diverse range of ketone transformations.[5–7] Developing an efficient pathway for synthesizing ketones remains an enduring area of research interest.[8,9] The synthesis of ketones from carboxylic acids requires certain activation steps, such as acid chloride, ester, and amide.[10–12] In recent times, Weinreb amides have emerged as prominent acylating agents.[13,14] Generally, adding an organometallic reagent to the Weinreb amide intermediate readily transforms it to the desired ketone. The formation of a five-member ring chelate intermediate helps to provide stability and operational efficiency.[15] While the procedure for the direct synthesis of ketones using excess organometallic reagents also exists, its application in organic synthesis remains limited.[16] Various metal-catalyzed processes have also been established for the construction of ketones, yet most of the methods involve using expensive metal catalysts (Scheme 1).[17,18] Very recently, DCC-based activation of carboxylic acids, followed by the addition of organolithium reagents to construct ketones, has been reported.[19] The process is limited to organolithium nucleophiles, requires an excess of the nucleophile, and produces a stoichiometric amount of byproduct, such as DCU (N, N′-dicyclohexylurea), complicating the separation of the desired product, making the process less feasible. Construction of ketones from carboxylic acids using tosyl chloride as an activator was also established; the applicability of the process was demonstrated only for ^{n}BuLi and methylmagnesium bromide nucleophiles.[20] The synthetic process requires an extra

stoichiometric amount of additive (DMAP) and low temperature (−20 °C), making the process less viable. Additionally, the process involves two steps: the first step involves activation of the carboxylic acid, and then the filtration of the reaction mixture under a N$_2$ atmosphere. The second step involves the addition of a nucleophile. Filtration of the reaction mixture under a nitrogen atmosphere may be a critical step. Addressing the aforementioned problems and developing a new, straightforward, one-pot synthetic method for constructing ketones from carboxylic acids is highly necessary. Carboxylic anhydrides represent an important class of organic compounds widely used as acylating agents and intermediates in various synthetic pathways.[21] Aromatic anhydrides are typically synthesized by reacting acyl chlorides with sodium salts of carboxylic acids or by using pyridine, followed by hydrolysis.[22] Another approach involves dehydrating carboxylic acids with reagents such as oxalyl chloride, thionyl chloride, phosphorus pentoxide, triphosgene, dicyclohexylcarbodiimide (DCC).[23–27] However, many
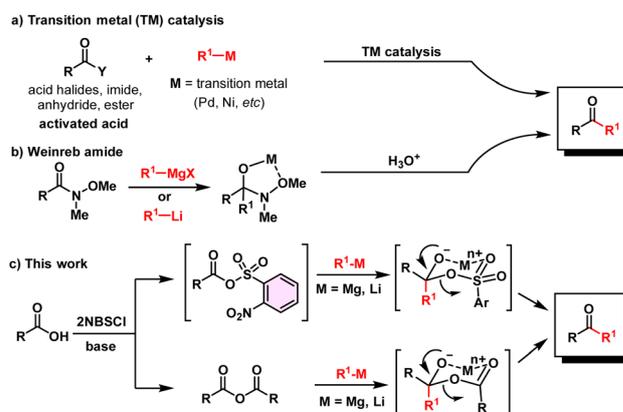
Scheme 1 Synthesis of ketones from carboxylic acid derivatives: (a) TM catalysis, (b) *via* Weinreb amide (five-member intermediate), (c) activation using 2-nitrobenzenesulfonyl chloride (*via* six-member chair-like intermediate).

