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Design and synthesis of novel chiral dihydroimidazolium cyclophanes as N-heterocyclic carbene precatalysts

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ABSTRACT

A series of novel diphenyl ethylenediamine (DPEN) derived C_2 symmetric dihydroimidazolium cyclophanes were designed and synthesized as organo NHC precatalysts. The resultant organo NHC-catalyzed reactions with superior enantioselectivity than traditional C_2 dihydroimidazolidine NHCs as exemplified by NHC-catalyzed asymmetric intramolecular Stetter reactions.

Due to the increasing demand for green synthesis and the concerns over metal contamination in the pharmaceutical industry, research on organocatalysis has attracted significant interest.[1] N-Heterocyclic carbenes (NHCs), are widely investigated categories of organocatalysts since their existence was first realized in the 1960s.[2,3] In spite of the considerable progress and elegant work,[2,4,5] the development of effective chiral NHCs for asymmetric organocatalysis remains a challenge.[6] This is even true for the 1*R*,2*R*-diphenyl ethylenediamine [(1*R*,2*R*)-DPEN] based NHC system.[2,7] When considering the many applications of C_2 symmetric (1*R*,2*R*)-DPEN as a chiral building block in asymmetric synthesis,[8] it would be attractive to develop (1*R*,2*R*)-DPEN derived dihydroimidazolidines (**1**, Scheme 1) as asymmetric NHC catalysts. However, very few studies based on this type of chiral dihydroimidazolidine NHC catalyzed reaction have been reported.[2,7] Moreover, due to the relatively unstable nature of the non-aromatic ring of dihydroimidazolidines,[2,9] the delivery of the chiral information from the remote carbon backbone of these chiral NHCs remains a challenge, especially for organocatalysis.[7,10]

As a general strategy for increasing the enantioselectivity of asymmetric NHC catalysis, catalysts with more complex topological chiralities have received increasing attention.[2] Saigo's group developed planar-chirality (cyclophane-type) imidazolyl NHCs (**2**, Scheme 1).[11] These cyclophane NHCs were found to impart better enantioselectivity in some reactions compared to traditional NHCs with simple point chirality. This may be attributed to the inclusion of the chiral center in a macrocyclic structure which can globally control the relay of chirality. However, epimerization of the chiral center was observed due to flexible long-chain 'rope-skipping' (inset, Scheme 1). Thus, the enantioselectivity achieved was attenuated.[11b] In addition, due to the high strain of the aliphatic macrocyclic structures, some of these planar chiral cyclophane precatalysts were difficult to obtain synthetically.

We planned to construct the (1*R*,2*R*)-DPEN derived chiral cyclophane NHC **3** (Scheme 1): instead of taking advantage of planar chirality, we expected that the efficiency of delivering point chirality originating from the C_2 symmetric (1*R*,2*R*)-DPEN backbone would be enhanced by confining the active carbene site(s) into a more sterically demanding macrocycle, which would further distinguish the two possible faces of the substrates.[12] Furthermore, unlike a long aliphatic chain linker, the planar aromatic linkage together with the phenyl groups on the chiral centers could effectively avoid the 'rope-skipping'.

As shown in Scheme 2, the initial synthesis attempt took advantage of the monomer **4** synthesized in our laboratory en route to colloidal polyimidazolium salts.[13] In contrast to the higher concentrations adopted for our previous polymer synthesis, by mixing **4** and dibromoxylene **5** in acetone at low concentration, we obtained the bis-NHC precatalyst **6**. Achiral imidazolium cations analogous to **6** have been studied intensely for their interesting conformations and strong size adjustment ability,[14] are widely utilized as ligands for metal-complexes for catalysis, and as 'hosts' for anion recognition of biomolecules.[15] Very recently, Veige's group reported the first chiral bis-imidazolium cyclophane as a ligand for asymmetric palladium catalysis.[16] In our work, for the first time,