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of these methods often suffer from limitations, including high cost, low efficiency, toxic byproducts, and instability during acid activation. Therefore, developing more practical, economical, and safer alternatives remains a key objective in synthetic chemistry.
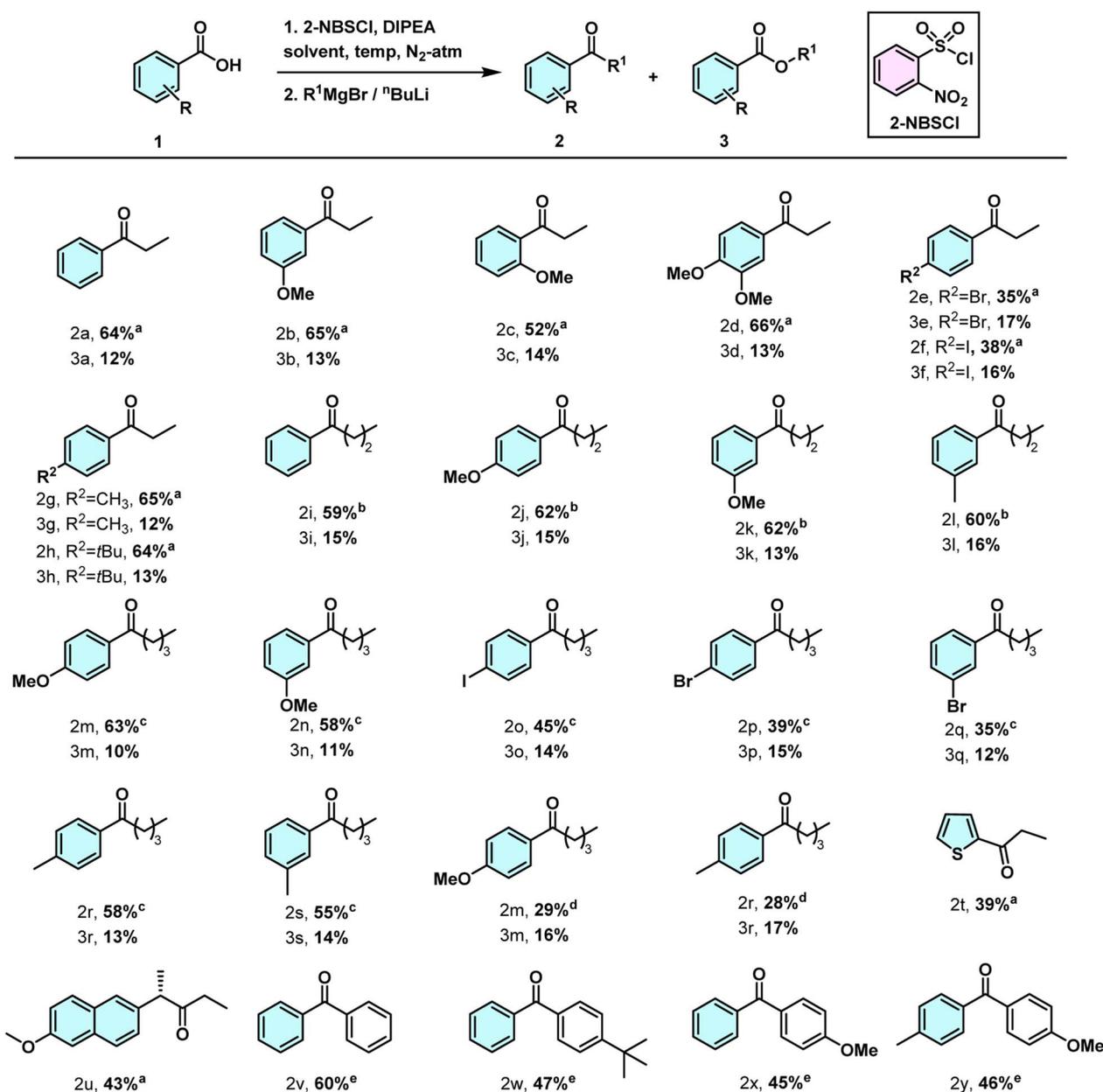
Results and discussion