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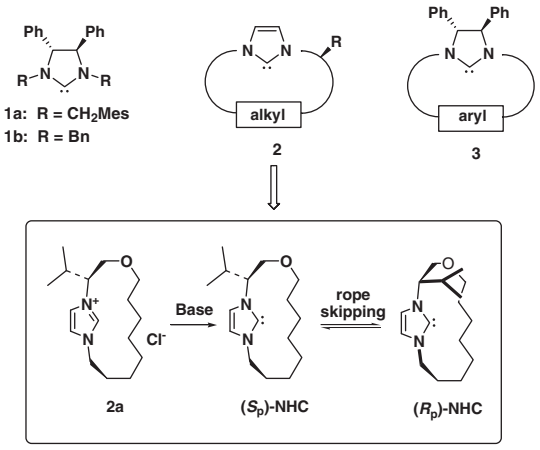
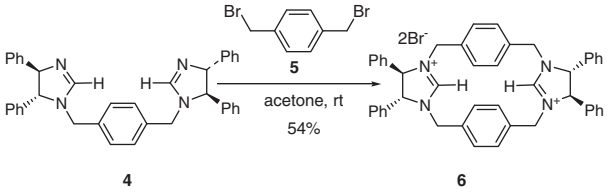


Scheme 1. Motifs of chiral acyclic and cyclophane NHCs.



Scheme 2. The synthesis of chiral cyclophane dihydroimidazolium salt **6**.

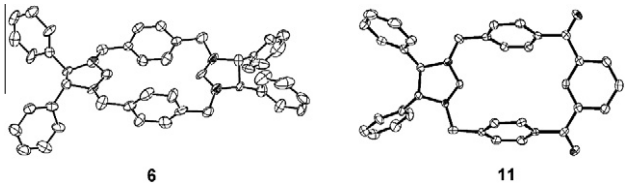
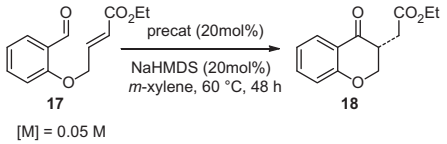


Figure 1. ORTEP structures of the cations **6** and **11**. Thermal ellipsoids are shown at 50% probability. The hydrogen atoms are omitted for clarity.

a chiral version of a bis-dihydroimidazolium cyclophane was synthesized for the purpose of asymmetric organo-NHC catalysis. The single crystal X-ray structure of the cation of **6** is shown in Figure 1. The two dihydroimidazolium groups are linked by the two *p*-xylenes to form a distorted square structure. As we expected, this rigid structure with the phenyl auxiliaries was free of benzene ring flipping. The classic asymmetric intramolecular Stetter reaction, previously usually performed under the catalysis of triazo- or thiazo-derived chiral NHCs,[17,18] when **6** was applied as the precatalyst, gave a slight enantiomeric excess with (*R*)-**18** as the major isomer (entries 3 and 4, Table 1). However, the reaction catalyzed by **6** was always sluggish and suffered from low yields and catalyst decomposition, no matter how we attempted to activate one (entry 3, Table 1) or both (entry 4, Table 1) of the carbene centers. This might be due to the extreme instability of the bis-NHC generated from the dihydroimidazolium salt.[9]

With these preliminary results, we modified our design of the precatalysts to include the mono-dihydroimidazolium cyclophane structural motif. The carbonyl linked cyclophane precatalyst **11** was synthesized in five steps with an 11% overall yield. The ether linked cyclophane precatalyst **16** was synthesized in a six-step sequence with a 9% overall yield as shown in Scheme 3. The solid state structure conformation of **11** was achieved by single crystal X-ray diffraction, as shown in Figure 1. The cyclophane forms a box (4.60 × 5.62 Å) and the two phenyl rings are parallel to each

Table 1
Intramolecular Stetter reactions catalyzed by DPEN derived chiral NHCs



Entry	Precatalyst	Yield[a] (%)	ee[b] (%)
1	**1b**• HCl	43	0
2	**1a**• HBF_4	38	9
3	**6**	33	16
4[c]	**6**	22	20
5	**11**	58[d]	68
6	**16**	47[e]	38

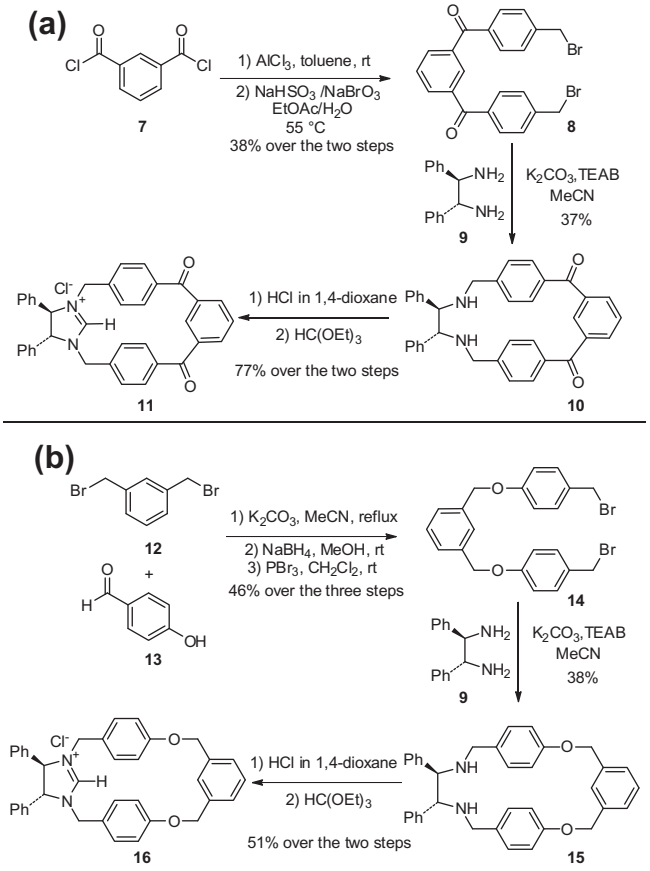
[a] Isolated yield.
[b] ee: Enantiomeric excess; determined by chiral HPLC.
[c] 40 mol % NaHMDS was added.
[d] 97% Yield based on recovery of **17**.
[e] 98% Yield based on recovery of **17**.

other. This box structure should help block the free space and locate the chiral information closer to the carbene center, leading to enhanced enantioselectivity.

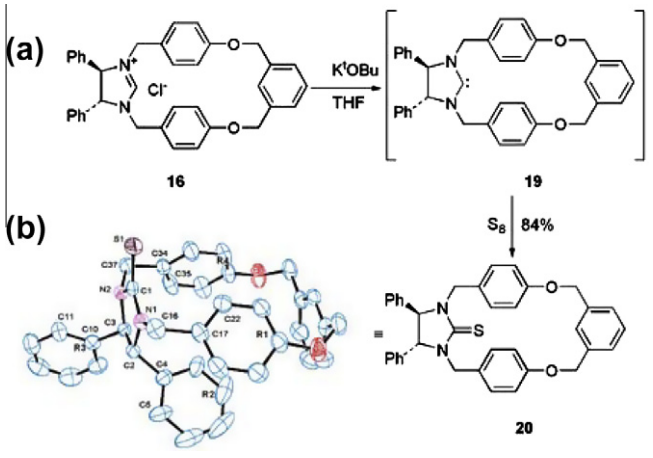
Synthetically, the C–O bond based carbonyl and ether linkages made the cyclophane structures more accessible than analogous simple aliphatic macrocycles by offering functional group transformations and the relief of macrocyclic strain. Furthermore, considering the metal affinity and the hydrogen-bonding acceptor nature of the oxygen atom, this type of dihydroimidazolium cyclophane might be more interesting for both asymmetric metallic and organo NHC catalysis.

The feasibility of applying these new dihydroimidazolium cyclophanes **11** and **16** as organo NHC precatalysts was quickly established by performing the intramolecular Stetter reaction of the salicylaldehyde-derived substrate **17**, using a slightly modified version of Rovis's procedure[19] (entries 5 and 6, Table 1). Unlike the previous two-carbene cyclophane **6** (entries 3 and 4), which suffered in yields and/or enantioselectivities, the one-carbene cyclophane precatalysts **11** (entry 5) and **16** (entry 6) gave much higher yields and enhanced enantioselectivities for the Stetter adduct **18** (especially using **11**). When compared to the acyclic analogues **1a** and **1b**, the enantioselectivity increased dramatically (entries 1, 2 vs 5, 6, Table 1) with comparable yields. This result indicates that these boxed cyclophane structures do help in delivery of the remote chiral information of the C_2 DPEN backbone as expected. The initial conditions were also tested on a series of salicylaldehyde-derived substrates (see Table 4, Supplementary data). In general, moderate enantioselectivities were obtained for most of these substrates (SI).