We envisioned that substituted nitrobenzenesulfonyl (Ns) chloride could activate the carboxylic acids efficiently, which can be easily converted to ketones with the treatment of organometallic reagents. Initially, benzoic acid (**1a**, 1 mmol) was activated using 2-nitrobenzenesulfonyl chloride (2-NBSCl, 1 mmol) and N,N-diisopropylethylamine (DIPEA, 1.3 mmol) in dry tetrahydrofuran (THF, 2 mL) under a nitrogen atmosphere at room temperature. After 30 minutes, TLC revealed the appearance of new spots in the reaction medium, possibly due to the formation of a mixed anhydride and other reactive intermediates. Next, we added CH_3CH_2MgBr (1.2 mmol, 1 M in THF) in a dropwise manner at −20 °C. A total 60% (46% ketone and 14% ester) yield was obtained in 6 h (entry 1, Table S1). The formation of ketone and ester products was confirmed by 1D (^1H, ^{13}C) NMR. Based on the primary result, we proceeded to optimize the reaction conditions for ketone synthesis in different solvents and temperatures. An improved yield (**2a**, 64%) of the ketone was obtained when the reaction was performed in dry toluene (entry 8, Table S1). Extending the reaction time did not significantly affect the ketone yield. The reaction was also tested with other substituted nitrobenzenesulfonyl (Ns) chlorides (4-nitrobenzenesulfonyl chloride, 4-chloro-2-nitrobenzenesulfonyl chloride, and 2,4-dinitrobenzenesulfonyl chloride) as activating reagents; however, no further improvement in yield was observed (entries 12–14, Table S1). Reaction with 2,4-dinitrobenzenesulfonyl chloride did not offer any ketone formation. Therefore, the conditions used in entry 8 of Table S1 were considered optimal. Under optimized conditions, various ketones were synthesized from aromatic and aliphatic acids and different Grignard reagents (Table 1). Aromatic acids reacted with aliphatic Grignard reagents to give ketones in moderate yields. The aromatic acids bearing electron-donating group (m-OMe, o-OMe, m-, p-OMe) reacted with CH_3CH_2MgBr to afford the desired ketones (**2b–2d**) with satisfactory yields (52–66%). The electron-withdrawing groups (p-Br, p-I) containing aromatic acids also responded under optimized conditions (**2e**, **2f**). Alkyl groups (p-Me, p-^{t}Bu) containing aromatic acids underwent smooth reaction, offering the desired ketones (**2g**, **2h**) with good yields. Increasing the number of methylene units in the Grignard reagent also satisfies the reaction conditions smoothly. The reaction of $CH_3CH_2CH_2MgBr$ with various aromatic acids offered the desired ketones with satisfactory yields. Aromatic acids bearing electron-donating groups (such as p-OMe, m-OMe, and m-Me) successfully met the reaction conditions and yielded the desired ketones (**2j–2l**) with satisfactory yields (60–62%). Further using $CH_3CH_2CH_2CH_2MgBr$, the reaction also responded well. The reaction of 4-methoxybenzoic acid and 3-methoxybenzoic acid under optimized conditions offered the desired ketones (**2m**, **2n**) with

satisfactory yields (63%, 58%). Halogen bearing benzoic acids, such as 4-I, 4-Br, and 3-Br, after activation, underwent reactions with $CH_3CH_2CH_2CH_2MgBr$, offering the desired ketones (**2o–2q**). Alkyl-substituted benzoic acids (p-Me, m-Me) reacting with $CH_3CH_2CH_2CH_2MgBr$ offered desired ketones (**2r**, **2s**) with satisfactory yields. The applicability of the process is not restricted to the Grignard reagent; Organo-lithium also satisfies the reaction conditions. Activated 4-methoxy and 4-methyl benzoic acids reacted with ^nBuLi readily, producing the desired ketones (**2m**, **2r**). The yields in these specific cases were very low, possibly due to the higher basic character of ^nBuLi compared to its nucleophilic character. Heterocyclic acid and an aromatic drug ((S)-Naproxen (NSAID)) containing an aliphatic carboxylic acid also satisfied the reaction conditions, affording the desired ketones (**2t**, **2u**) in moderate yields. In some cases, a small percentage of esters was formed along with the ketone product. We also performed the ketone synthesis with aromatic Grignards, which satisfy the reaction conditions and offer the desired ketones (**2v–2y**) with satisfactory yields. In the case of aromatic Grignard reagents, no significant ester formation was observed.