The rigid cyclophane dihydroimidazolidine precatalysts **11** and **16** demonstrated significant improvement in both activity and enantioselectivity in this intramolecular Stetter reaction, as compared to the acyclic DPEN derived dihydroimidazolidines **1a** and **1b**. This triggered our interest in understanding the role of the cyclophane motif in the catalytic cycle leading to the enhanced enantioselectivity. The direct isolation of the free carbene **19** by deprotonation of the precatalyst **16** was not successful (Scheme 4), due to the high reactivity of carbenes generated from dihydroimidazolium salts.[9] However, the unstable free carbene **19** was successfully trapped by sulfur in situ. In the presence of an excess of colloidal sulfur in tetrahydrofuran, treatment of the dihydroimidazolium salt **16** with K^{t}OBu gave the thiourea **20** in 84% yield (Scheme 4).[20] The single crystal X-ray analysis of **20** indicated a highly twisted conformation of the thiourea cyclophane structure



Scheme 3. Syntheses of the chiral cyclophane dihydroimidazolium salts **11** (a) and **16** (b).



Scheme 4. NHC generation and trapping.

(Scheme 4). As the sulfur (S1) is attached to the carbene carbon (C1), the macrocyclic ring is pushed to one side and is almost perpendicular to the dihydroimidazole ring. Thus, the phenyl rings R1 and R2 are twisted as compared to the phenyl rings R3 and R4. This can be seen from the difference in the torsion angles: <N1–C16–C17–C22: 57.54°; <N1–C37–C34–C35: 95.52°; <C3–C2–C4–C5: 51.13°; <C2–C3–C10–C11: 84.75°. The C1–S1 bond distance is 1.681 Å.[21] This interesting structure clearly demonstrates that the rigid macrocyclic ring is forced perpendicular to the dihydroimidazole ring by carbene additives, which strongly interact with the back-side phenyl ring. This interaction between the rigid macrocyclic ring and the back-side phenyl ring efficiently prevents any flipping motion, and makes the active carbene site even more sterically demanding than its precursor **16**. It could also relay the chiral information from the backbone to the carbene center as trapped by other electrophiles. This observation is in accordance with our original hypothesis and the preliminary results of the obtained superior enantioselectivities with the chiral dihydroimidazolium cyclophanes as precatalysts.

In summary, we have developed a series of novel C_2 symmetric chiral cyclophane dihydroimidazolium salts as asymmetric organo NHC precatalysts with designed rigid macrocyclic structures. Superior enantioselectivities were observed when compared with traditional chiral C_2 dihydroimidazolidine NHCs in intramolecular Stetter reactions. The rigid cyclophane ring plays a key role in efficiently preventing ring flipping and in transferring the chiral information from the backbone to the carbene center. Further structural modifications and applications of these novel C_2 DPEN dihydroimidazolidine based cyclophanes in asymmetric catalysis are currently ongoing in our group.

Acknowledgments

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Supplementary data

Supplementary data (a description of materials and methods for experiments, along with spectroscopic data are included in the supporting information) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.09.116.