A lower yield percentage of ketone was observed in most cases. We carefully observed the reaction to determine the cause of the lower yield percentage. During the activation of the benzoic acid with 2-nitrobenznesulfonyl chloride, some new spots were found in TLC. When we allowed the intermediate formation for quite a long time (~2 h), the reaction offered the formation of symmetrical anhydride (benzoic anhydride **4a**, Table 2a) of benzoic acid, which was characterized by NMR (^1H, ^{13}C) and HRMS analysis. Thus, the formation of such symmetrical anhydrides lowered the amounts of activated acids, hence lowering the ketone yields. Also, the formation of ester byproducts in the reactions lowered the desired yield percentage of ketones. After successfully identifying the symmetrical anhydride formation, we proceeded with reactions to synthesize some symmetrical anhydrides with different aromatic acids (Table 2a). Electron-donating group containing benzoic acid, such as 4-methoxybenzoic acid, readily underwent a reaction, offering good yield of anhydride formation (**4b**, 78%). Electron-withdrawing group containing benzoic acid (4-Cl benzoic acid) also smoothly participated in the reaction, allowing the formation of symmetrical anhydride **4c** with satisfactory yield. The crystal structure of **4b** (CCDC: 2483964, SI, Fig. S1 and Table S2) and **4c** (CCDC: 2483963, SI, Fig. S1 and Table S2) further confirmed the symmetrical anhydride formation. Alkyl groups (p-Me, p-^{t}Bu) containing acids offered the desired anhydrides (**4d**, **4e**) with satisfactory yields. After synthesizing some symmetrical anhydrides, Next, we proceeded to synthesize the ketones using these symmetrical anhydrides (Table 2b). Benzoic anhydride (1 mmol) reacted with CH_3CH_2-MgBr (1.2 mmol), offering the desired ketone **2a** with good yield. The reaction of 4-methoxybenzoic anhydride with CH_3-CH_2MgBr offered ketone **2z1** satisfactorily. 4-Methyl and 4-(tert-butyl) benzoic anhydrides readily underwent the reactions with $CH_3CH_2CH_2MgBr$, offering the desired ketones (**2z2**, **2z3**) with good yields. Additionally, the reaction of benzoic anhydride with a relatively long-chain Grignard reagent

Table 1 Scope of ketones[a]

2a, **64%**[a]
3a, **12%**

2b, **65%**[a]
3b, **13%**

2c, **52%**[a]
3c, **14%**

2d, **66%**[a]
3d, **13%**

2e, R^2=Br, **35%**[a]
3e, R^2=Br, **17%**
2f, R^2=I, **38%**[a]
3f, R^2=I, **16%**

2g, R^2=CH$_3$, **65%**[a]
3g, R^2=CH$_3$, **12%**
2h, R^2=tBu, **64%**[a]
3h, R^2=tBu, **13%**

2i, **59%**[b]
3i, **15%**

2j, **62%**[b]
3j, **15%**

2k, **62%**[b]
3k, **13%**

2l, **60%**[b]
3l, **16%**

2m, **63%**[c]
3m, **10%**

2n, **58%**[c]
3n, **11%**

2o, **45%**[c]
3o, **14%**

2p, **39%**[c]
3p, **15%**

2q, **35%**[c]
3q, **12%**

2r, **58%**[c]
3r, **13%**

2s, **55%**[c]
3s, **14%**

2m, **29%**[d]
3m, **16%**

2r, **28%**[d]
3r, **17%**

2t, **39%**[a]

2u, **43%**[a]

2v, **60%**[e]

2w, **47%**[e]

2x, **45%**[e]

2y, **46%**[e]

[a] Reaction conditions: **1** (1 mmol, 1 equiv), 2-NBSCl (1 mmol, 1 equiv), DIPEA (1.3 mmol, 1.3 equiv), toluene, 0 °C, N$_2$-atm; [a]CH$_3$CH$_2$MgBr (1.2 mmol, 1.2 equiv, 1 M in THF); [b]CH$_3$(CH$_2$)$_2$MgBr (1.2 mmol, 1.2 equiv, 1 M in THF); [c]CH$_3$(CH$_2$)$_3$MgBr (1.2 mmol, 1.2 equiv, 1 M in THF); [d]CH$_3$(CH$_2$)$_3$Li (1.2 mmol, 1.2 equiv, 2 M in cyclohexane); [e]ArMgBr (1.2 mmol, 1.2 equiv, 1 M in THF), solvent: THF; 35 min-6 h, Isolated yields.
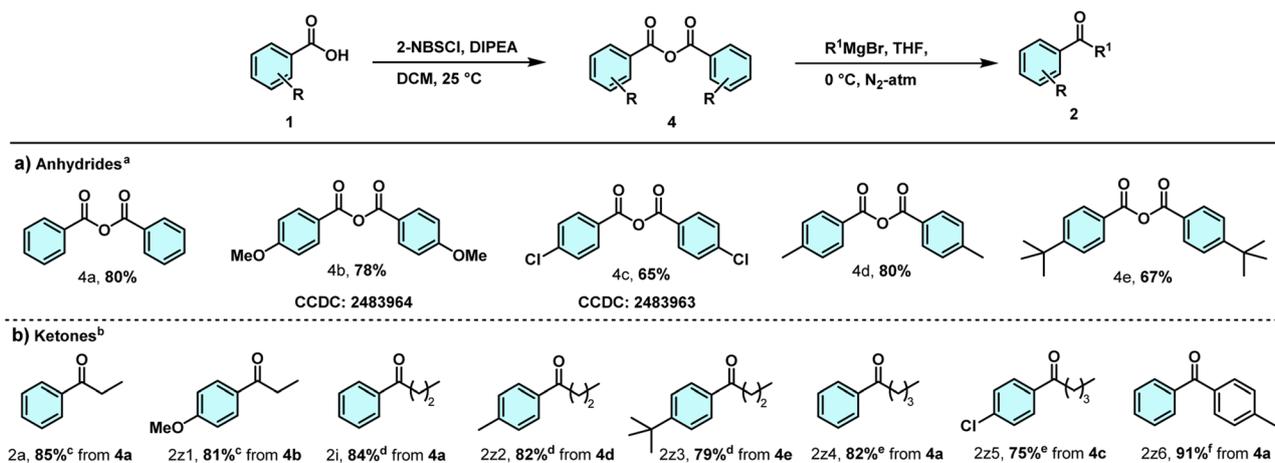
(CH$_3$CH$_2$CH$_2$CH$_2$MgBr) yielded the targeted ketone **2z4** with a good yield. 4-Chlorobenzoic anhydride also offered the targeted ketone **2z5** with a moderate yield. *p*-Tolylmagnesium bromide reacted efficiently with benzoic anhydride to afford the target ketone **2z6** in excellent yield (91%).

A proposed mechanism for ketone formation is illustrated in Scheme 2a.[20] The reaction of a carboxylic acid with 2-nitrobenzenesulfonyl chloride leads to the *in situ* formation of a mixture of mixed anhydride **A** and symmetrical anhydride **C**. Subsequent slow addition of an organometallic nucleophile

may result in the formation of intermediate **B** and **D**. These intermediates can be stabilized through chelation with metal ions, forming a six-membered chair-like intermediate. Direct elimination of the aryl sulfonate or carboxylate group from the intermediate may then yield the corresponding ketone. The strong electron-withdrawing nature of the nitro group makes the sulfonyl sulfur electron-deficient, thereby enhancing the leaving-group ability of the resulting sulfonate moiety.