References and notes

1. For selected recent reviews on organocatalysis, see: (a) Grondal, C.; Jeanty, M.; Enders, D. *Nature Chem.* **2010**, *2*, 167–178; (b) Macmillan, D. W. D. *Nature* **2008**, *455*, 304–308; (c) Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471–5569.
2. For recent reviews on NHCs for organocatalysis, see: (a) Biju, A. T.; Kuhl, N.; Glorius, F. *Acc. Chem. Res.* **2011**, *44*, 1182–1195; (b) Vora, H. U.; Rovis, T. *Aldrichimica Acta* **2011**, *44*, 3–11; (c) Chiang, P.-C.; Bode, J. W. *TCI MAIL* **2011**, *149*, 2–17; (d) Moore, J. L.; Rovis, T. *Top. Curr. Chem. Res.* **2010**, *291*, 77–144; (e) Phillips, E. M.; Chan, A.; Scheidt, K. A. *Aldrichimica Acta* **2009**, *42*, 55–66; (f) Read de Alaniz, J.; Rovis, T. *Synlett* **2009**, 1189–1207; (g) Chiang, P.-C.; Bode, J. W. In *N-Heterocyclic Carbenes*; Díez-González, S., Ed.; The Royal Society of Chemistry, 2011; pp 399–435; (h) Nair, V.; Vellalath, S.; Babu, B. P. *Chem. Soc. Rev.* **2008**, *37*, 2691–2698; (i) Marion, N.; Díez-González, S.; Nolan, S. P. *Angew. Chem., Int. Ed.* **2007**, *46*, 2988–3000; (j) Enders, D.; Niemeier, O. A. Henseler, A *Chem. Rev.* **2007**, *107*, 5606–5655.
3. Wanzlick, H. W. *Angew. Chem., Int. Ed. Engl.* **1962**, *1*, 75–80.
4. (a) Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 239–258; (b) Bugaut, X.; Glorius, F. *Chem. Soc. Rev.* **2012**, 3511–3522. and references therein.
5. (a) Stetter, H.; Kuhlmann, H. In *Organic Reactions*; Paquette, L. A., Ed.; John Wiley & Sons: New York, 1991; vol. 40, pp 407–496; (b) Wong, F. T.; Patra, P. K.; Seayad, J.; Zhang, Y. G.; Ying, J. Y. *Org. Lett.* **2008**, *10*, 2333–2336; (c) Kang, Q.; Zhang, Y. G. *Org. Biomol. Chem.* **2011**, *9*, 6715–6720; (d) Seayad, J.; Patra, P. K.; Zhang, Y. G.; Ying, J. Y. *Org. Lett.* **2008**, *10*, 953–956.
6. Enders, D.; Breuer, K.; Runsink, J.; Teles, J. H. *Helv. Chim. Acta* **1996**, *79*, 1899–1902.
7. For recent examples of C_2 1,2-diamine derived dihydroimidazolines as organo NHC catalysts, see: (a) Matsumoto, Y.; Tomioka, K. *Tetrahedron Lett.* **2006**, *47*, 5843–5846; (b) Duguet, N.; Donaldson, A.; Leckie, S. M.; Kallström, E. A.; Campbell, C. D.; Shapland, P.; Brown, T. B.; Slawin, A. M. Z.; Smith, A. D *Tetrahedron: Asymmetry* **2010**, *21*, 601–606; (c) Duguet, N.; Donaldson, A.; Leckie, S. M.; Douglas, J.; Shapland, P.; Brown, T. B.; Churchill, G.; Slawin, A. M. Z.; Smith, A. D *Tetrahedron: Asymmetry* **2010**, *21*, 582–600; (d) Duguet, N.; Campbell, C. D.; Slawin, A. M. Z.; Smith, A. D. *Org. Biomol. Chem.* **2008**, *6*, 1108–1113.
8. For classic examples of C_2 DPEN derivatives for asymmetric catalysis, see: (a) Doucet, H.; Ohkuma, T.; Murata, K.; Yokozawa, T.; Kozawa, E.; England, A. F.; Ikariya, T.; Noyori, R. *Angew. Chem., Int. Ed.* **1998**, *37*, 1703–1707; (b) Corey, E. J.;

Lee, D.; Sarshar, S. *Tetrahedron: Asymmetry* **1995**, *6*, 3–6; (c) Corey, E. J.; Imwinkelried, R.; Pikul, S.; Xiang, Y.-B. *J. Am. Chem. Soc.* **1989**, *111*, 5493–5495; (d) Mangeney, P.; Alexakis, A.; Normant, J. F. *Tetrahedron Lett.* **1988**, *29*, 2677–2680; For a representative example of C_2 DPEN derived dihydroimidazolidine for asymmetric catalysis, see: (e) Funk, T. W.; Berlin, J. M.; Grubbs, R. H. *J. Am Chem. Soc.* **2006**, *128*, 1840–1846.