The electron-deficient sulfonyl sulfur withdraws electron density from the ester oxygen, which in turn increases the

Table 2   Scope of anhydrides and ketones[a]

a) **Anhydrides**[a]

4a, 80%   4b, 78%   4c, 65%   4d, 80%   4e, 67%
            CCDC: 2483964   CCDC: 2483963

b) **Ketones**[b]

2a, 85%[c] from **4a**   2z1, 81%[c] from **4b**   2i, 84%[d] from **4a**   2z2, 82%[d] from **4d**   2z3, 79%[d] from **4e**   2z4, 82%[e] from **4a**   2z5, 75%[e] from **4c**   2z6, 91%[f] from **4a**

[a] Reaction conditions: [a]**1** (1 mmol, 1 equiv.), 2-NBSCl (0.5 mmol, 0.5 equiv), DIPEA (1 mmol, 1 equiv), DCM, 25 °C, yields were calculated w.r.t. 0.5 mmol (2-NBSCl); [b]**4** (1 mmol, 1 equiv, Isolated), R[1]MgBr (1.2 mmol, 1.2 equiv, 1 M in THF), THF (2 mL), 0 °C, N_2-atm; [c]EtMgBr (1.2 mmol, 1.2 equiv, 1 M in THF); [d]$CH_3(CH_2)_2MgBr$ (1.2 mmol, 1.2 equiv, 1 M in THF); [e]$CH_3(CH_2)_3MgBr$ (1.2 mmol, 1.2 equiv, 1 M in THF); [f]4-MePhMgBr (1.2 mmol, 1.2 equiv, 1 M in THF); 2–6 h, Isolated yields.
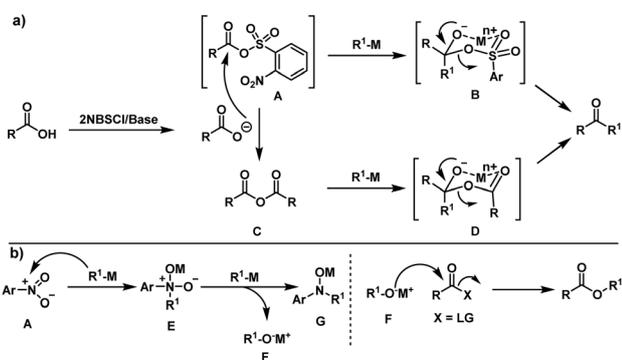
Scheme 2   (a) Plausible mechanistic pathway for ketone formation. (b) Plausible mechanistic pathway for ester byproduct formation.

electrophilic character of the carbonyl carbon, allowing nucleophilic attack to the carbonyl carbon more readily. The reaction of small amounts of the Grignard reagent with the nitro group of intermediate **A** may lead to the formation of N-hydroxylamine derivative with the elimination of alkoxide **F**.[28,29] The reaction of alkoxide **F** with activated carboxylic acid may lead to the formation of ester side product in some cases (Scheme 2b). In addition, the presence of unreacted alkyl bromide can react with the carboxylate and may also form small amounts of ester side product in some cases.

Conclusions

In conclusion, we have successfully developed a one-pot synthesis of ketones directly from carboxylic acids. The method involves activation of carboxylic acids using 2-nitrobenzenesulfonyl chloride, followed by nucleophilic addition of organomagnesium or organolithium reagents to yield

the desired ketones. Notably, the extended activation time of acids promotes the formation of symmetrical anhydrides. These protocols offer significant advantages, including near-stoichiometric use of organometallic reagents, broad substrate scopes, and straightforward methods.

Conflicts of interest

The authors declare no conflicts of interest.

Data availability

Supporting data are available in the supplementary information (SI). Supplementary information: experimental details, characterization data and spectra (NMR) for all compounds. See DOI: https://doi.org/10.1039/d5ra08605a.

CCDC 2483964 (**4b**) and 2483963 (**4c**) contain the supplementary crystallographic data for this paper.[30a,b]

Acknowledgements

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