9. For a recent mini review on a stability study of dihydro-imidazoline NHCs, see: Kirmse, W. *Angew. Chem., Int. Ed.* **2010**, *49*, 8798–8801. and references therein..
10. For recent efforts in developing C_2 DPEN derived dihydroimidazoline NHCs as ligands for metal catalysis, see: Wu, L.; Falivene, L.; Drinklel, E.; Grant, S.; Linden, A.; Cavallo, L.; Dorta, R. *Angew. Chem., Int. Ed.* **2012**, *51*, 2870–2873. and references therein..
11. (a) Ishida, Y.; Iwasa, E.; Matsuoka, Y.; Miyauachi, H.; Saigo, K. *Chem. Commun.* **2009**, 3401–3403; (b) Matsuoka, Y.; Ishida, Y.; Sasaki, D.; Saigo, K. *Chem. Eur. J.* **2008**, *14*, 9215–9221; (c) Winkelmann, O.; Linder, D.; Lacour, J.; Näther, C.; Lüning, U. *Eur. J. Org. Chem.* **2007**, 3687–3697; (d) Ishida, Y.; Miyauachi, H.; Saigo, K. *Chem. Commun.* **2002**, 2240–2241.
12. Čorić, L.; List, B. *Nature* **2012**, *483*, 315–319.
13. (a) Zhang, Y. G.; Zhao, L.; Patra, P. K.; Hu, D.; Ying, J. Y. *Nano Today* **2009**, *4*, 13–20; (b) Tan, M. X.; Zhang, Y. G.; Ying, J. Y. *Adv. Synth. Catal.* **2009**, 1390–1395.
14. For recent reviews on bis-imidazolium derived cyclophanes, see: (a) Xu, Z.; Kim, S. K.; Yoon, J. *Chem. Soc. Rev.* **2010**, *39*, 1457–1466; (b) Baker, M. V.; Brown, D. H. *Mini-Rev. Org. Chem.* **2006**, *3*, 333–354.
15. For recent selected elegant examples, see: (a) Baker, M. V.; Brown, D. H.; Haque, R. A.; Skelton, B. W.; White, A. H. *Dalton Trans.* **2010**, *39*, 70–72; (b) Baker, M. V.; Brown, D. H.; Simpson, P. V.; Skelton, B. W.; White, A. H. *Dalton Trans.* **2009**, 7294–7307; (c) Baker, M. V.; Brown, D. H.; Haque, R. A.; Simpson, P. V.; Skelton, B. W.; White, A. H.; Williams, C. C. *Organometallics* **2009**, *28*, 3793–3803; (d) Baker, M. V.; Brown, D. H.; Heath, C. H.; Skelton, B. W.; White, A. H.; Williams, C. C. *J. Org. Chem.* **2008**, *73*, 9340–9352; (e) Neelakandan, P. P.; Ramaiah, D. *Angew. Chem., Int. Ed.* **2008**, *47*, 8407–8411; (f) Alcalde, E.; Mesquida, N.; Pérez-García, L1. *Eur. J. Org. Chem.* **2006**, 3988–3996; (g) Liu, L.; Huang, Y.; Riduan, S. N.; Gao, S.; Yang, Y.; Fan, W.; Zhang, Y. G. *Biomaterials* **2012**. http://dx.doi.org/10.1016/j.biomaterials. 2012.08.006.
16. Jeletic, M. S.; Ghiviriga, I.; Abboud, K. A.; Veige, A. S. *Dalton Trans.* **2010**, *39*, 6392–6394.
17. For recent elegant examples of asymmetric NHC-catalyzed intermolecular Stetter reactions, see: (a) Fang, X.; Chen, X.; Lv, H.; Chi, Y. R. *Angew. Chem., Int. Ed.* **2011**, *50*, 11782–11785; (b) Dirocco, D. A.; Rovis, T. *J. Am. Chem. Soc.* **2011**, *133*, 10402–10405; (c) Jousseaume, T.; Wurz, N. E.; Glorius, F. *Angew. Chem., Int. Ed.* **2011**, *50*, 1410–1414; (d) Kim, S. M.; Jin, M. Y.; Kim, M. J.; Cui, Y.; Kim, Y. S.; Zhang, L.; Song, C. E.; Ryu, D. Y.; Yang, J. W. *Org. Biomol. Chem.* **2011**, *9*, 2069–2071; (e) Liu, Q.; Rovis, T. *Org. Lett.* **2009**, *11*, 2856–2859; (f) Dirocco, D. A.; Oberg, K. M.; Dalton, D. M.; Rovis, T. *J. Am. Chem. Soc.* **2009**, *131*, 10872–10874; (g) Enders, D.; Han, J.; Henseler, A. *Chem. Commun.* **2008**, 3989–3991; (h) Liu, A.; Perreault, S.; Rovis, T. *J. Am. Chem. Soc.* **2008**, *130*, 14066–14067.
18. For a review and elegant examples of asymmetric intramolecular Stetter reactions, see: (a) Read de Alzniz, J.; Rovis, T. *Synlett* **2009**, 1189. and references cited therein.; For an example thereafter, see: (b) Jia, M.-Q.; Li, Y.; Rong, Z.-Q.; You, S.-L. *Org. Biomol. Chem.* **2011**, *9*, 2072–2074.
19. Kerr, M. S.; Alaniz, J. R.; Rovis, T. *J. Am. Chem. Soc.* **2002**, *124*, 10298–12099.
20. ^{1}H NMR yield using mesitylene as the internal reference. A 40% isolated yield was obtained, as the product partly decomposed during the silica gel chromatographic purification.
21. The supplementary crystallographic data for this Letter have been deposited at the CCDC. The numbers are: for **6**, CCDC 878009; for **11**, CCDC 878010; for **20**, CCDC 878011. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. See also the Supplementary data.